

# Chemical Biology

## Antibiotics from chlorinated natural products



Understanding the enzymatic chlorination of aromatic and aliphatic biomolecules could lead to new antibiotics says a microbiologist from Ireland.  
*Alison Stoddart*

C D Murphy  
*Nat. Prod. Rep.*, 2006 (DOI: 10.1039/b516588c)

## Probes reveal cell biology



Two techniques for studying biological mechanisms within living cells have emerged as powerful tools with enormous potential: chemical genetics and RNA interference (RNAi).  
*Sophia Anderton*

U S Eggert *et al*  
*Mol. BioSyst.*, 2006, **2**, 93

## Enzyme activity made clearer



Advances in single molecule techniques could revolutionise the study of enzymes, according to researchers from the Netherlands and Belgium, and indicate that enzymes are only active in short bursts.  
*Sarah Dixon*

H Engelkamp *et al*  
*Chem. Commun.*, 2006, 935

## Understanding lignan synthesis



Researchers in the US are closer to understanding the synthesis of plant-derived compounds with antiviral and anticancer properties.  
*Michael Smith*

S G A Moinuddin *et al*  
*Org. Biomol. Chem.*, 2006, **4**, 808



See <http://www.rsc.org/Publishing/ChemicalBiology/> for full versions of these articles

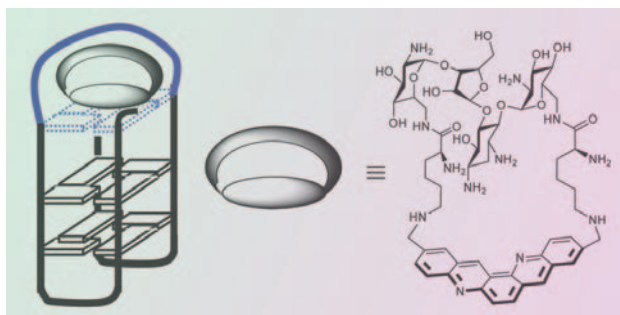
# Research highlights

Macrocycles could be next generation of anticancer agents

## Ringing the changes to combat cancer

A new class of targeted anticancer drugs could soon be developed thanks to researchers from France who have prepared cyclic macromolecules that selectively bind four-stranded DNA structures.

Quadruplex-binding molecules, like the macrocycles developed by Marie-Paul Teulade-Fichou at the Collège de France in Paris, and co-workers, combat cancer by targeting the end section of DNA called the telomere. Telomeres carry no genetic information but are essential for DNA replication. Quadruplex-binding molecules induce the telomere to fold up into a four-stranded quadruplex and the structure formed is known as G quadruplex DNA. The quadruplex structure impairs DNA replication and consequently the cells' ability



**Macrocycles selectively bind four-stranded DNA structures**

to divide, limiting the increase of cancer cells.

The macrocycles prepared consist of an aminoglycoside tethered at each end to an aromatic platform to form a ring. Teulade-Fichou combined the nucleic acid-binding properties of aminoglycosides with

the ability of aromatic molecules to insert into DNA.

The cyclic nature of the molecules causes the aminoglycoside components to be curved like a dome, which binds within the loops of the folded quadruplex DNA. The dome-like shape also results in the macrocycle having a low affinity for normal linear DNA.

Having shown that the new macrocycles can bind pre-formed quadruplexes, the next step will be to test their ability to induce quadruplexes to form from single strand DNA. The new molecules are 'attractive structural scaffolds for further developments aimed at the discovery of new and more selective anticancer agents,' said Teulade-Fichou.

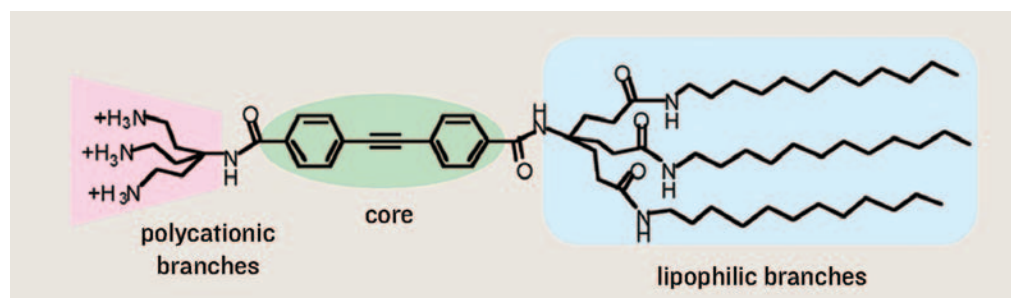
James Mitchell Crow

### Reference

M Kaiser *et al.*, *Org. Biomol. Chem.*, 2006, 4, 1039/ b516378a

Dendritic molecules show potential for cancer therapy

## Gene delivery with dendrimers



Dendritic molecules developed as gene carriers show potential for cancer therapy say scientists in Switzerland.

Gene transfection, the delivery of genetic material into a cell, is currently most efficient using viral vectors. In a step towards the development of synthetic vectors for use in drug delivery and gene therapy, François Diederich and colleagues at the Swiss federal institute of technology (ETH) Zürich have synthesised a family of dendritic molecules which have proved effective *in vitro*.

Diederich and colleagues

have shown that small structural changes to dendrimers affect biological activity and cytotoxicity. Understanding the relationship between structure and biological activity is 'knowledge that could then be used to create better drug delivery systems,' said Diederich.

The success of viral gene carriers is partly attributed to their self assembly as this improves their passage through the cell membrane. With this in mind, the Swiss team incorporated lipophilic branches into the dendrimer. The lipophilic section was linked by an aromatic group to cationic branches involved

### Structural changes affect transfection ability of self-assembling dendrimers

### Reference

M Guillot *et al.*, *Org. Biomol. Chem.*, 2006, 4, 766

in cellular uptake.

The structure of the two branched sections and the linking group were varied to determine their influence on the biological activity of the molecules in human cervical cancer cells. Their behaviour in Langmuir films was also analysed to investigate the potential correlation between the self assembly and the transfection efficiency of the dendrimers.

The nature of the lipophilic branches was found to be an important factor for the self assembly of the molecules into a film and for the transfection efficiency. The biological activity fell if the packing of the molecules was impaired. Varying the structure of the cationic branches had little effect on the biological activity; however, the aromatic core of the dendrimer also had some influence on the biological activity.

The challenge remains to create a dendrimer which is an efficient synthetic gene carrier *in vivo* and has low cytotoxicity, said Diederich.

Alison Stoddart

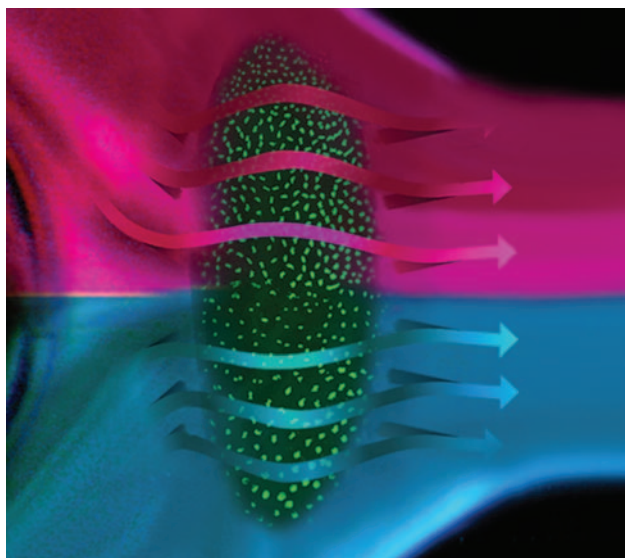
## Monitoring protein expression in fruit flies

The impact of temperature on protein expression in fruit flies can now be studied using a microfluidic device thanks to chemists from the US.

Rustem Ismagilov and colleagues at the University of Chicago controlled the temperature across fly embryos so that one half of the embryo was cooler than the other. They used multi-stream laminar flow to control the local temperature of live *Drosophila melanogaster* fruit fly embryos. Two flowing streams at different temperatures were then employed to control the temperature of each half of the embryo. The change in temperature was found to locally affect protein expression.

'Biochemical processes are sensitive to small differences in environmental temperature,' said Ismagilov. The rates of protein expression were disrupted depending on which area of flow a given part of the embryo was exposed to. The temperature affected the order in which proteins were expressed within the *Drosophila* embryo. This was visible on the embryo itself as a striped or banded patterning with the bands formed on the warm side first.

The laminar flow was visualised



**Microfluidic device used to measure the impact of temperature on protein expression in fruit flies**

### Reference

E M Lucchetta, M S Munson and R F Ismagilov, *Lab Chip*, 2006, **6**, 185

by labelling the streams with ink or fluorescent microspheres to verify the existence of a temperature gradient. The heat difference was confirmed using a suspension of liquid crystals, which responded to changes in temperature.

'The microfluidic platform could prove useful in understanding the dynamics of biochemical methods as they respond to changes in temperature,' said Ismagilov. *Michael J Spencelayh*

## Molecular imaging with red light

Red light activated fluorescent probes for biological imaging, which are less destructive and more efficient than those controlled by green or blue light, have been developed.

Donal O'Shea and colleagues at University College Dublin, Ireland, have made a series of fluorescent molecules based on boron difluorides that can be used in biosensors and activated by red light. Target substrates such as carbohydrates or peptides are detected by a receptor and quantified by a fluorophore on the same molecule. These two components are separated from one another by a methylene spacer. The receptors can be further modified depending on the substrate being monitored.

High sensitivity fluorescence detection and imaging is a common tool for studying molecular processes *in vitro* and for monitoring cells *in vivo* for diagnostic purposes. Most existing probes operate with light wavelengths of 300–550nm, the blue/green range of the spectrum. This leads to interference problems caused by background absorbance and even spontaneous fluorescence by the biomolecules themselves. Light of wavelengths greater than 650nm, the visible red and near infrared region, does not cause these problems and has the additional bonus of being less destructive to cells, says O'Shea.

'Advances in this field of molecular sensing and imaging will provide future tools to assist in the continuing drive to understand biological processes at the molecular level,' said O'Shea. Future work to optimise *in vivo* fluorescence sensors and to improve their specificity towards various target substrates is underway by O'Shea's group. *Suzanne Abbott*

### Reference

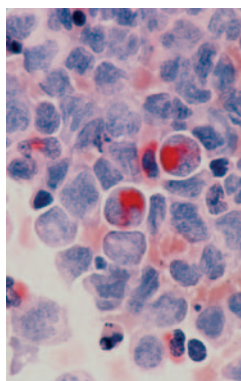
M J Hall, L T Allen and D F O'Shea, *Org. Biomol. Chem.*, 2006, **4**, 776

## Sugar enantiomers fight against disease

Additional pharmaceutical products could be developed thanks to researchers who have tested the enzyme inhibition activities of unnatural sugar enantiomers of two known drugs.

Keith Clinch from Industrial Research Limited, New Zealand, and colleagues have prepared the L-nucleoside analogues of two D-nucleoside pharmaceuticals currently undergoing clinical trials in order to try to find new drugs.

Immucillin-H is in Phase II trials as an anti-leukaemia agent and DADMe-Immucillin-H is in Phase I trials as an anti-psoriasis drug. The L-enantiomers of these drugs were prepared and tested as enzyme inhibitors by their ability to



### Reference

K Clinch *et al*, *Org. Biomol. Chem.*, 2006 (DOI: 10.1039/b517883e)

bind the enzyme purine nucleoside phosphorylase (PNPase). The human and bovine forms of the PNPases were tested and compared with those obtained for the original, D-nucleoside forms of the drugs.

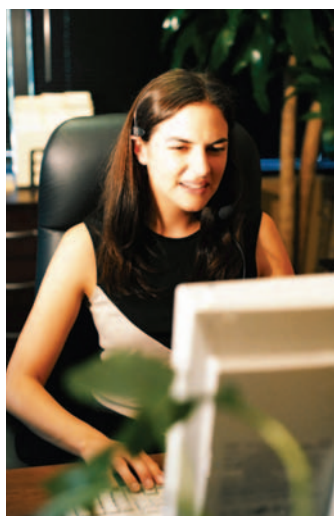
Despite being less active than the D-enantiomer, the L-enantiomer of Immucillin-H was still potent. L-Immucillin-H was found to be more active than some analogues of D-Immucillin-H as an inhibitor of the human PNPase enzyme. L-DADMe-Immucillin-H proved to be quite potent as a sub-nanomolar inhibitor against human and bovine PNPase enzymes. Interest in these compounds has increased as they too have the potential to become pharmaceutical products. *Elinor L Richards*

## ReSource gets even better

A new release of the RSC author and referee portal, ReSource, has just been launched complete with a new look and increased functionality.

'User-friendly' and 'intuitive' are just two words that have already been used by authors and referees describing the improved service. Most notable changes to the functionality include the option of saving submissions at key stages during the process (a much-welcomed option for researchers wishing to submit manuscripts, whilst juggling a hectic research schedule!), and online help facilities. Checklists and support notes are now available throughout the submission and refereeing processes, assisting and guiding authors and referees every step of the way.

These new features are complemented by a fresh new look, designed to ease navigation



and orientation within the site. User profiles are more visible, presenting individuals with an improved overview of their account details.

The new developments to ReSource were the result of

continued communication between RSC staff and the authors and referees that have used the service since its launch in October 2004 and feedback obtained from authors and referees during a survey in September 2005. 'We were overwhelmed with the response from authors and referees who contributed such constructive feedback as part of our survey last year' comments Sula Armstrong, Electronic Products Manager at the RSC, 'We have taken this on board and are delighted to present this new and improved service to RSC authors and referees. Tens of thousands of papers have been submitted or collected from the portal since its launch, proving how popular the service already is. This improved service will no doubt add to this success.'

To find out more, visit: [www.rsc.org/resource](http://www.rsc.org/resource)

## Getting under your skin



Can diet help protect against skin cancer? This topic is among the emotive subjects brought together in a recent issue of *Photochemical & Photobiological Sciences*. Researchers from around the world have published their latest findings on photodamage, in Issue 2 (February), 2006 of the increasingly popular photoscience journal. Other highlights include the role of mtDNA, photoaging, photocarcinogenesis and hair damage.

To find out more, visit: [www.rsc.org/pps](http://www.rsc.org/pps)

## Cover competition sparks voting frenzy

Faced with the task of selecting the best cover artwork from the creative designs that appeared on journal covers during 2005, RSC Publishing staff recently decided to put it to the vote. The resulting online competition, in which readers could pick their favourite cover from each of sixteen participating titles, closed with thousands of votes having been cast.



'Following the introduction of the new journal cover designs at the beginning of 2005, the contributing authors and our in-house team of designers have provided some stunning cover artwork' commented David

Riddick, Production Manager. 'Staff had their own personal favourites, but we were keen to find out what our readers thought. Their response has been tremendous.' A number of prizes, awarded to randomly selected voters, were offered as an incentive.

To view the winning covers and details of the prize-winners, visit: [www.rsc.org/Publishing/Journals/News/covercompetition.asp](http://www.rsc.org/Publishing/Journals/News/covercompetition.asp)

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