No 4 Autumn 2003

RS•C
ROYAL SOCIETY OF CHEMISTRY

ChemBiol News

THE NEWSLETTER OF THE CHEMICAL BIOLOGY FORUM

Chemical Biology – a win-win situation?

Human life can ultimately be described in terms of the interaction of chemical entities. As we journey ever deeper into a cell, we get closer to describing life at a chemical level. At these rarefied depths, however, the biologist cannot explore alone: it's time to call in a chemist.

How comfortable are biologists and chemists on such joint expeditions? Though many successful partnerships exist, chemists and biologists generally follow different agendas. The Wellcome Trust and the RSC are holding a series of workshops (see below), enabling chemists and biologists to explore territory in common and obstacles to greater collaboration.

Workshops

Joint workshops have been held in Bath, Durham and Edinburgh, and further workshops are planned for Cardiff and Dublin. The workshops have already had practical benefits: 'matchmaking' at Durham has fostered several new discussions between chemists and biologists, and following the Bath event, Dr James Dowden (pharmacy) and Dr Robert Kelsh (biology) cemented a collaboration that has led to a successful grant application to explore zebrafish embryo development using new chemical probes.

The potential for collaboration is surprisingly great. 'Chemical biology' uses chemical principles and techniques to study biological systems and exploits this knowledge in medicine and therapeutics.

Chemical biology approaches are being used in many areas of research. Computational chemists investigate the structure and properties of biological molecules and how they fold. Single molecule technologies are being developed to probe the mechanical interactions between individual protein molecules.

Small molecules, big potential

Much of the discussion at the Edinburgh workshop focused on small organic molecules, their synthesis and application in biological research. Small molecules similar to an enzyme's normal substrates can be used to explore and probe function. In chemical genetics, the gene is left intact, but a small molecule is used to inhibit the protein encoded by the gene.

So small-molecule studies are an area ripe for collaboration. For biologists, they provide an arsenal of tools to probe the function of genes and proteins.

Biologists and chemists have grown up talking different languages. Chemical synthesis pathways resemble hieroglyphics to many biologists. Chemists tend to mix with other chemists, and biologists with biologists. There is also the vexed issue of funding: chemists and biologists tend to be funded from different sources, and finding money for interdisciplinary research can be problematic. Shared seminars can provide a forum to encourage interaction and dispel myths.

Taken from '*Friends again*', Wellcome News, Summer 2003. The full article can be viewed at **www.wellcome.ac.uk**

In this issue

Publication note

Any comments on the ChemBiol newsletter and on the Chemical Biology Forum's activities should be emailed to:
ChemBiol@rsc.org
or log on to
www.rsc.org/chembiol

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The coming months...

The Chemical Biology Forum is continuing to develop a programme of activities throughout 2003 and into 2004 building on the foundations laid down last year. The forum activities continue to be based around discussion workshops, one-day meetings, RSC symposia and residential discussion style meetings.

Frontiers in Chemical Biology

Frontiers in Chemical Biology: the chemical biology of cancer is to be held in London on the **8 - 10 September 2004**. This conference will bring together the chemistry and cancer communities to discuss a number of the currently most significant areas. For more information email the conferences office (conferences@rsc.org). Details will appear on the conferences homepage (**www.rsc.org/conferences**) later in the year.

Other meetings

Bio-Nanotechnology, Institute of Physics, London
26 November 2003
A one-day symposium in co-organised with the Institute of Physics. This meeting will draw on the experiences of researchers across chemistry, biology and physics all with interests in different aspects of nanotechnology.
email: conferences@rsc.org

Advances and Challenges in Biotransformation,
Imperial College, London, 30 March 2004
Contact: Elaine Wellingham, Conference Secretariat,
Field End House, Bude Close, Nailsea, Bristol, BS48 2FQ
email: confsec@blueyonder.co.uk

NACON VI, Department of Chemistry, University of Sheffield
4 – 8 April 2004
email: i.haq@sheffield.ac.uk
www.sheffield.ac.uk/nacon/index.htm

Workshops

Chemical Genetics

Focusing on probing the genome using small molecules this workshop will focus on how the United Kingdom can engage the community in developing research in this arena.

Workshops are free but places are limited. If you are interested in attending please get in touch ChemBiol@rsc.org

Subject Groups

There are a number of groups with interests in the biosciences currently related to the Chemical Biology Forum:

Agriculture Sector
Analytical Biosciences Group
Biological and Medicinal Chemistry
Bio-organic Group
Biophysical Chemistry Group
Biotechnology Group
Carbohydrate Group
Food Chemistry Group
Inorganic Biochemistry Discussion Group
Inorganic Reaction Mechanisms Group
Molecular Modelling Group
Nucleic Acids Group
Organic Reaction Mechanisms Group
Protein and Peptide Science Group
Water Science Forum

For more details about these groups see: **www.rsc.org/lap/rsccom/dab/subgroup.htm**

CBF Newsletter

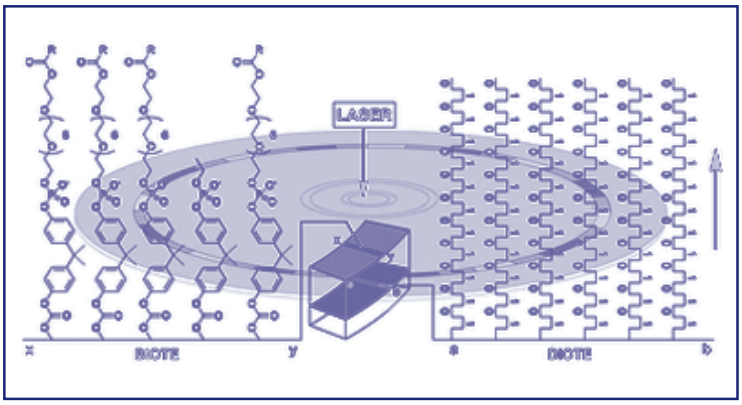
The Chemical Biology Forum is always looking for contributions to the newsletter and gateway.
Please get in contact if you have ideas or material you would like to be covered.

Recent papers in RSC journals

Development of novel cell-permeable DNA sensitive dyes using combinatorial synthesis and cell-based screening
*Jae Wook Lee, Michelle Jung, Gustavo R Rosania, Young-Tae Chang**

DNA sensitive fluorescent probes are important tools in molecular biology but very few are cell permeable. Chang and coworkers screened a library of styryl compounds against melanoma cells and isolated 8 that localised to the nucleus. They re-synthesised these in larger quantities and singled out one compound for its strong increase in fluorescence on binding to DNA. The team believe that this approach of combinatorial synthesis and cell-based screening will prove useful in developing further organelle specific cell permeable sensors.

Chem. Commun. 2003, 1852-1853



Molecular screening on a compact disc
*James J La Clair, Michael D Burkhart**

Identification of molecular recognition events is central to advances in biomedical research and diagnostics. However, while many methods exist to perform high through-put molecular screening, the expense of these systems limits their use to well-funded laboratories.

In this paper, Burkhart and La Clair demonstrate how a standard recordable compact disc can be utilised for routine screening of biomolecules. After chemical modification of the surface of the CD they print tracks of ligands using an inkjet printer to generate molecular arrays coupled to a PC with CD-ROM drive for reading. Binding of biomolecules to the ligands interferes with the optical transmission of the CD, creating errors in reading and revealing where, and therefore to which ligands, the biomolecule is bound. Using globally accessible, inexpensive and durable materials, the authors have demonstrated a practical new method for molecular screening.

Org. Biomol. Chem. 2003, 3244 - 3249
(see figure, left - ***reproduced by permission of Royal Society of Chemistry***)

Synthesis of HyBeacons and dual-labelled probes containing 2'-fluorescent groups for use in genetic analysis
*Neil Dobson, David G McDowell, David J French, Lynda J Brown, John M Mellor and Tom Brown**

The ability to rapidly detect single nucleotide polymorphisms (SNPs) is of fundamental importance in the study of genetic disease. In this communication, Brown and coworkers describe a novel route to effective 'HyBeacon' probes where the fluorophore lies in the minor groove of the DNA target. They show that the methodology can also be applied to the synthesis of dual-labelled FRET probes.

Chem. Commun. 2003, 1234-1235

Detection of DNA probes using Diels Alder cycloaddition and SERRS
Duncan Graham, Ljiljana Fruk, W Ewen Smith

An important, emerging area of biological chemistry is the development of new methods for the detection of specific sequences of DNA. These techniques play a huge role in the diagnosis of genetic disorders and the examination of gene expression.

This paper by Duncan Graham and co-workers, published in *The Analyst*, shows how sequences may be detected by surface enhanced resonance Raman scattering (SERRS) following labelling with a vibrationally active probe. Initially the oligonucleotide under study is tagged with a furan residue. The diene functionality of the furan ring then undergoes a Diels-Alder reaction with a specially designed azo dye, resulting in a SERRS active label. This new approach offers promising selectivity, sensitivity and simplicity and can be applied to the detection of very small (attomole) amounts of DNA in complex matrices.

Analyst 2003, 692-699

All these articles are listed in the **Chemical Biology Virtual Journal**

To receive free fortnightly email alerts of new content visit:

www.rsc.org/chembiolvj and click on email alerts

or email: **chembiol@rsc.org**

Perspective - Chemical Genetics to Chemical Genomics

David Spring discusses the emerging field of chemical genetics, the pitfalls and the barriers and how we might overcome some of these hurdles through inter-disciplinary research…

Post-docs, when they return from Harvard's Institute for Chemistry and Cell biology, are often asked: 'What is Chemical Genetics/Genomics?' This perspective article attempts to answer this question. Broadly defined chemical genetics is the study of biological processes using small molecule ('chemical') intervention instead of genetic intervention. Genetics has been used widely to study biology by manipulating the biological system at the level of the gene. Genes encode products such as proteins and it is the function of these gene products that we would like to understand. In order to identify the function of a protein you need to perturb its function. Genetically this is done by modulating gene function through a mutation and then observing the phenotype (physiological effect). Chemical genetics studies biology by using small molecules to modulate protein function. The classic example is the use of the natural product colchicine to study mitosis and identify the protein tubulin. Genetics on a genome wide scale is known as genomics. Correspondingly, chemical genomics is the extension of chemical genetics to a genome-wide scale.

Genetics has been divided into forward genetics (random mutations followed by phenotypic screening) and reverse genetics (mutation of a specific gene and characterise phenotype). So genetics in the 'forward' direction is from phenotype to gene; in the 'reverse' direction it is from gene to phenotype. Chemical genetics can be divided similarly. Forward chemical genetics is the use of small molecules (the 'mutations') to screen for the desired phenotypic effect on your biological system. Once a suitable small molecule has been identified, the gene product that the small molecule is modulating must be identified. Reverse chemical genetics is the use of small molecules against a protein (gene product) of interest, once binding partners have been chosen they are screened to identify the phenotypic effect of adding the small molecule. So chemical genetics in the 'forward' direction is from phenotype to protein, in 'reverse' it is from protein to phenotype.

This is what chemical genetics/genomics is, but why do we need to bother when we have genetics already! There are several advantages of chemical genetics over genetics. For example, small molecules most often induce their biological effect reversibly. To do this genetically you need what is known as a conditional allele, such as a temperature sensitive mutation. These are difficult to identify and the pleiotropic (multiple) effects can be problematic in identifying the effect of modulating the gene product, e.g. the heat shock response. In animal models induction of the conditional allele is rarely possible – would you ever heat shock a mouse? All small molecules can be used in a conditional manner, you either add them or not. Moreover, the biological effect of small molecules is usually rapid, allowing immediate-early effects to be characterised. With a genetic knockout only steady-state effects are observed. Another advantage is that we can use small molecules to study critical genes at any developmental stage. If a cell line is not viable with a particular gene knockout then chemical genetics still allows us to study the biological effect of a knockout gene product by using small molecules. Furthermore, multiple chemical genetic 'knockouts' can be easily combined.

The main disadvantage of a chemical genetic approach is that it cannot be applied generally. In principle, any gene can be manipulated by genetics; however, chemical genetics requires a small molecule ligand to the protein you wish to study. At this point in time only a tiny fraction of known proteins have a ligand partner identified. Identified ligand partners include natural products, such as penicillin, and pharmaceutical drugs, such as ciprofloxacin. The current rate of protein-ligand partnership discovery must be dramatically increased if we want to make the chemical genetic approach as generally applicable as genetics. This is the aim of chemical genomics.

In order to achieve this aim we require at least three things: small molecules, proteins and ultra high-throughput technologies to screen and handle data. The 'rational' design of protein-ligands has been increasingly successful, especially in the pharmaceutical industry. To work well it requires a good understanding of the macromolecular structure, usually requiring X-ray crystal structures. The advent of structural genomics will help this approach; however, the number of small molecules required for chemical genomics cannot be designed on a genome-wide scale. Forward genetics generates large numbers of random mutants and screens for the desired phenotype. Forward chemical genetics can use a large collection of small molecules ('mutations') to exploit the same strategy. But we have a problem, where are all the 'random' compounds going to come from, and incidentally, what should they look like? A single geneticist in a lab can easily make millions of genetic mutants; however, a single chemist in the lab cannot, at present, make millions of small molecules in a useful way. It has taken pharmaceutical companies decades, huge sums of money and hundred of chemists to put together a million compounds in their proprietary compound libraries! Recently, some companies have started to sell small compound libraries, but they are typically very, very expensive. Combinatorial chemistry now does allow for the synthesis of vast numbers of compounds. But this is not enough since all the compounds produced in libraries so far have a limited structural diversity. Structural diversity is essential since compounds that look the same structurally will have a similar binding pattern and thus similar biological profile within a few orders of magnitude, although there are exceptions. Furthermore, the compounds should be structurally-complex since we need the ligands to selectively bind to any gene product, not just enzymes or receptors. The efficient, simultaneous synthesis of structurally-complex and structurally-diverse compounds is a significant challenge to modern synthetic

chemistry which is only just beginning to be addressed by diversity-oriented synthesis (DOS).

The proteins are another significant challenge, this time to biologists. Chemical genomics requires the whole proteome to be expressed, purified and isolated. As insurmountable as this seems, a number of labs are making progress to provide this invaluable resource required for many applications. The move to ultra high-throughput technologies is also absolutely essential for chemical genomics. There are many challenges ahead for chemists, biologists, engineers, computer scientists, etc. And this is perhaps the most important take home message if we want UK academia to be involved in this area. Individual labs can contribute to advances in DOS, high-throughput compound purification and storage, screening, assay design, informatics, etc. But all components must be combined together to be truly competitive. Large pharmaceutical companies are in a great position to do this, but the success of chemical genetics/genomics in the UK academic environment will be dependent upon interdisciplinary cooperation and collaboration, and funding on a national scale. Impossible? Well the research councils, headed by BBSRC are already looking into chemical genomics: UK academics and industrialists, and representatives from the research councils are meeting in January 2004 for a two day workshop discussing the best way forward for the UK to compete and direct the field.

David Spring, University of Cambridge

As part of the developing activities in chemical biology at the RSC two groups have recently become part of the Chemical Biology Forum. These two groups, formerly joint groups with the Biochemical Society, are developing programmes of meetings and actively engaging in the development of the Forum…

Nucleic Acids Group (NAG)

The Nucleic Acids Group, originally formed in the late 1960's, has recently become an Interest Group of the RSC under the aegis of the Chemical Biology Forum. The Group exists to promote the subject of nucleic acids primarily *via* organisation of meetings covering a range of nucleic acid based topics. The Group's activities are administered by a committee consisting of 11 elected members, including a Chair, Secretary and Treasurer. The focus of meetings include nucleic acid structure, ligand-nucleic acid or protein-nucleic acid interactions, molecular biology, nucleic acids as enzymes, tools or therapeutic targets. There are usually three or four such meetings each year.

Key topics covered by the Group includes:

- **Nucleic Acids and Catalysis**
- **DNA Damage and Repair**
- **Genomes and Genomics**
- **Novel Concepts and Technologies**

The Group also sponsors independent meetings, not organising by them, but with a topic relevant to the Group.

Events

NACON VI
University of Sheffield
4 – 8 April 2004
Sixth International Meeting on Nucleic Acid Recognition Studies
email: i.haq@sheffield.ac.uk
www.sheffield.ac.uk/nacon/index.htm

EMBO Workshop/Harden Conference
Robinson College, Cambridge
3 – 7 April 2004
Mechanisms of Telomere Maintenance and Genome Stability
email: meetings@biochemistry.org

Contact

For more information on the group go to: **www.rsc.org/lap/rsccom/dab/perk005.htm**

Or contact the group secretary: **Dr Jon Sayers**, University of Sheffield, Division of Molecular and Genetic Medicine, M Floor Royal Hallamshire Hospital, Sheffield S10 2JF email: j.r.sayers@sheffield.ac.uk

Protein and Peptide Science Group (PPSG)

With a historic basis in peptide chemistry the Protein and Peptide Science Group has recently become an Interest Group of the RSC under the aegis of the Chemical Biology Forum. The Group's aim is to maintain the logical progression of molecular science through chemistry into biochemistry, biology, medicine, plant and food science.

Thus, it has an interdisciplinary approach, representing the protein science interests of chemists, molecular biologists, structural biologists, peptide chemists and biologists, medics, members of the biotechnology, food and pharmaceutical industries.

Topics covered by the Group includes:

- **Protein prediction and structure determination**
- **Combinatorial synthesis**
- **Protein design and engineering**
- **Functional genomics, proteomics and bioinformatics**

Events

7th International Symposium on Biomolecular Chemistry (ISBOC-7)
University of Sheffield
27 June - 1 July 2004
Interface of organic chemistry with biological and medicinal science
email: conferences@rsc.org

www.rsc.org/lap/confs/isboc7.htm
Other meetings can be found by using the RSC chemsoc database (**www.chemsoc.org**)

Contact

For more information on the group go to: **www.rsc.org/lap/rsccom/dab/perk007.htm**
Or contact the group secretary: Dr Brent Irvine, School of Biology & Biochemistry, The Queen's University of Belfast Medical Biology Centre, Belfast BT9 7BL email: b.irvine@qub.ac.uk

Joining the Groups

The annual fee to be a member of each group is £5. To join the group email subsrecords@rsc.org with your membership number. Further details about joining an RSC group can be found at: **www.rsc.org/lap/rsccom/dab/joingroup.htm**

Chemical Biology Diary

Date	Title of Conference/Event	Venue	Contact
2003			
12 November	Antibodies for Diagnostic Technology	*Geological Society, London, UK*	Diana Hort e: hortd@rsc.org
26 November	Bionanotechnology	*Institute of Physics, London, UK*	Christine Charlton e: conferences@rsc.org
15 December	RSC BioOrganic Group Pre-Doctoral Meeting	*GlaxoSmithkline, Harlow, UK*	Mark Bamford e: Mark_J_Bamford@gsk.com
2004			
30 March	Chemistry of the Cell	*University of Birmingham, UK*	David Minnikin e: d.e.minnikin@bham.ac.uk
30 March	Advances and Challenges in Biotransformation	*Imperial College London, UK*	Elaine Wellingham e: confsec@blueyonder.co.uk
4 April	NACON VI	*University of Sheffield, UK*	Sham Haq e: i.haq@sheffield.ac.uk
20 April	Chemistry at the Biology Interface	*London School of Pharmacy. UK*	Stanley Langer e: langers@rsc.org
27 June - 1 July	7th International Symposium on Biomolecular Chemistry - ISBOC-7	*University of Sheffield, UK*	Nicola Cuthbert e: cuthbertn@rsc.org
18 - 22 July	BioScience 2004	*Scottish Exhibition + Conference Centre (SECC), Glasgow, UK*	e: info@BioScience2004.org
23 – 27 July	22nd International Carbohydrate Symposium	*Scottish Exhibition + Conference Centre (SECC), Glasgow, UK*	Nicola Cuthbert e: cuthbertn@rsc.org

For more information on any of the above events, please email the relevant contact(s).

A complete list of events can be found on:
www.rsc.org/conferences or email: **conferences@rsc.org** to request copy of the Diary 2004, quoting ref: **ChemBiol News.**

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advancing the chemical sciences

22nd International

CARBOHYDRATE SYMPOSIUM

Scottish Exhibition + Conference Centre (SECC), Glasgow, UK
23 – 27 July 2004

The 22nd International Carboyhdrate Symposium (ICS) will be the most prestigious meeting of the year for the discussion of the **Chemistry, Biochemistry and Medicine of Carbohydrates and Glycoconjugates.**

This symposium is truly international, being organised on behalf of the International Carbohydrate Organisation, which has board members from 29 Countries, with representative of many of these as invited plenary (10) and keynote (23) speakers. The three themes of the meeting have been designated:

- **Carbohydrate Chemistry and Enzymology**
- **Carbohydrates in Medicine and Biology**
- **Carbohydrate Materials and Biopolymers**

The ICS will pick up on several of the themes of the conference Bioscience 2004, occuring back-to-back at the SECC in Glasgow.

www.rsc.org/lap/confs/ICS22.htm

conferences@rsc.org

2004
International Carbohydrate Symposium

and don't forget 5th International Symposium on Transition Metals in Organic Synthesis, Glasgow, UK on the 15 - 17 September 2004
email: conferences@rsc.org for details

10MMIII/MMM