Organic & Biomolecular Chemistry

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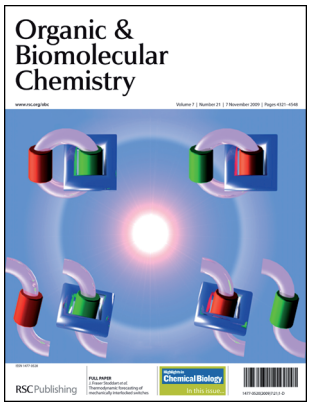
ISSN 1477-0520 CODEN OBCRAK 7(21) 4321–4548 (2009)



Cover

See J. Fraser Stoddart *et al.*, pp. 4391–4405.
The effects of structural modifications on the difference in free energy (ΔG^{o}) for the equilibrium processes in switchable mechanically interlocked molecules can be predicted by considering, firstly, the interactions present in their precursor pseudorotaxanes. Artwork by Mark A. Olson.

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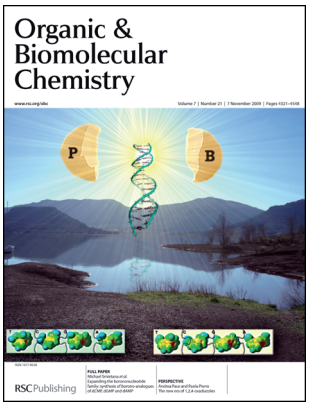

Inside cover

See Michael Smietana *et al.*, pp. 4369–4377.
Inspired by Salvator Dali's painting "jaune d'oeuf soleil" this artwork, representing the Salagou Lake near Montpellier, asks the question whether boron might have played a role in the pre-RNA world. We describe here the synthesis of the four 2'-deoxybononucleotide analogues of natural nucleotide monophosphates and demonstrate that these analogues form a new borono-based internucleosidic linkage with uridine.

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HIGHLIGHTS IN CHEMICAL BIOLOGY

Highlights in Chemical Biology provides a 'snapshot' of the latest developments in chemical biology from all RSC publications, showcasing newsworthy articles and significant scientific advances.

November 2009/Volume 4/Issue 11

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PERSPECTIVE

This survey includes historical background, general features and state-of-the-art applications about the synthesis, the chemical and photochemical reactivity, and the use of 1,2,4-oxadiazoles in materials and as bioactive compounds.

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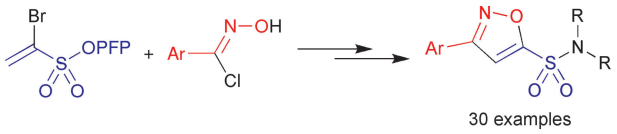

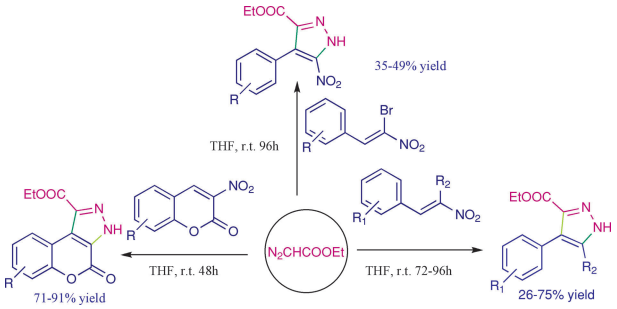

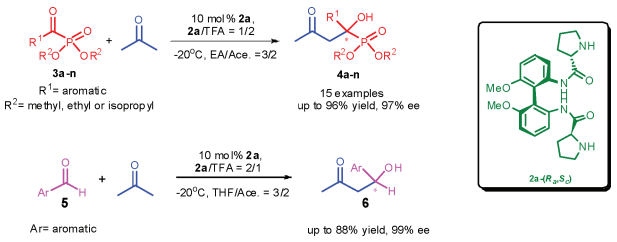

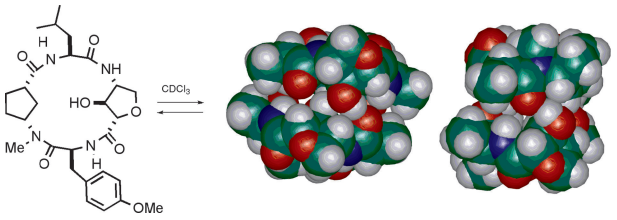

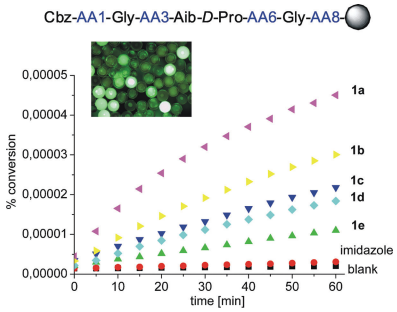

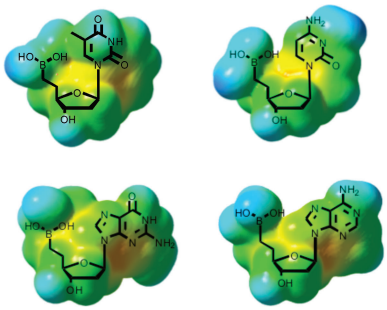

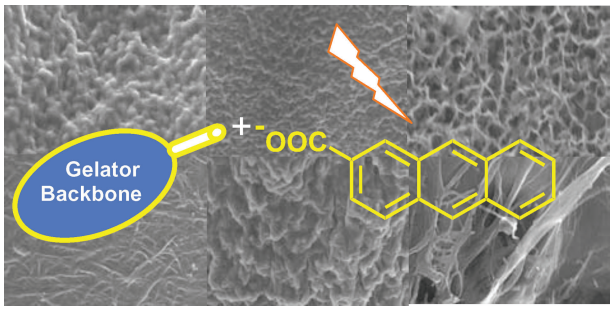

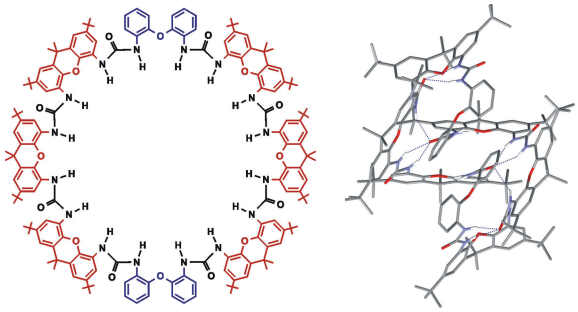

2010 Meetings (in chronological order)

NF-κB in Inflammation & Disease
Advances in Biopharmaceuticals
Structural Biology
Structural Genomics: Expanding the Horizons of Structural Biology
Triglycerides & Triglyceride-Rich Particles in Health & Disease (new!)
Alzheimer's Disease Beyond Aβ
Molecular Basis for Biological Membrane Organization & Dynamics
HIV Biology & Pathogenesis
RNA Silencing: Mechanism, Biology & Application
Molecular Basis for Chromatin Structure & Regulation
Hypoxia: Molecular Mechanisms of Oxygen Sensing & Response Pathways
Adipose Tissue Biology
Neuronal Control of Appetite, Metabolism & Weight*
New Insights into Healthspan & Diseases of Aging
Role of Inflammation in Oncogenesis
Molecular and Cellular Biology of Immune Escape in Cancer
Advances in Molecular Mechanisms of Atherosclerosis
The Macrophage: Intersection of Pathogenic & Protective Inflammation
Antibiotics & Resistance: Challenges & Solutions (new!)
Stem Cell Differentiation & Dedifferentiation
Cell Biology of Virus Entry, Replication & Pathogenesis
RNA Silencing Mechanisms in Plants (new!)
Tolerance & Autoimmunity
Cilia, Signaling & Human Disease
Lymphocyte Activation & Gene Expression
Angiogenesis in Health & Disease
Cardiovascular Development & Repair
Biomolecular Interaction Networks: Function & Disease (new!)
Cell Death Pathways: Apoptosis, Autophagy & Necrosis
Metabolism & Cancer Progression (new!)
Receptors and Signaling in Plant Development & Biotic Interactions
HIV Vaccines
Viral Immunity
Nuclear Receptors: Signaling, Gene Regulation & Cancer
Nuclear Receptors: Development, Physiology & Disease
New Paradigms in Cancer Therapeutics
Integration of Developmental Signaling Pathways
G Protein-Coupled Receptors
Dynamics of Eukaryotic Transcription During Development
Synapses: Formation, Function & Misfunction
Towards Defining the Pathophysiology of Autistic Behavior
Malaria: New Approaches to Understanding Host-Parasite Interactions
Molecular Targets for Control of Vector-Borne Diseases: Bridging Lab & Field Research*
Islet Biology
Diabetes
Computer-Aided Drug Design
New Directions in Small Molecule Drug Discovery (new!)
Developmental Origins & Epigenesis in Human Health and Disease (new!)
Bioactive Lipids: Biochemistry & Diseases
Innate Immunity: Mechanisms Linking with Adaptive Immunity

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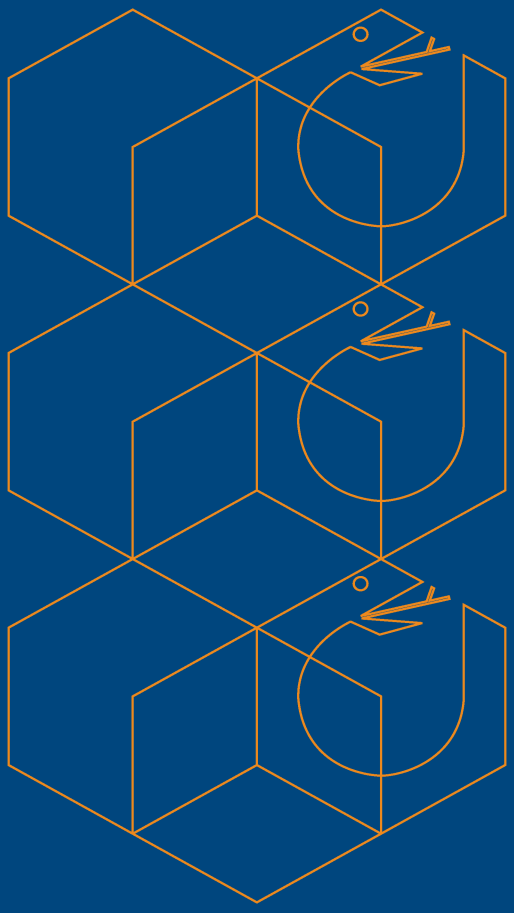
Deadline: january 31, 2010

The awards will be conferred on the occasion of the XXIth EFMC "International Symposium on Medicinal Chemistry" (ISMC) to be held in Brussels, Belgium, September 5-9, 2010



The Nauta Award for Pharmacochemistry

For the advancement of medicinal chemistry and the development of international organizational structures in Medicinal Chemistry. The Award will be given for outstanding achievements in the field of Medicinal Chemistry.

The UCB-Ehrlich Award for Excellence in Medicinal Chemistry

To acknowledge and recognise outstanding research in the field of Medicinal Chemistry in its broadest sense by a young scientist. This Award has been established with the support of UCB Pharma.

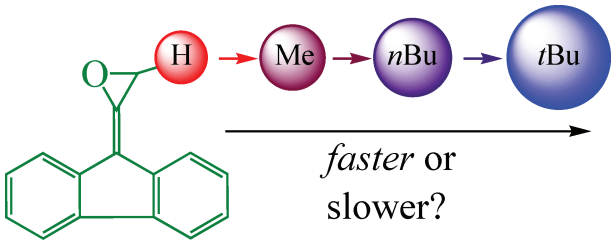
The Prous Institute-Overton and Meyer Award for New Technologies in Drug Discovery

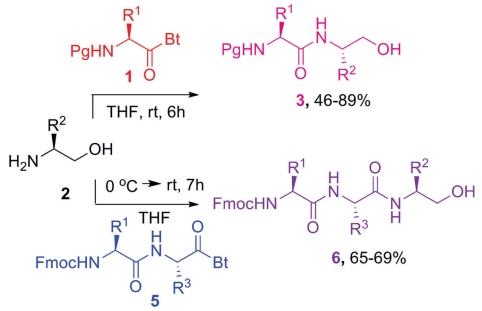
To encourage innovation and investigation in technological development related to drug discovery, this Award established with the support of Prous Institute will be given for the discovery, evaluation or use of new technologies.

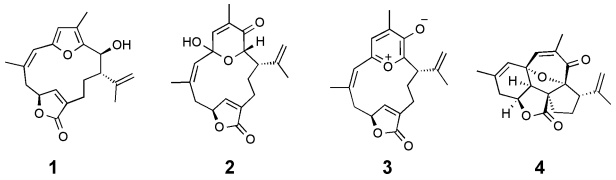
The nominations should be submitted to the Chairman of the Juries, Professor Gerhard Ecker, President of EFMC, Department of Medicinal Chemistry, University of Vienna, Althanstrasse 14, A-1090 Wien, Austria Fax: +43-1-4277-9551 E-mail: awards@efmc.info

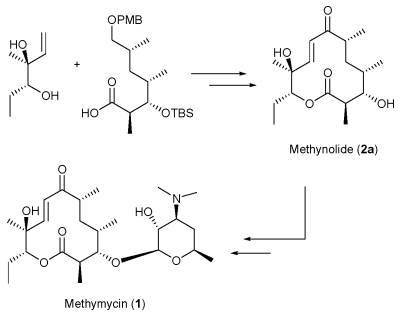
Please visit www.efmc.info for more informations and Award regulations

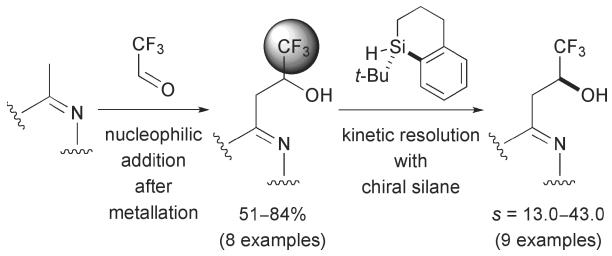
EUROPEAN FEDERATION FOR MEDICINAL CHEMISTRY







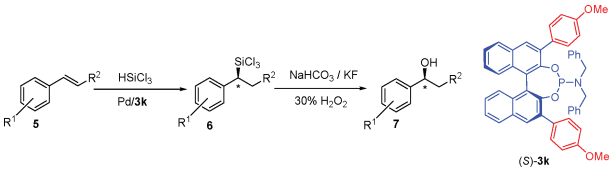




Facile preparation of CF_3-substituted carbinols with an azine donor and subsequent kinetic resolution through stereoselective Si–O coupling

Anne Steves and Martin Oestreich*

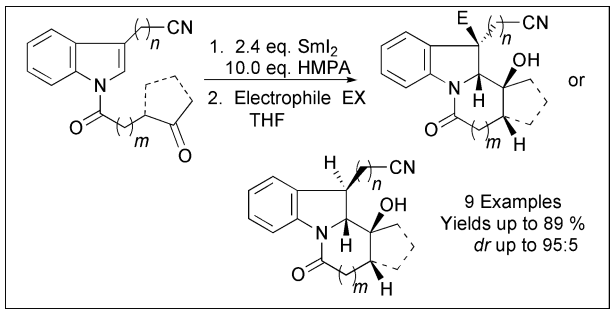
Enantiomerically enriched, α-CF_3-substituted carbinols containing an azine donor are prepared from fluoral followed by reagent-controlled Si–O coupling.



Synthesis and application of bulky phosphoramidites: highly effective monophosphorus ligands for asymmetric hydrosilylation of styrenes

Feng Zhang and Qing-Hua Fan*

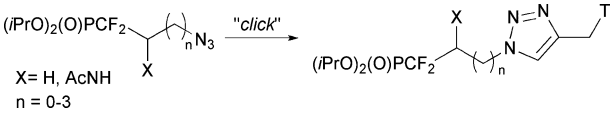
New bulky binaphthol based phosphoramidite ligands were prepared and successfully applied in the Pd-catalyzed asymmetric hydrosilylation of styrenes with high enantioselectivities, and excellent catalytic activities and productivities.



Highly diastereoselective samarium diiodide induced cyclizations of new 3-substituted indole derivatives

Christine Beemelmanns and Hans-Ulrich Reissig*

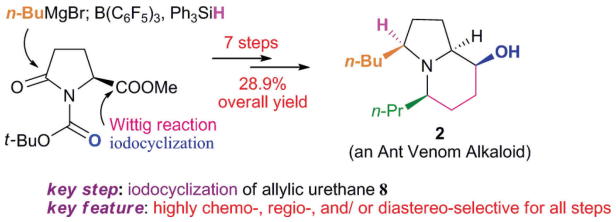
Starting from new N-acyl indole derivatives, we obtained highly functionalized tricyclic and tetracyclic indole derivatives in moderate to very good yields and with excellent diastereoselectivities. Further transformations to synthetically useful intermediates were also possible.

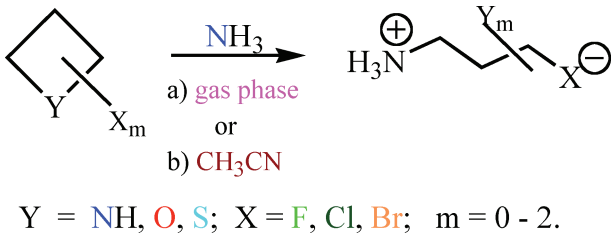


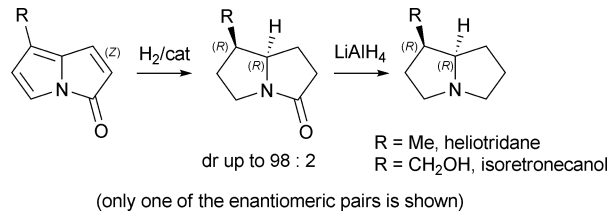
Synthesis of fluorophosphonylated acyclic nucleotide analogues *via* copper(I)-catalyzed Huisgen 1-3 dipolar cycloaddition

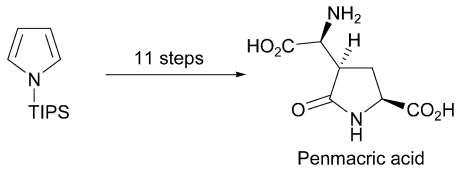
Sonia Amel Diab, Antje Hienzch, Cyril Lebargy, Stéphane Guillarme, Emmanuel Pfund and Thierry Lequeux*

The syntheses of fluorophosphonylated purine and pyrimidine derivatives are reported as new and rapid access to potential nucleoside phosphorylase inhibitors.









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Highlights in Chemical Biology

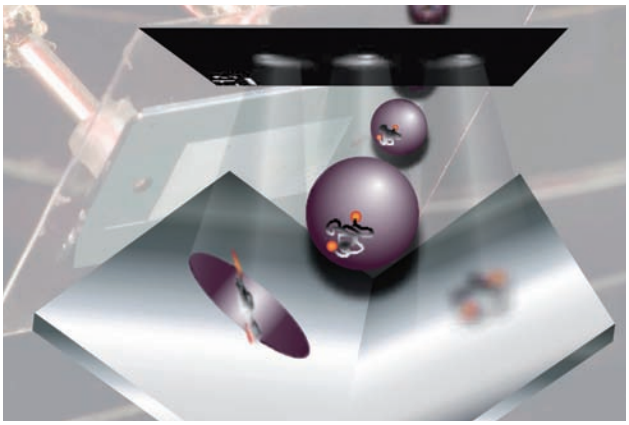
Reflecting chip allows fast 3D DNA observation

Scrutinising cells with mirrors

A chip that can be used to track biological processes in three dimensions inside living cells has been developed in France.

Aurélien Bancaud and co-workers from the University of Toulouse, made the device, which uses microscale V-shaped mirrors to provide simultaneous views of biological specimens from different vantages. This allows the team to use a regular upright microscope to follow cell processes in 3D on a fast timescale.

'Modern live cell imaging calls for new methods that achieve fast and minimally invasive 3D observation,' explains Bancaud. Current methods can involve acquiring several views of the same specimen, meaning high doses of illumination are needed – which can be detrimental to the cells. The multiple observation process is also slower, so fast events cannot be easily tracked. Pyramidal mirrors have been proposed for multiple vantage point imaging and 3D tracking in vitro, but these systems were not integrated in a lab-on-a-chip device, limiting their applicability for live cell imaging, says Bancaud.



Bancaud's mirrored chip can be used to study chromatin dynamics inside cells

Bancaud's group made the device using micromachining technology to form metal coated trenches in a silicon wafer. The metal coating acts as a mirror and particles such as cells can be introduced into the V-shaped trenches. The researchers incorporated their device into a standard fluorescence microscope and loaded the wafer with yeast cells modified to express a fluorescent protein. The group was able to use the device to follow the fluorescent protein and so study fast DNA movements in chromosomes within the cell nuclei.

Enrico Gratton, an expert in fluorescence microscopy for imaging live cells from the University of California, Irvine, US, says the lab-on-chip device is 'a very clever use of microfabrication. The advantage of the method is that it only requires a normal wide field microscope and the chip,' he adds.

Bancaud suggests that in future the technology might be useful for observing processes in cells from different biological systems where fast tracking is necessary. He adds that it might be tempting to try adding temperature sensors or actuators to this type of device, to further control the cell environment.

Fay Nolan-Neylan

Reference
H Hajjoul *et al*, *Lab Chip*, 2009, DOI: 10.1039/b909016a

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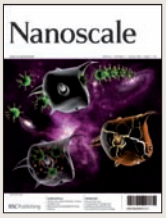
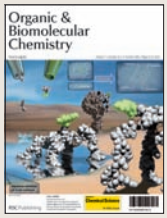




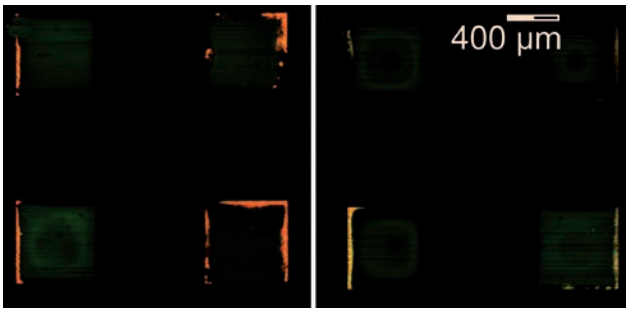
Research highlights

Combined technologies distinguish cells differing by one DNA base mutation

Screening genes from clones – fast

A high throughput genetic screening method developed by Swedish scientists could eventually lead to personalised medical treatment for genetic diseases, they claim. The method takes single cells and grows them in colonies before analysing their DNA.

The Swedish team, led by Helene Andersson-Svahn at the Royal Institute of Technology, Stockholm, combined several established technologies into an integrated system. Clones are grown in parallel from single cells held in microscale wells within a chip. The cells are then broken open to release their DNA and a polymerase chain reaction (PCR) is used to multiply the amount of DNA. This double stranded DNA is then captured onto magnetic beads and denatured to form single stranded DNA. Finally, a reporter molecule that fluoresces when it binds a particular DNA sequence is added, allowing mutations or differences between samples to be spotted. The researchers were able to use the system to distinguish cells from two human cell lines differing by one base mutation in their DNA.



Fluorescent reporters spot the difference between the DNA of two cell lines in microwells

The integrated system means that all the steps can be carried out on the one chip – for example, a magnetic field can be applied to keep the magnetic beads and DNA in the wells while the surrounding medium is changed. The result is the 'first study that links clonal expansion with PCR and genetic sequencing in one system,' says Andersson-Svahn.

Ulf Landegren, an expert in molecular medicine at Uppsala University, Sweden, explains why analysing cell colonies derived from a single cell is important. 'It is becoming increasingly clear that analyses of cells in bulk may miss important factors like the division of labour among cells in a tissue and variation among cells according to state of development, cell cycle phase and influence by external factors,' he says. This is behind the 'rapidly increasing interest in single cell analyses to study the molecular properties of individual cells,' he adds.

Andersson-Svahn says that the ultimate aim of developing the technology is to allow fast, high throughput and low cost genetic screening. Such screening would be an important step for developing personalised treatment for genetic diseases and some types of cancer, she adds.

Russell Johnson

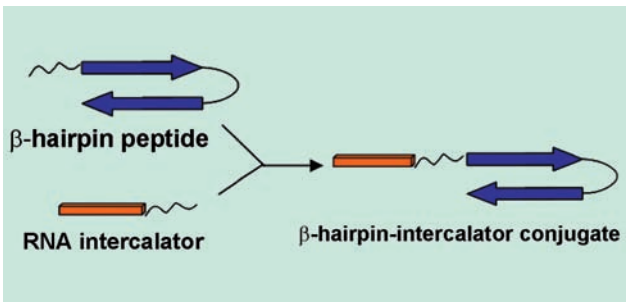
Reference
S Lindström *et al*, *Lab Chip*, 2009, DOI: 10.1039/b912596e

Linking ligands gives RNA binder far better than the sum of its parts

Two-pronged approach to RNA binding

The prospect of using RNA as a drug target is of great interest to scientists, but due to its complex structure, designing ligands that bind to it is challenging. Scientists from the University of North Carolina at Chapel Hill, US, have overcome these difficulties by combining two weak ligands to make an RNA-binding conjugate that is far better than the sum of its parts.

'Although cooperative binding has been explored in the past,' says Marcey Waters, who carried out the research with Lauren Cline, 'our system is the first example of coupling a sequence-selective threading intercalator with a β-hairpin peptide that is known to selectively bind unpaired bases.' The result is a system that simultaneously targets both the single- and double-stranded regions of RNA. While the intercalator threads between two G–C base pairs adjacent to bulges in the RNA, the peptide targets exposed bases in the RNA's single-stranded loops and bulges, resulting in binding that is at least 30 times more favourable than for either unit alone.



Combining two RNA-binding ligands gives a conjugate that binds both single and double stranded regions of RNA

Yitzhak Tor, who investigates RNA–small molecule interactions at the University of California, San Diego, US, says that Waters' results are an important step forward. 'Increasing the affinity and selectivity of designer ligands to RNA is challenging and this work elegantly demonstrates the advantage of combining two distinct recognition modes.' He suggests that similar combined ligand systems could ultimately be useful if they are applied to RNA sequences that are validated as therapeutic targets.

Waters agrees that targeting medicinally relevant RNA structures is an important future goal in this area. 'The ability to develop high affinity, high selectivity ligands would open up RNA as a feasible drug target for the treatment of many types of disease, such as HIV,' she says.

Bailey Fallon

Reference
L L Cline and M L Waters, *Org. Biomol. Chem.*, 2009, DOI: 10.1039/b913024a

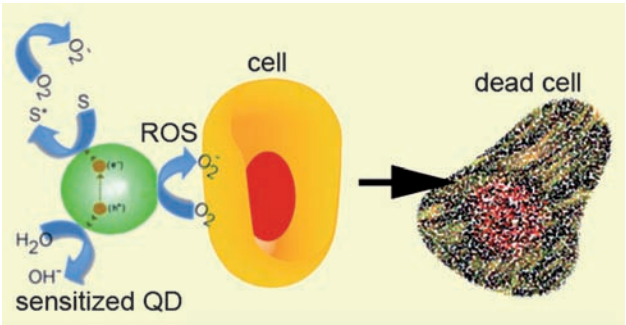
Singlet oxygen release suggests cancer therapy use for dopamine-bound particles

Topical treatment for quantum dots?

Resolving questions surrounding nanoparticle toxicity has led North American researchers to suggest the particles as a potential skin cancer treatment.

Jay Nadeau from McGill University, Montreal, and colleagues in the US and Canada are investigating using semiconductor nanoparticles, called quantum dots, as photosensitisers – compounds that release reactive oxygen species, such as singlet oxygen, when exposed to light. Photosensitisers can be used in photodynamic therapy, which applies the reactive oxygen species to kill cancer cells. Nadeau's team has measured the reactive oxygen species produced by quantum dots and observed their subsequent effects on cells using a series of assays.

Currently there is a lot of controversy whether quantum dots do produce reactive oxygen species, and if so which ones. Nadeau says she believes her team has finally been able to resolve the issue by standardising experiments. 'Figuring out which assays are best to use will allow you to screen compounds in a way that is valid, so will allow different groups to at least coordinate their results,' she says.



Dopamine-conjugated quantum dots release cytotoxic reactive oxygen species when treated with UV-to-blue light

Reference
D R Cooper, N M Dimitrijevic and J L Nadeau, *Nanoscale*, 2009, DOI: 10.1039/b9nr00130a

According to Nadeau 'some nanoparticles don't make singlet oxygen but they do when they are connected to small molecules like [the neurotransmitter] dopamine. That opens up a whole other avenue for investigation,' she says. Her team also found that the dopamine-conjugated quantum dots can be used to kill mammalian cells but only on irradiation with UV-to-blue light. This means the quantum dots are unlikely to be toxic in the body, where the light cannot penetrate, but could have an effect on skin, the researchers claim. They suggest that similar conjugated nanoparticles could potentially be used in photodynamic therapy for skin cancer treatment.

Juan Mareque-Rivas, an expert in fluorescent nanoparticles, from the University of Edinburgh, UK, says 'this is a long overdue investigation. It is nice to see a study in which generation of different reactive oxygen species is demonstrated, quantified and rationalised, and linked to interactions with dopamine – it warns that biomolecules can enhance the phototoxicity of quantum dots.'

Nadeau's team next plans to move the project into an in vivo melanoma model, to see if dopamine-conjugated quantum dots collect in tumours. Further plans include using quantum dots to develop a cream for healing surgical wounds. *Jennifer Newton*

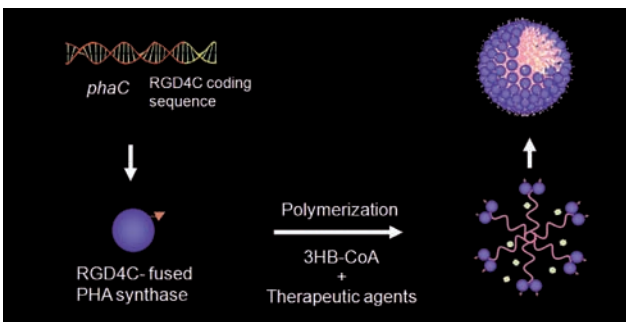
Protein–polymer species forms nanocarriers that recognise breast cancer cells

A biological approach to drug delivery

An all-in-one approach to prepare tumour-targeting polymer spheres has been developed in Korea.

Polymeric micelles made from protein–polymer hybrid materials are promising for drug delivery as the hollow spheres can surround and protect the therapeutic compounds until they reach their target. Typically, the micelles are self-assembled in solution, but they need to then be functionalised with specific ligands to improve their delivery efficiency, making the process lengthy and complicated.

Now, Young-Rok Kim and co-workers from Kyung Hee University, Yongin, have developed a single-step procedure to make nanocarriers that target cancer cells. They achieved this by exploiting a key feature of the enzyme PHA synthase, which catalyses polyhydroxyalkanoate (PHA) biosynthesis. 'PHA synthesised by PHA synthase remains covalently attached to the enzyme,' explains Kim. 'I thought that this could be an excellent way of synthesising a protein–polymer hybrid.' The group modified PHA synthase with an amino acid sequence that targets tumours by recognising integrin, a cancer-specific marker. They found that the resulting micelles bound effectively to breast cancer cells.



A modified polymer-synthesising enzyme forms micelles with its PHA product

Reference
H-N Kim *et al*, *Chem. Commun.*, 2009, DOI: 10.1039/b912871a

Vladimir Torchilin, director of the Center for Pharmaceutical Biotechnology and Nanomedicine at Northeastern University, Boston, US, says Kim's method 'is an interesting idea.' However, he warns that 'the problems with more traditional approaches are not that serious,' so the approach may not supplant current methods.

Kim agrees that traditional approaches might be better for functionalising nanocarriers with relatively simple ligands, but adds that 'our approach is suitable for introducing more elaborate functionalities to the nanocarrier, which is hard to achieve with current methods. I believe this will provide much more freedom in designing new macromolecular architectures with precise biological functionality.' *Bailey Fallon*

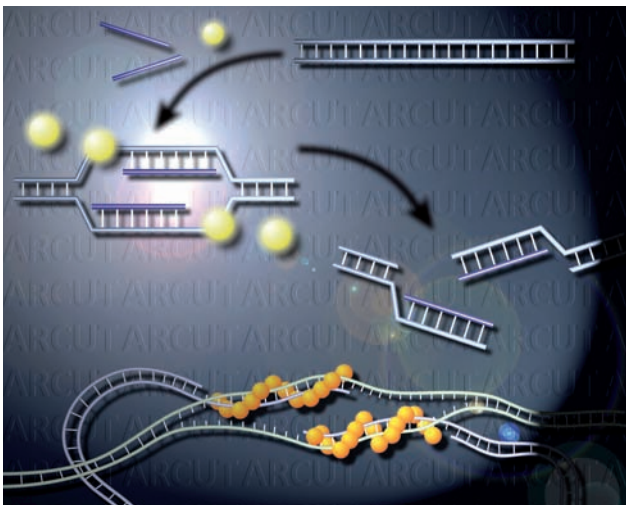
DNA scissors cut human genomic DNA at one target site

Cutting and pasting with the human genome

A DNA cutting tool that can manipulate human genomic DNA could ultimately find applications in gene therapy, say Japanese scientists.

Makoto Komiyama, Narumi Shigi and colleagues at the University of Tokyo recently made the DNA cutter – ARCUT – and used it to cut bacterial DNA at one target site. Now they have shown that it can be tuned to cut human genomic DNA selectively and also to repair it.

ARCUT consists of a cerium(IV) complex which cuts the DNA and a recognition system of peptide nucleic acids, which resemble natural nucleic acids but with a peptide rather than a sugar backbone. The cutter's target site is predetermined by base pairing between the DNA being cut and the bases in the cutter, which can be easily designed to bind a specific scission site. This is currently not possible with naturally occurring DNA cutting enzymes, which cut the genome repeatedly every 44 or 46 base pairs (approximately 700 000 times in human DNA). ARCUT's selectivity meant that the Tokyo team was able to use the cutter to target one site in human genomic DNA – a system 1000 times larger than the *Escherichia coli* DNA they tested previously.



ARCUT cleaves DNA at a target site allowing further manipulation such as in DNA repair

The researchers have also shown that ARCUT can promote homologous recombination, a process in which nucleic acid fragments are exchanged between lengths of DNA. Whilst several technologies already exist that do this by introducing double strand breaks in DNA, their design and preparation is often difficult and slow. This is because they use protein based nucleic acid cleaving enzymes which recognise the DNA target site through complex protein–DNA interactions. 'We have been working on chemistry based artificial cutting enzymes believing that they could be the solution to these problems,' says Komiyama.

Peter Nielsen works with peptide nucleic acids at the University of Copenhagen, Denmark, and is an expert in DNA recognition and gene targeting. He comments that, although further work is needed to test ARCUT in vivo, it is an exciting breakthrough. 'The DNA cleavage system is very interesting, being a truly chemical system with good efficiency,' he says. 'It is also interesting in connection with regimes for gene repair.'

Indeed, the team has already used ARCUT to repair damaged DNA in human cells. The next step for the group is to apply the system in vivo so that it can be used for gene therapy and preliminary experiments have been encouraging. Komiyama's team has demonstrated that blue fluorescent protein incorporated into the human genome can be converted to its green analogue using ARCUT-promoted homologous recombination.

Philippa Ross

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Lars J C Jeuken, *Nat. Prod. Rep.*, 2009, **26**, 1234 (DOI: 10.1039/b903252e)

Read more at www.rsc.org/highlightschembiol

Interview

Evolving evolution

Frances Arnold is using evolution to improve on nature's designs. Joanne Thomson investigates

Frances Arnold

Frances Arnold is the Dick and Barbara Dickinson professor of chemical engineering and biochemistry at California Institute of Technology, Pasadena, US. Her work focuses on elucidating the principles of biological design using laboratory evolution experiments.

What inspired you to become a scientist?
I wasn't sure I wanted to become a scientist until I actually became one. I was always good at math and science and that was the easiest way for me to get into Princeton University (US). I did mechanical and aerospace engineering, which had the fewest requirements, but I always thought I'd be a diplomat or perhaps the CEO of a corporation. I had no thought that I'd become a scientist, because I was far more interested in economics and languages. But after college I started working as an engineer in Brazil and at the Solar Energy Research Institute in Colorado (under President Carter, who believed that alternative energy research was important) and found that I enjoyed it. It wasn't until I went to graduate school to get a PhD in chemical engineering, however, that I realised how much I loved biochemistry and that I could have a marvelous career in research.

Darwin's view of evolution describes mutation and natural selection over millions of years. How can you study evolution in the lab in such reduced timeframes?
What we do is not exactly like natural evolution – it's actually artificial selection. Even Darwin (see portrait below) recognised that under strong selection pressure, such as what you impose during plant and animal breeding, large phenotypic changes can manifest themselves very quickly, in just a few generations. I do the same thing, but with molecules, and call it directed evolution. We mutate or recombine genes to create genetic diversity and clone the altered genes into plasmids for expression in a host organism. We screen the mutants for properties of interest, isolate the improved genes, and repeat the cycle until we have bred the molecule(s) we want.

What are you working on at the moment?
I'm interested in engineering new enzymes for bioenergy and 'green' chemistry. Nature is a very good chemist, but there is still room for improvement. For example, cellulases are the enzymes that degrade cellulose into sugars. Cellulose is a very abundant source of sugar but it is really difficult and costly to extract the sugar from it for renewable fuels or chemicals. We need much better enzymes than the ones we find in nature, and I have some ideas for creating those in the laboratory.

I'm also interested in what laboratory evolutionary experiments tell us about how natural evolution might have occurred, how things evolved in the natural world.

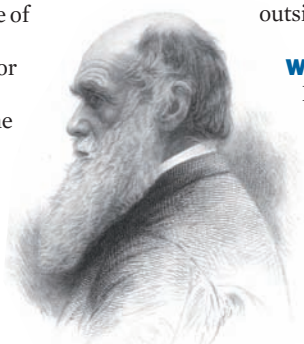
You construct synthetic enzymes. If you could make a synthetic human, what new or improved feature would you try to engineer and why?
Great wisdom, for obvious reasons.

What is your greatest achievement so far?
I think that this must be helping to educate the brilliant students and postdocs who come to the California Institute of Technology. I've been there for 24 years and I've had the pleasure of interacting with well over 100 of some of the smartest young scientists and engineers in the world. If I can help inspire them to use their remarkable brains to solve important problems, and enjoy the process, I feel I have done something really useful.

How has the global recession affected science?
Personally, I have not really suffered. I've never had much trouble getting funding. But I do see that the recession has limited the job market for graduates. The opportunities for young people are fewer now, in industry as well as in academic research. I hope that does not dampen their enthusiasm for tackling the most important problems.

You travel the world attending conferences. Which destination is your favourite?
I love the whole world – I can't choose a favourite. Five years ago, I took all three of my sons around the world for a whole year. They went to school in Australia, Africa, and Wales that year. I love to go to new places, and find that almost every place has something wonderful to offer.

What do you do in your spare time?
I have three sons, whom I adore. I enjoy doing things and traveling with them. Scuba diving and yoga are great. I also have a rustic (no water, no electricity) cabin in the mountains where I go to relax or work. I am deeply concerned about climate change and renewable energy and spend considerable time outside of my research on these issues.



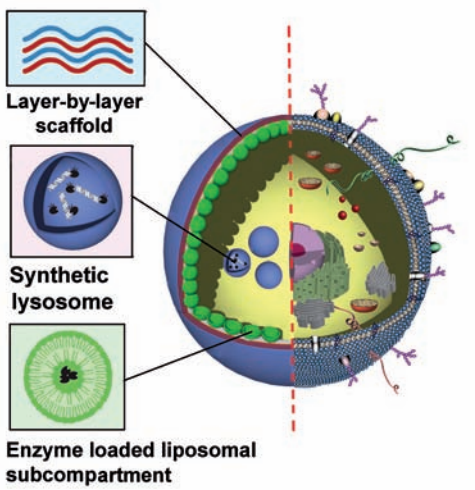
What would you be if you weren't a scientist?
I would love to be a musician and composer, but sadly don't have any real talent for it.

For which scientific discovery would you like to have been responsible?
The theory of natural selection, of course!

Instant insight

Making synthetic cells

Cell and organelle mimics typically perform one simple function. Frank Caruso and team at the University of Melbourne, Australia, contemplate more complicated systems



Synthetic mimics (left) can share many similarities with biological cells (right)

Artificial cells and organelles are expected to become powerful therapeutic tools to perform missing or lost cell functions – essentially to make, convert or degrade biomolecules. Amongst their potential applications, replenishing absent or malfunctioning enzymes is a valuable goal as this might provide a long-term solution for chronic diseases. But the field is still in its infancy, with the most successful examples of synthetic cells and organelles typically performing only a single, simple function.

Nevertheless, recent efforts have led to substantial improvements in the design of these synthetic microreactors. In particular, advances have been seen in more structurally stable scaffolds to house the synthetic machinery, enhance reagent and nutrient exchange between the vessels and their surrounding environment, and in introducing subcompartments within the vessels, allowing researchers to conduct multiple, spatially separated and/or continuous reactions.

The field has also been boosted significantly by the advent of polymer capsules assembled by layer-by-layer techniques. In this procedure interacting polymers are deposited sequentially onto a sacrificial colloidal template which is eventually removed. Two prominent polymer pairs that form stable, micrometre- or smaller-sized capsules are based on poly(allylamine hydrochloride)/polystyrene sulfonate and poly(*N*-vinyl pyrrolidone)/poly(methacrylic acid). While the former capsules are not biodegradable and have potential use in creating organelles with extended lifetimes, the latter polymer pair is used to obtain biodegradable capsules stabilised by deconstructible disulfide linkages.

Progress in cargo loading has meant that peptides, nucleic acids and intact proteins can be trapped inside such polymer capsules, making them particularly promising candidates in the design of therapeutic artificial cells and organelles. The first examples of enzymatic reactions within the capsules have brought these vehicles one step closer towards this. The most well studied class of these reactions involves the enzyme-catalysed conversion of small molecules, as the capsules' semipermeable nature allows small substrates and products (for example ions) to diffuse in and out while the larger macromolecules are blocked.

A number of enzymes have now been successfully encapsulated, retained their activity and performed their function within capsules. We recently reported DNA degradation triggered by a nuclease within a polymer capsule, a function reminiscent of that of the cellular lysosome, an organelle containing several digestive enzymes. This was one of the first examples of a layer-by-layer assembled capsule mimicking an organelle.

A nature-inspired approach towards synthetic reactors that allow multiple, spatially separated and parallel reactions, requires that the vessels be subdivided. Specific examples include two-compartment polymer capsules, smaller lipid or polymeric vesicles embedded in larger vesicles, and smaller capsules embedded in cross-linked gel beads.

We have developed an approach to obtain polymer carrier capsules with thousands of liposomal subcompartments (see green spherical structures in figure). Termed capsosomes, these vehicles preserve the positive features from both systems – the polymer hydrogel carrier capsule provides a structurally stable scaffold, while the liposomal subcompartments trap and protect small and/or fragile biomolecules. Capsosomes can retain a model enzyme and preserve its activity for at least two weeks.

The progress in the design of layer-by-layer-derived polymer capsules, including the choice of building blocks to obtain stable capsules, the creation of subdivided systems, and the successful encapsulation of enzyme-catalysed reactions, illustrate the potential of these vehicles as synthetic cell and organelle mimics. While many challenges still need to be addressed, including creating systems that can self-replicate, self-repair, and recognise a target, the field is undoubtably on the verge of creating medically relevant examples.

Read more in the Minireview 'Polymer hydrogel capsules: en route toward synthetic cellular systems' in issue 1, 2009, of Nanoscale.

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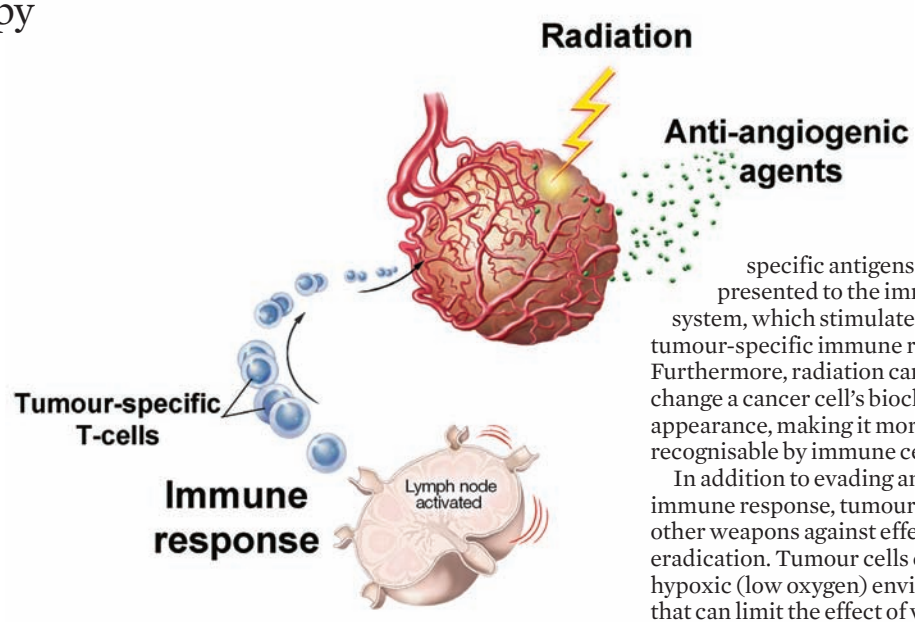
Instant insight

Triple therapy to target tumours

Drs Bernstein, Kamrava, Camphausen and Hodge at the National Institutes of Health, Bethesda, Maryland, US, explain why good things come in threes when it comes to cancer therapy



Combining radiation therapy, immunotherapy, and antiangiogenesis exploits weaknesses in cancer cell defences

Using several concurrent approaches to treat a single disease is not a novel concept anymore. When treating some of the most common illnesses affecting people today, the best outcomes are often achieved with more than one therapy or medication, especially when those therapies have different mechanisms of action.

For instance, treatment for hypertension frequently starts with a diuretic to decrease the fluid volume in the blood stream, and so lower the arterial pressure. If blood pressure remains uncontrolled, a beta-blocker may be added to the regimen. This lowers the blood's force as it is pumped through the vessels. Along with this, an angiotensin-converting enzyme (ACE) inhibitor may be prescribed to dilate the arteries. Similarly, controlling hyperglycemia in diabetic patients often requires combining one medication to stimulate the pancreas to release more insulin with another medication to prevent the liver from releasing stored sugar. This approach of targeting different aspects of a disease with different drugs often succeeds because the actions of one agent complement, or even enhance, the actions of the second or third.

This approach is now being applied in the challenging field of cancer treatment. Because some single therapies have shown limited clinical benefit, oncologists are increasingly using combination therapies to try to improve outcomes for cancer sufferers. For example, many patients first have their tumours removed surgically, then go on to receive postoperative chemotherapy, radiation therapy, or a combination of both. Unfortunately, while this and other advances in cancer treatment have shown promising results, malignancy has remained the second most common cause of death for decades, making cancer research one of the most dynamic fields in medicine.

In one potential approach, three different treatments – radiation therapy, immunotherapy (harnessing the immune system), and antiangiogenesis (reorganising the tumour's blood supply) – could be applied to treat cancer. The rationale is the same as for the combinatorial approach to treating hypertension and diabetes. Each of these three cancer therapies affects a different aspect of a tumour's biology and microenvironment, which could facilitate and enhance the actions of the other two.

Cancer cells can grow and replicate stealthily, without setting off the usual alarms that activate the host's immune system. Besides its traditional role of directly killing tumour cells, radiation can also be used to sound these alarms and activate an immune response. Exposing a tumour to radiation can break the silent barrier and cause the tumour to release unique proteins. A rich supply of tumour-specific antigens is then presented to the immune system, which stimulates a tumour-specific immune response. Furthermore, radiation can change a cancer cell's biochemical appearance, making it more readily recognisable by immune cells.

In addition to evading an immune response, tumours have other weapons against effective eradication. Tumour cells create a hypoxic (low oxygen) environment that can limit the effect of various therapies. This has spurred research into angiogenesis inhibitors, which normalise blood vessels in the tumour and limit hypoxia. By increasing oxygen availability and blood supply, antiangiogenic agents can both enhance the effects of radiation therapy and facilitate immune cells' access to the tumour.

Preclinical and clinical studies support the rationale for combining antiangiogenic agents with radiation and immunotherapy in cancer treatment. This particular combination of therapies not only exploits weaknesses in cancer cell defences, but also boosts the strengths of the individual methods. We are just beginning to recognise the potential benefits of this combination, but the evidence suggests that it provides a reasonable option for cancer patients and deserves further investigation.

Read more in the review 'Combining radiation, immunotherapy, and antiangiogenesis agents in the management of cancer: the Three Musketeers or just another quixotic combination?' in Molecular BioSystems.

Reference
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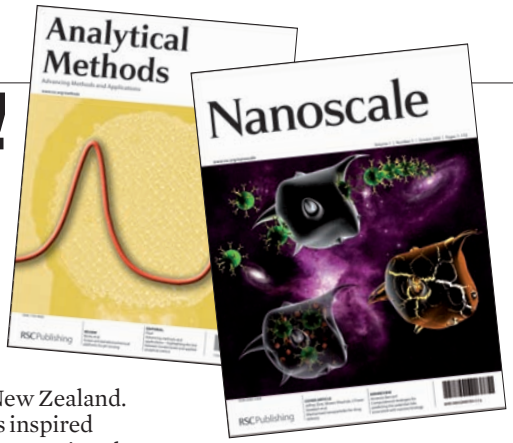
Essential elements



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Packed with the highest quality, high-impact research, that readers can expect in *Analytical Methods*, issue 1 includes a paper on Raman spectroscopic prediction of the solid fat content of anhydrous milk fat by Keith Gordon and colleagues from the University of Otago, Dunedin, New Zealand. The cover image is inspired by an article on screen printed electrochemical platforms for pH sensing by Craig Banks and colleagues of Manchester Metropolitan University, UK.

Nanoscale (www.rsc.org/nanoscale), published in collaboration with the National Center for Nanoscience and Technology, Beijing, China, showcases important and high quality nano-research, providing a forum that will be essential reading for all scientific communities working at the nanoscale.

The 20 articles in issue 1 cover a broad spectrum of exciting work from some of the very best research groups in the field, including those of Fraser Stoddart, C N R Rao, Markus Antonietti, Kazunari Domen, Luis Liz-Marzán and Naomi Halas.

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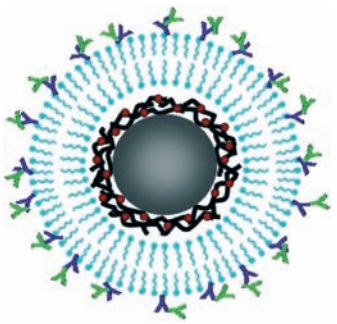

One of the Top 5 – a bioinspired colloidal system

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