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Chemical Society Reviews

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Cover

Developmental stages during the first 24 hours of zebrafish embryogenesis and the chemical structures of three molecules used to perturb or observe patterning mechanisms (from left: tetracycline, cycloamine, and Fura-2).

Image reproduced by permission of Ilya A. Shestopalov and James K. Chen from *Chem. Soc. Rev.*, 2008, **37**, 1294.



Inside Cover

See R. Chowdhury, A. Hardy and C. J. Schofield, page 1308.

A representation of the interaction between HIF-1 α and pVHL; a key point in the regulation of the hypoxic response in metazoans. Image reproduced by permission of Rasheduzzaman Chowdhury, Adam Hardy and Christopher J. Schofield from *Chem. Soc. Rev.*, 2008, **37**, 1308.

CHEMICAL BIOLOGY

B49

Drawing together research highlights and news from all RSC publications, *Chemical Biology* provides a 'snapshot' of the latest developments in chemical biology, showcasing newsworthy articles and significant scientific advances.

Chemical Biology

July 2008/Volume 3/Issue 7

www.rsc.org/chembiology

EDITORIAL

1293

Editorial: the chemistry–biology interface

David Spring

Guest editor David Spring introduces the reviews in this thematic issue of *Chemical Society Reviews* on the chemistry–biology interface.



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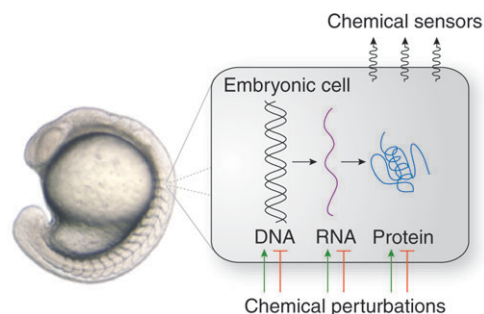
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1294

Chemical technologies for probing embryonic development

Ilya A. Shestopalov and James K. Chen*

From cyclopic sheep to fish without tails, chemical technologies have provided key insights into the mechanisms of embryonic development.

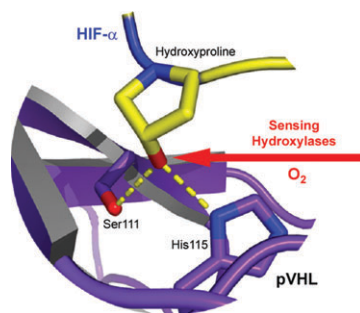


1308

The human oxygen sensing machinery and its manipulation

Rasheduzzaman Chowdhury, Adam Hardy and Christopher J. Schofield*

The metazoan response to hypoxia is mediated *via* hypoxia inducible factor (HIF), the activity of which is regulated by hydroxylation catalysed by 2-oxoglutarate dependent oxygenases that act as oxygen sensors.

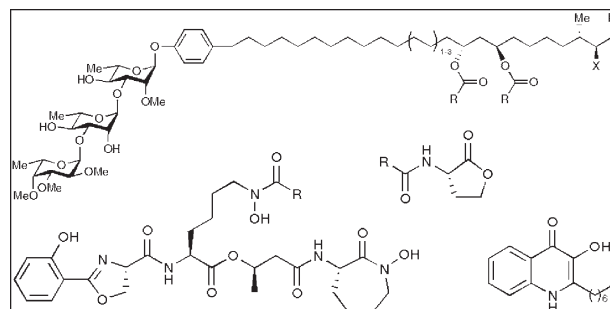


1320

Small molecule inhibition of microbial natural product biosynthesis—an emerging antibiotic strategy

Justin S. Cisar and Derek S. Tan*

Many natural products modulate critical processes in microorganisms and inhibition of the corresponding biosynthetic pathways is a promising new antibiotic strategy.

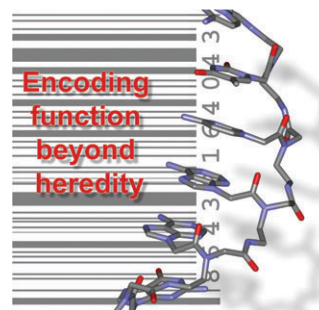


1330

Nucleic acid encoding to program self-assembly in chemical biology

Zbigniew L. Pianowski and Nicolas Winssinger*

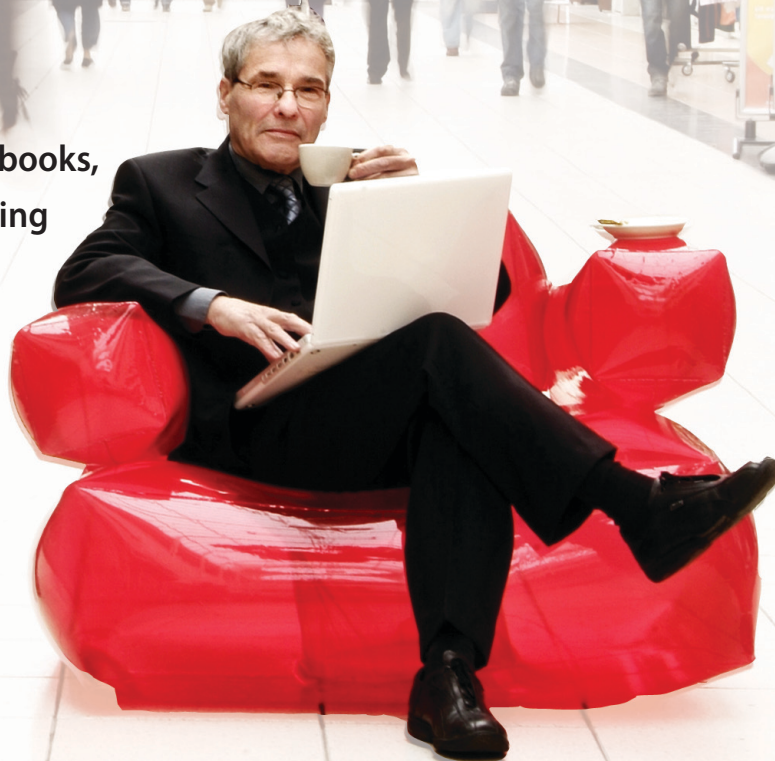
The capacity of natural or unnatural oligonucleotides to program assemblies has important applications in chemical biology which are highlighted starting with the use of nucleic acid tags to program self-assembled microarrays of small and macromolecules, followed by the use of nucleic acid templated reactions for the purpose of DNA or RNA sensing and finally, the use of nucleic acid templates to display ligands.



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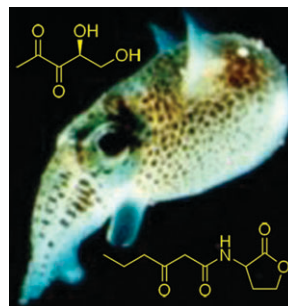
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1337

Interspecies and interkingdom communication mediated by bacterial quorum sensing

Colin A. Lowery, Tobin J. Dickerson* and Kim D. Janda*

Quorum sensing provides for the brilliant symbiosis between the squid *Euprymna scolopes* and the bacteria *Vibrio fischeri*.

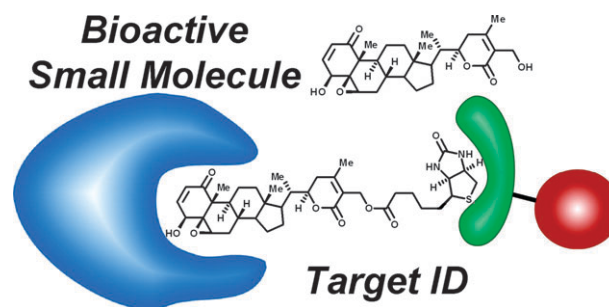


1347

Identification of the cellular targets of bioactive small organic molecules using affinity reagents

Benjamin J. Leslie and Paul J. Hergenrother*

This review surveys techniques employed to discover, from complex proteomic mixtures, the molecular targets of bioactive small molecules.

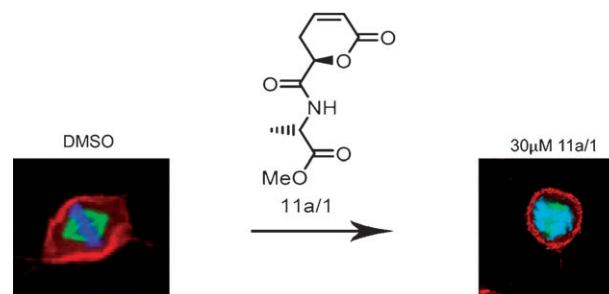


1361

Chemical biology—identification of small molecule modulators of cellular activity by natural product inspired synthesis

Katja Hübel, Torben Leßmann and Herbert Waldmann*

An overview is given on the concept, synthesis and application of natural product-inspired compound collections as an important field in chemical biology.

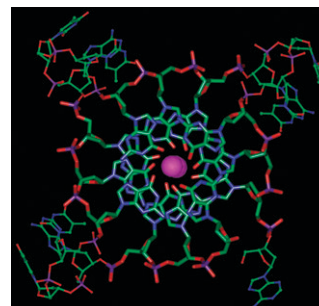


1375

Four-stranded nucleic acids: structure, function and targeting of G-quadruplexes

Julian Leon Huppert

Four-stranded G-quadruplex nucleic acids form interesting structures and play a wide variety of physiological roles.



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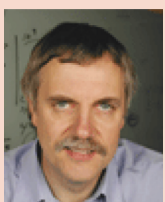
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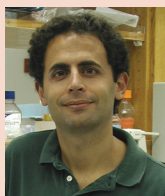
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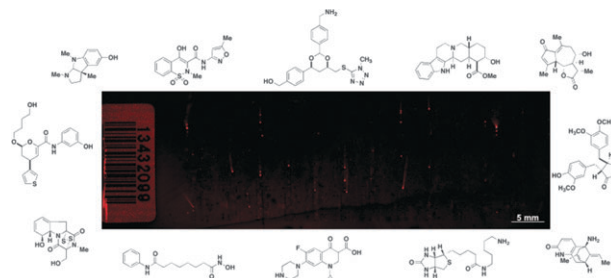
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1385

Small-molecule microarrays as tools in ligand discovery

Arturo J. Vegas, Jason H. Fuller and Angela N. Koehler*

Small-molecule microarrays are general screening tools that may be used to identify ligands for proteins without defined structure or function.

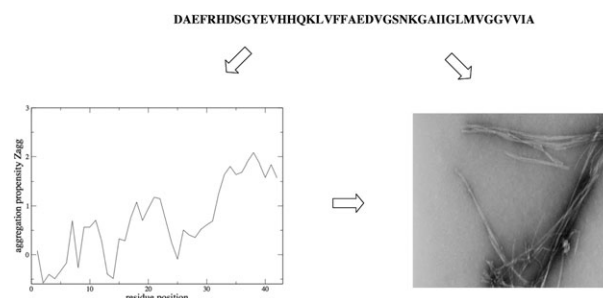


1395

The Zyggregator method for predicting protein aggregation propensities

Gian Gaetano Tartaglia and Michele Vendruscolo*

Protein sequences hold the information to form amyloid fibrils—the code is unravelling.

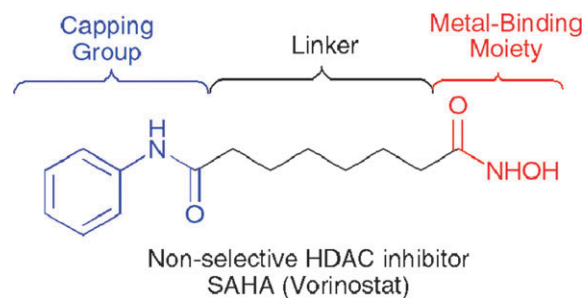


1402

Isoform-selective histone deacetylase inhibitors

Anton V. Bieliauskas and Mary Kay H. Pflum*

Efforts to create selective HDAC inhibitors have seen increased attention over the past several years, leading to class-selective and some isoform-selective inhibitors.

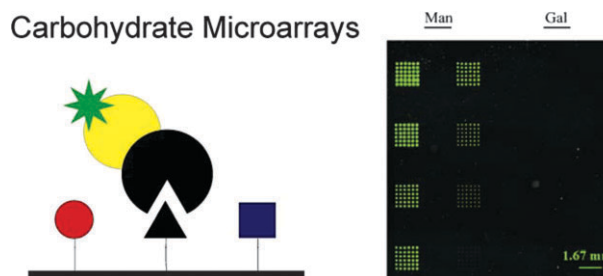


1414

Carbohydrate arrays as tools for research and diagnostics

Tim Horlacher and Peter H. Seeberger*

Carbohydrate microarrays—a detailed overview ranging from the fabrication of the arrays, the conduct of the experiments to selected applications.



Dynamic Stereochemistry of Chiral Compounds

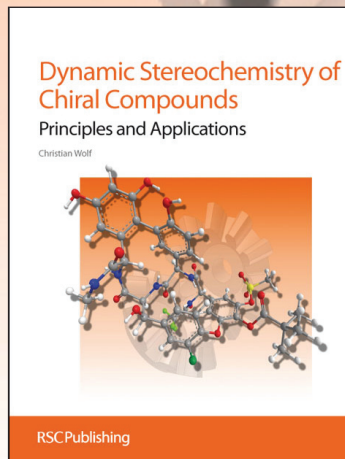
This book provides an overview of fundamental concepts of asymmetric synthesis highlighting the significance of stereochemical and stereodynamic reaction control. Topics include kinetic resolution (KR), dynamic kinetic resolution (DKR), dynamic kinetic asymmetric transformation (DYKAT), and dynamic thermodynamic resolution (DTR). In-depth discussions of asymmetric synthesis with chiral organolithium compounds, atropisomeric biaryl synthesis, self-regeneration of stereogenicity (SRS), chiral amplification with chiral relays and other commonly used strategies are also provided. Particular emphasis is given to selective introduction, interconversion and translocation of central, axial, planar, and helical chirality.

A systematic coverage of stereochemical principles and stereodynamic properties of chiral compounds guides the reader through the book and establishes a conceptual linkage to asymmetric synthesis, interconversion of stereoisomers, molecular devices that resemble the structure and stereomutations of propellers, bevel gears, switches and motors, and topologically chiral assemblies such as catenanes and rotaxanes. Racemization and diastereomerization reactions of numerous chiral compounds are discussed as well as the principles, scope and compatibility of commonly used analytical techniques.

- More than 550 figures, schemes and tables illustrating mechanisms of numerous asymmetric reactions and stereomutations of chiral compounds
- Technical drawings illustrating the conceptual linkage between macroscopic devices such as turnstiles, ratchets, brakes, bevel gears, propellers or knots and molecular analogs
- More than 3000 references to encourage further reading and facilitate additional literature research
- A comprehensive glossary with stereochemical definitions and terms which facilitate understanding and reinforce learning

This book will be of particular interest to advanced undergraduates, graduates and professionals working and researching in the fields of synthetic organic chemistry and stereochemistry.

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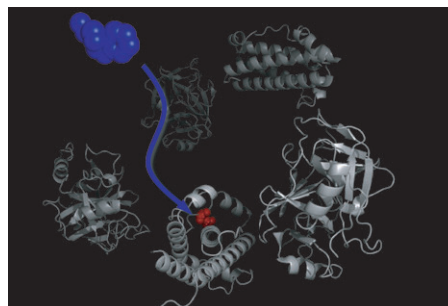
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1423

Chemoselective modification of proteins: hitting the target

Isaac S. Carrico*

Chemistry driven strategies that allow the precise tailoring of polypeptides both *in vitro* and *in vivo*.



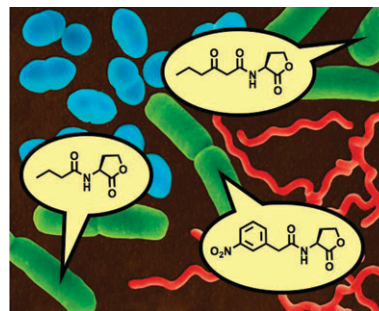
CRITICAL REVIEW

1432

Expanding dialogues: from natural autoinducers to non-natural analogues that modulate quorum sensing in Gram-negative bacteria


Grant D. Geske, Jennifer C. O'Neill and Helen E. Blackwell*

Look who's talking—bacteria use a chemical language for cell–cell communication (*i.e.*, quorum sensing) that is only now being translated.



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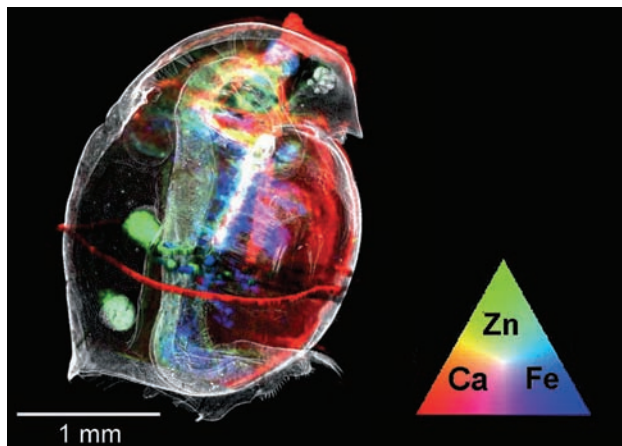
Chemical Biology

Combined imaging techniques allow fleas to show their metal 3D biological metal detection

The water flea is the testbed for a non-destructive 3D imaging method that pinpoints metals in vivo. Laszlo Vincze, from Ghent University, Belgium, and his colleagues in Belgium, Hungary and Germany have combined x-ray techniques to allow them to detect metal ions and their locations in biological samples – including living systems.

The study of trace metals within organisms – metallomics – is a rapidly expanding research area as metals play many vital roles in biological systems. Yet most of the techniques currently used in the field are destructive and give no clues about metal distribution.

Vincze had already used one such technique, mass spectrometry, to study metal uptake by water fleas and the relative contributions from different exposure routes, such as water or diet. But the total decomposition of the flea required to prepare the samples for this experiment meant that it was impossible to distinguish local metal



accumulation in the different tissues. Instead, by combining synchrotron radiation x-ray fluorescence and laboratory x-ray absorption microtomography, Vincze's team unravelled the metal distributions in the fleas without invasive sample preparation techniques.

Vincze explains the techniques' advantages: 'A sample can be

Elementary: x-ray techniques reveal the metal distribution in a water flea

Reference
B De Samber *et al*, *J. Anal. At. Spectrom.*, 2008, **23**, 829
(DOI: 10.1039/b800343m)

investigated in three dimensions in an essentially non-destructive manner, leaving most – if not all – other analytical techniques behind. Owing to recent advances in x-ray science, imaging of transition metal distributions with micrometre to nanometre spatial resolution and with parts per billion sensitivity is becoming possible.'

Vincze warns that although the techniques are not immediately destructive, there are other issues to consider. 'With biological imaging, the problem of radiation damage is one of the most challenging aspects of future scanning x-ray fluorescence measurements,' he says. Nevertheless, he adds that he can imagine the combined techniques being used in a wide variety of disciplines. 'We expect to see a rapid evolution towards in situ elemental imaging on the nanoscopic scale in areas including earth and environmental science, material science, archaeology and functional biology,' he says. *Edward Morgan*

In this issue

Genetic code does the twist

Computational model reveals how DNA and RNA fold into hairpins

Synthetic chaperones lead to protein reform

Nature provides inspiration for nanoparticle protein folders

Sugar rush

Interview: Peter Seeberger talks about rapid carbohydrate synthesis and the fight against malaria

Chemical developments

This month's Instant insight looks at how chemistry can be used to probe the earliest processes of life



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Research highlights

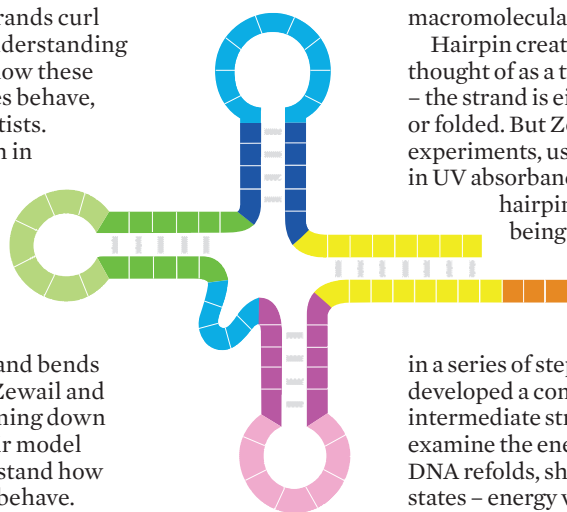
Computational model reveals how DNA and RNA fold into hairpins

Genetic code does the twist

Revealing how DNA strands curl up is the first step to understanding how structure affects how these big biological molecules behave, says a team of US scientists.

The group, at Caltech in Pasadena, has developed a computational model to discover how DNA and RNA strands fold into hairpins – loops that form when the strand bends back on itself. Ahmed Zewail and colleagues say that pinning down this process shows their model could be used to understand how larger DNA molecules behave.

‘Hairpins are a very important structural feature of DNA,’ says Zewail, ‘and they are a manageable size to test our ideas on how long,



Nucleic acids can fold to form hairpin bends

macromolecular DNA strands fold.’

Hairpin creation is typically thought of as a two-state process – the strand is either unfolded or folded. But Zewail’s recent experiments, using changes in UV absorbance to follow a hairpin refolding after being subjected to a laser induced temperature jump, suggest the process occurs in a series of steps. Now Zewail has developed a computational kinetic intermediate structure model to examine the energy landscape as DNA refolds, showing intermediate states – energy valleys – as the hairpins zip up.

Zewail’s model successfully predicts that the zipping process varies depending on the structure

of the hairpin – including whether folding starts from the loop or the free ends of the hairpin. ‘We were surprised that a simple two-coordinate model gives accurate predictions,’ says Zewail. ‘We’re now using it to work on bigger systems, and the results are very promising.’

Philip Bevilacqua, who studies RNA folding at Pennsylvania State University, University Park, US, says the model will be a useful tool. ‘It corroborates data already out there and it should make useful predictions to guide future experiments. It will be well used because it’s simple to use.’

James Mitchell Crow

Reference

M M Lin *et al*, *Phys. Chem. Chem. Phys.*, 2008, DOI: 10.1039/b804675c

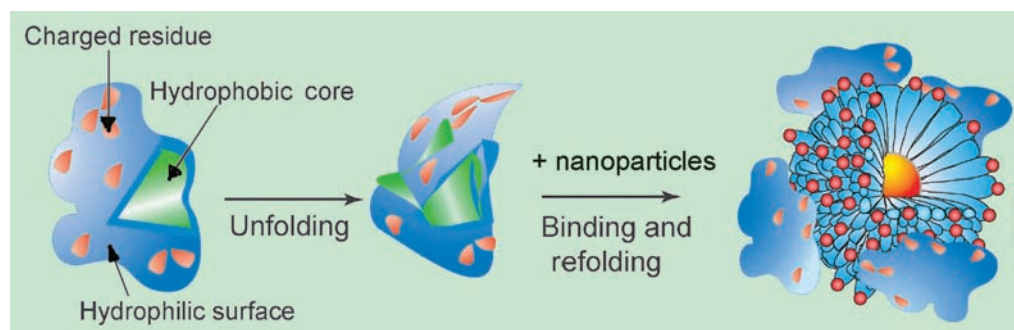
Nature provides inspiration for nanoparticle protein folders

Synthetic chaperones lead to protein reform

US chemists are going for gold to fold unravelled proteins. A team at the University of Massachusetts, Amherst, has demonstrated that anionic gold nanoparticles can be used to reorganise these biopolymers.

Vincent Rotello and Mrinmoy De took their inspiration from nature. They studied natural biological chaperones, which are proteins with surfaces tailored to unfold and refold misfolded proteins, and had the idea to use nanoparticles as their synthetic equivalent. Rotello explains: ‘Nanoparticles can be made in sizes consistent with biological chaperones and fine-tuned with a wide range of ligands.’

Rotello and De used nanoparticles supporting carboxylate ligands to fold three denatured cationic proteins, α -chymotrypsin, papain and lysozyme. The gold nanoparticles promote protein refolding through electrostatic interactions between the exposed charged residues on the unfolded protein and the oppositely charged ligands on the gold nanoparticles. The overall high



Gold nanoparticles promote refolding of an unfolded protein

negative charge of the nanoparticle–protein complex prevents the proteins from aggregating and, by drawing the charged residues on the protein to its exterior, the nanoparticle promotes refolding.

Previously, unfolded proteins have been refolded into their native form using surfactants or by changing the protein’s environment. ‘Prior approaches have generally targeted hydrophobic portions of the protein,’ says Rotello. ‘Our approach focuses on the charged residues, opening the possibility of refolding proteins intractable to other methods.’

Sam Gellman, an expert in protein folding at the University of Wisconsin, Madison, US, says the approach is ‘a very creative and potentially versatile strategy for protein refolding. The use of nanoparticles as artificial chaperones is intriguing because their surface properties can be tailored in diverse ways.’

‘It will be interesting to see whether this technique can be used to refold proteins in chemically denatured states, as is often required in biotechnology,’ Gellman adds. *Janet Crombie*

Reference

M De and V M Rotello, *Chem. Commun.*, 2008, DOI: 10.1039/b805242e

Pumpkin plants pick-up particles



US scientists have shown that plants can absorb nanoparticles from their environment – meaning that the particles could find their way into the human food chain, the team claims.

Yan Jin and colleagues at the University of Delaware, in Newark, found that pumpkin plants can take up nanoparticles through their roots and that the particles are transported around the plant. The study is part of an effort to assess nanoparticles' environmental and biological fate if they are released into soil or groundwater, says Jin.

Jin and her team grew their pumpkin plants in a medium containing magnetite – magnetic iron oxide – nanoparticles. They then used a vibrating sample magnetometer, which detects weak

Pumpkin plants can take up iron oxide particles through their roots and accumulate them in their leaves

Reference

H Zhu *et al.*, *J. Environ. Monit.*, 2008, **10**, 713 (DOI: 10.1039/b805998e)

magnetic signals, to measure the magnetite content in samples from different plant parts. Their studies showed that the plants had taken up significant amounts of particles which accumulated mainly in the roots and the leaves.

Jin points out that despite rapid developments in nanotechnology in recent years, investigations into the environmental and health impacts of nanomaterials are still in their infancy. While researchers have looked increasingly at nanoparticle toxicity to human cells, bacteria and rodents, until now very few have examined the particles' effects on ecological species such as plants. Since nanoparticles can be highly toxic 'it is imperative that we conduct more comprehensive studies to evaluate the potential risk of nanoparticle accumulation in the food chain by plant uptake of nanoparticles from soil, sediments, and water bodies,' explains Jin.

'I am very impressed,' comments Chuanyi Wang, a nanomaterials researcher at the University of Missouri, in Kansas City, US. 'The researchers give a clear picture of the particles' transportation pathway and distribution in pumpkin plants. Since human or animal tissues are generally the focus when evaluating the potential risk of nanomaterials, this work opens a new window in the field.' Sarah Dixon

Weighing up cells

How much does a cell weigh? US chemists are using miniature cantilevers to find out.

'Cell mass is directly related to cell growth and division,' says Rashid Bashir at the University of Illinois at Urbana-Champaign. In an effort to understand this relationship, Bashir and colleagues have designed a device to measure a cell's mass as it grows in fluid.

The device contains an array of cantilevers overhanging microfluidic channels. As cell suspensions flow through the channels, cells can be captured on the cantilevers using alternating electric fields. As the cells grow, their change in mass is calculated from the change in the cantilever resonance frequency.



As cells grow on cantilevers their change in mass can be monitored through a change in the cantilever resonance

The team now plans to refine the method by trapping cells on suspended pedestals. This will allow them to control cell position on the cantilevers and should improve the technique's sensitivity.

'Eventually we want to measure cell mass as a function of time,' says Bashir. He explains that directly measuring the mass of a single cell, rather than the average cell mass in a sample, ultimately could let scientists follow a single cell's mass as it progresses through the cell cycle. 'Ideally we would like to monitor one cell as it splits into two,' Bashir adds. Russell Johnson

Reference

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Cell migration study on-chip

A device designed to monitor how cells move could help scientists understand cell migration, important in processes from embryonic development to wound healing and cancer metastasis.

Jing Cheng and colleagues at Tsinghua University, Beijing, China, made the lab-on-a-chip style device which creates artificial wounds and monitors the surrounding cells as they move to heal the wound.

Whilst wound assays are the most common way to measure cell migration rates, they are often based on optical measurements which are not quantitative and can suffer from low repeatability. The new method avoids these problems and 'the device is almost fully automated,' says Cheng.

In the device, a self-assembled monolayer, made from an organic thiol, forms on a gold electrode and is surrounded by a monolayer of cells. An electrical pulse is applied to the electrode, which desorbs the thiol to create a void – an artificial wound – in the cell layer. As cells migrate into the void, their migration rate is measured by following how the cell growth affects the current in the electrode.

The Chinese team tested the device by measuring the migration rates for four different cell types. In further experiments with the antimigratory agent colchicine, the researchers demonstrated that the device can detect changes in cell migration rates caused by small molecule drugs. This suggests that it could be used in drug discovery, says Cheng.

'The cell migration assay on chip has important advantages compared to conventional methods, such as being quantitative and real time,' says Helene Andersson Svahn, an expert in nanobiotechnology at the Royal Institute of Technology, Stockholm, Sweden. 'It will be interesting to see the impact of this new technology in drug screening and cancer therapy, for example,' she adds.

Russell Johnson

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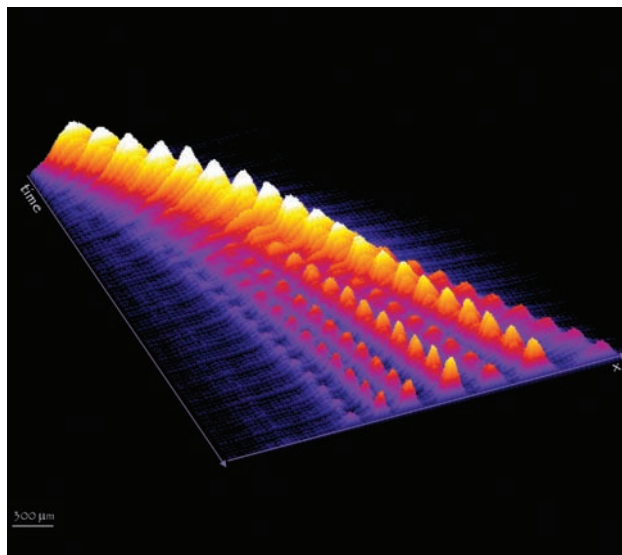
Miniature gradient sorts mixed up biomolecules

Sizing up proteins on-chip

Gels are being formed on-chip for easier and cheaper protein separation. Amy Herr, at the University of California, Berkeley, US, and colleagues designed the miniature customisable gels to sort proteins by size.

Protein mixtures are often separated on slabs of polyacrylamide gel. By applying a potential difference across the gel, the negatively-charged proteins travel through the pores in the gel towards the anode – with larger proteins having more difficulty moving through the gel pores and so taking longer to migrate. For higher resolution protein sizing, particularly in proteomics, biologists can use gels with pore-size gradients. Now Herr and co-workers have made these gradient gels reproducibly inside a chip.

The researchers used two solutions of different acrylamide concentration to create the gradient. Using a high concentration solution they fill a channel in a microfluidic device and shine light on one end to photopolymerise the acrylamide, plugging the end with a small pore-size gel. They then flush



the other end of the channel with a low concentration solution, which will form a larger pore-size gel. They allow the two solutions to diffuse into each other and a second exposure to light results in a reproducible pore-size gradient gel.

This is the first time such gels have been prepared on-chip and the team sees the method as a means to optimise chip systems for

Gradient gels allow different sized proteins to be separated, with larger proteins taking longer to migrate through the gel

biomolecule separation. 'The gels' planar geometry makes integrating them with sample processing, analysis, and collection achievable,' says Herr, 'something that is possible, but can be cumbersome, in capillary systems.'

Herr's team can separate protein mixtures using gels as short as 0.3cm and can change both the gel length and pore-size gradient to customise the separation for different mixtures. The ultra-short channel lengths also reduce the electric potential required for the separation. 'This eliminates the need for high voltage power supplies – making the system more amenable to portability and non-laboratory settings,' say the scientists.

Rustem Ismagilov, an expert on microfluidics and proteomics from the University of Chicago in the US, is impressed with the work. 'This is a good idea, and has a wide range of potential applications in proteomics,' he says.

Freya Mearns

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Sugar rush

Peter Seeberger talks to Joanne Thomson about rapid carbohydrate synthesis and the fight against malaria



Peter Seeberger

Peter Seeberger is professor of organic chemistry at the Swiss Federal Institute of Technology Zurich, Switzerland, and an affiliate professor at the Burnham Institute in La Jolla, US. He works at the interface of chemistry and biology, focusing on the rapid synthesis of complex carbohydrates and their role in biological processes. Peter is also co-founder of Ancora Pharmaceuticals Inc., which develops carbohydrate-based therapeutics.

What inspired you to become a chemist?

I wanted to do something challenging that would not only involve theory but also practice. With chemistry, you have to know something but you also have to be good with your hands and that combination seemed very attractive.

Much of your research focuses on the synthesis of oligosaccharides. What is it in particular that fascinates you about this type of molecule?

I did my PhD in biochemistry, working on both DNA and peptides. While there were good ways to make these types of molecules, carbohydrate synthesis at that time was very complicated. Since carbohydrates form such a large class of compounds and they are biologically very relevant, it seemed to me to make sense to do synthesis and chemistry on them because it would have the biggest possible biological and medical impact.

You embrace new technologies in your work, including automated oligosaccharide synthesis. How have these helped advance your research?

Instrumentation can only be a means to an end. For us, the ultimate role of automated synthesis is to make carbohydrate chemistry accessible for non-chemists, such as biologists and medical researchers. We want to get this tool into the hands of all people interested in natural products, in this case carbohydrates. For our laboratory, it is never the end of the research to make the instrumentation. The end should be to do better chemistry, to be quicker and more efficient and to do reactions that we couldn't do beforehand.

What do you think are the major challenges in carbohydrate research?

I think there are still interesting challenges at very basic levels of carbohydrate chemistry involving the creation of glycosidic linkages and protecting groups. Right now, the two major challenges in my opinion are synthesising protected building blocks for automated assembly and the sequencing of complex oligosaccharides.

You have won a number of awards throughout your career and last year you were voted amongst the top 100 Swiss. What is the secret to your success?

I think the awards are usually the result of the hard work of my co-workers. Of course, I also participate

in this work but I have a very good team around me. I have been lucky over the past 10 years to have very smart, dedicated, creative young people in my group. I think it is this team effort that has made it possible for us to do research that other people have felt worthy of awards.

You are a founding member of the Testfa-Ilf 'Hope for Africa' foundation. Could you tell me about its aims?

About five years ago, some of our research on malaria vaccines was covered on Swiss and German television. A group of people approached me and asked how they could fund our research because they thought creating such a vaccine could be interesting. In particular, an Ethiopian who had lived in Switzerland for the past twenty years and had lost her brother to malaria in Ethiopia was very keen to help. Since vaccine research is so immensely expensive – we are talking about \$800 million to develop a vaccine – it seemed more prudent to focus the limited funds of private people on immediate relief.

The Testfa-Ilf foundation was created to advance healthcare in Africa, in particular Ethiopia, with a focus on malaria. Our first success has been the creation of a bed-net factory. Usually Ethiopians buy the insecticide-treated bed-nets from Asia. By a relatively modest investment, we were able to create five hundred new jobs in Ethiopia and make those bed-nets available at prices that people can afford, without them relying on donations but actually making them themselves. Malaria vaccines are important but there are many other things we can do to help and that is what we created the foundation for.

Most people associate carbohydrates with the food we eat. What is your favourite food?

My favourite food is dessert so again sugars in this case!

What do you do in your spare time?

I try to spend it with my wife and daughter whenever possible. That is usually the only spare time I have right now.

If you weren't a scientist, what would you be?

I would be in business so I could manage my own company.

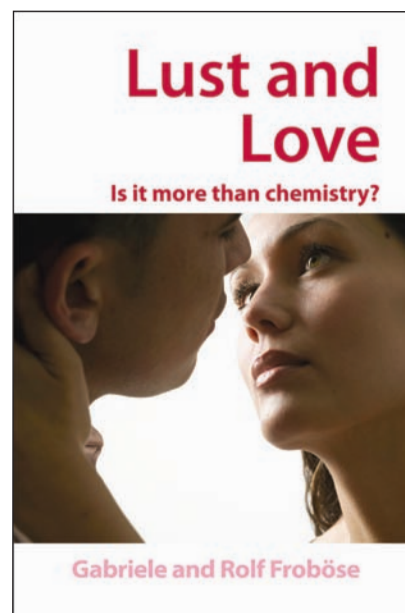
Lust and Love

Is it more than chemistry?

By Gabriele and Rolf Froböse

**Why do people fall in love? Why do we find some people attractive?
How does our physiology affect the way we feel?**

Lust and Love: Is it more than chemistry? provides answers to some of these questions through the eyes of science. Covering research from the fields of chemistry, biochemistry, neurology, psychiatry, psychology, physics and medicine the book looks at our current knowledge of the science behind these feelings.



Explores the science behind love, sex and passion

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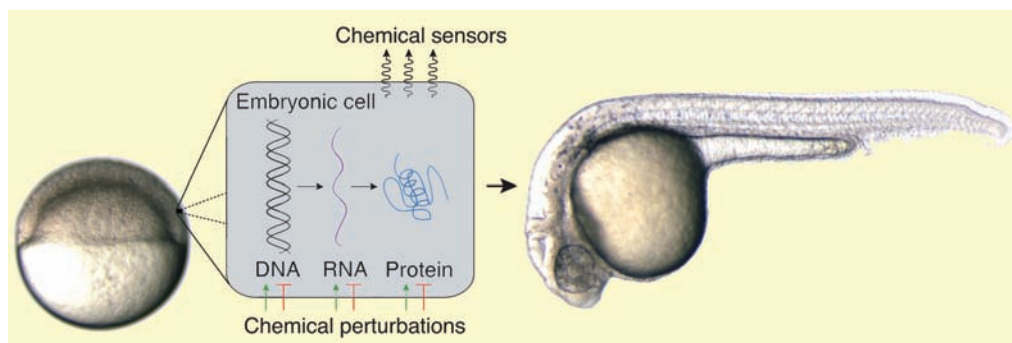
Chemical developments

Ilya Shestopalov and James Chen of Stanford University, US, look at how chemistry can be used to probe the earliest processes of life

How does the human newborn—composed of approximately one trillion cells and over 200 cell types—arise from a single, fertilised egg? Since the time of Aristotle, scientists have strived to explain this fascinating transformation, using a perturb-and-observe approach to study model organisms. These pioneering developmental biologists examined embryos from sea urchins, chickens, frogs, and other animals, using dyes to follow cell lineages and surgical procedures to study interactions between tissues. Their investigations revealed conserved embryological processes among evolutionarily diverse organisms and introduced concepts such as morphogen gradients – gradients of cell signalling molecules that influence tissue growth patterns.

Modern developmental biology has focused on deciphering the molecular mechanisms that regulate tissue patterning. For example, computational models of cell signalling networks have been used to simulate how a developing fruit fly wing orients hundreds of tiny hairs in the same direction. But while many discoveries have arisen from advances in molecular biology, transgenic organisms, and genome sequencing, chemistry has also made important contributions.

Since embryonic patterning arises from spatially and temporally controlled gene function, chemical technologies, which allow scientists to perturb-and-observe molecular events with spatiotemporal precision, have been used to target multiple steps in the process. These include DNA transcription into RNA, RNA translation into proteins, and protein function. For example, several approaches for regulating gene transcription with small molecules have been developed. Engineered transcriptional activators and repressors can be used to regulate gene expression with



Chemical technologies can be used to perturb-and-observe the molecular mechanisms that regulate embryo development

respect to time and activity level, simply by controlling the timing and dosage of small molecule administration.

The chemical regulation of RNA function has been achieved largely through artificial oligonucleotides rather than small molecules. The oligomers can target specific genes so that RNA processing, translation, or stability can be perturbed. Unlike small molecules, synthetic oligonucleotides are not membrane permeable and typically must be introduced into embryos by microinjection. Yet this 'limitation' also allows the reagents to be used to perturb gene function in selected cell populations within an embryo.

Rapid kinetic control of embryonic patterning can also be achieved with small molecules. Accordingly, several compounds that inhibit or activate developmental signalling proteins have been discovered through studies of natural teratogens and high-throughput screens of synthetic chemical libraries. The plant-derived alkaloid cyclopamine is one of the best known small molecule modulators of embryonic development, and was discovered to be the cause of an outbreak of cyclopic lambs during the 1950s. It is now used routinely in the laboratory to

block Hedgehog signalling, a key pathway in animal development, and compounds targeting other developmental pathways have also been identified.

While these and other chemical strategies have provided key insights into the molecular processes that regulate embryonic patterning, technology development for the 'observe' half of the perturb-and-observe approach is a relatively unexplored frontier. Photoactivatable markers have replaced the dyes used in the 1920s for visualising cell lineages, and synthetic sensors have enabled real-time calcium imaging during embryo development. Chemists have an opportunity to make unique and significant contributions to developmental biology that are unlikely to be fulfilled by scientists trained in other disciplines. New synthetic probes of gene expression, protein function and other biological processes would revolutionise how we interrogate fundamental questions in embryology. Thus, chemical technologies could be the key to merging the molecular discoveries of the post-genomic era with the scientific tradition of embryological observation.

Read more in Shestopalov and Chen's tutorial review in ChemSocRev issue 7, 2008 – a thematic issue examining the chemical biology interface.

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Expanding the chemical sciences

RSC Publishing is set to increase its journal portfolio from 2009 following announcement of the launch of two new RSC journals. A press release on June 12th confirmed that two interdisciplinary titles, *Integrative Biology* and *Metallomics*, will both publish their first issue in January 2009.

Integrative Biology will provide a unique venue for research that leads to a greater understanding of biological processes and mechanisms. A highly interdisciplinary journal, it will focus on quantitative multi-scale biology using enabling technologies and tools to exploit the convergence of biology with physics, chemistry, engineering, imaging and informatics. The editorial board chair for this prestigious new journal will be Mina Bissell from Lawrence Berkeley National Laboratory, US.



Metallomics will cover the research fields related to metals in biological systems and is expected to be the core publication for the emerging metallomics community. *Metallomics* is receiving great attention as a new frontier of trace elements in biology and is expected to develop as an interdisciplinary science complementary to genomics and proteomics. Joseph Caruso of the University of Cincinnati/Agilent Technologies *Metallomics* Center of the Americas and a leading player in this emerging

field, will chair the editorial board of this timely new journal.

RSC Publishing boasts an accomplished record in launching new products. With *Integrative Biology* and *Metallomics* set to follow in the footsteps of success stories like *Soft Matter* and *Molecular BioSystems*, RSC Publishing again reinforces its position as a world-class scientific publisher.

From launch, the latest issues of both *Integrative Biology* and *Metallomics* will be made freely available to all readers via the website. Free institutional access to all issues of each journal published in 2009 and 2010 will be available following a simple registration process.

Watch www.rsc.org/journals for all the latest news

Molecules of Murder

This fascinating new book by John Emsley, due for publication in August 2008, is about infamous murderers and famous victims! It includes the stories of people such as Harold Shipman, Alexander Litvinenko, Adelaide Bartlett and Georgi Markov and takes the reader on a journey of discovery into the world of poisons. Few books on poisons analyse these crimes from the viewpoint of the poison itself, and doing so throws a new light on how the murders or attempted murders were carried out and ultimately how the perpetrators were uncovered and brought to justice. *Molecules of Murder* looks at how forensic chemists have developed cunning ways to detect minute traces of dangerous substances, and why some of these poisons are now being researched as possible life-savers!

John Emsley is a great science communicator. His entertaining books have contributed to the advancement of a positive awareness of science. In 2004 John was elected as an honorary member of The Society of Chemical Industry (SCI) in recognition of a lifetime of achievement and contributions to chemistry. He has written numerous popular science books and articles.

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