A Research Council Chemical Biology Workshop: Collaboration between Academia and Industry

Thursday 10 June 2010,
One Whitehall Place, London, SW1A 2EJ

REPORT

Introduction

The broad area of chemical biology (also referred to as biomolecular chemistry, chemistry-biology interface, etc.) is currently funded by three Research Councils (BBSRC, EPSRC and MRC) and represents a grant portfolio of research and training totalling approximately an annual spend of £100 million.

In 2009, the International Review (IR) of Chemistry highlighted this area as a key strength of the UK Research Landscape (see http://www.epsrc.ac.uk/research/intrevs/2009ChemistryIR/Pages/default.aspx). The IR panel also identified the area of Drug Discovery as one of three areas (alongside Energy and Materials for Medicine) where the UK 'chemistry' community in its broadest sense has the potential to make a significant contribution to worldwide societal challenges, but can only do so in partnership with the UK pharmaceutical and biotechnology sector.

With this workshop the Research Councils are working together to foster collaboration between academia and industry to accelerate the take-up and exploitation of its funded research.

Objectives

The meeting held in London on the 10th June was intended to:

1. Explore the broad scientific challenges faced by industry in chemical biology, using the four themes identified below and any others that emerge on the day.
2. Demonstrate how chemical biology can benefit the life sciences community more broadly.
3. Challenge both the industry and academic parties to explore and establish new ways of working.
4. To foster collaborations between the academic and industrial communities.
5. To showcase universities' capabilities in this area and how these might be used to help tackle industrial problems.

The Research Councils selected participants to attend the workshop.

The meeting was well attended by those invited from across the three Council's remits and industry and stakeholder bodies to represent the range of disciplines and industries interested in this area. (Participants list attached in Annex 1.)

Plenary sessions

The workshop was opened with talks from Dr Tony Wood, Vice President and Head of Worldwide Medicinal Chemistry at Pfizer and Professor Hagan Bayley, University of Oxford and Chair of the RSC's Chemistry Biology Interface Forum. A summary of their key discussion points are captured below.

Dr Tony Wood, Pfizer

- Despite the large R&D budgets of the major pharmaceutical companies, each individual company still represents only a small fraction of the world investment in biomedical research.
- Pfizer has world class medicinal chemistry but we recognise that in emerging areas like chemical biology we need to collaborate with experts in academia and biotech to be successful.
- Chemical biology offers the opportunity to change the way we identify and quantify targets.
- Genomics including functional aspects will increasingly allow us to identify high confidence targets.
- These will provide new research challenges in the design of high-quality small molecules.
- Chemoinformatics is well established but will continue to grow in industry and academia with large scale data mining representing a new challenge.
- The world of molecules does not have to be small or large – both are valid and inform one another. Chemistry has the opportunity to lead in the interface between the two.

Professor Hagan Bayley, University of Oxford

- It is well known that large Pharmaceutical companies have several serious difficulties, including generics, cost and regulatory constraints, weak pipeline, etc.
- These issues are especially critical in the UK.
- There is concern about producing affordable new medicines and not the marginal improvement of existing drugs for immediate profit.
- It is incontestable that the UK has a brilliant track record of academic research that has contributed directly and indirectly to the discovery of new therapies and medical devices.
- The initial discoveries in the UK came for the most part from unmanaged, speculative research.

- A largely unfettered approach to academic research in Chemical Biology and related areas should be reestablished; Pharma must pay attention to new developments and take them on board quickly.

- Funding for fundamental science should not be cut at this critical time. Indeed increased funding must be used to solve the structural problems that have led to reduced ambition in UK academic science.

- Collaboration between academia and industry could be better at the basic science level. Pharmaceutical companies should be scouting for new discoveries rather than giving out small grants for synthesis projects.

Case studies

These talks were followed by four case studies designed to provide an overview of recent advances in academia and industry. A summary of some of the main points are captured in Annex 2. Adam Nelson (University of Leeds) gave a synthetic chemistry example working with GSK through the EPSRC-GSK Flow Chemistry call. Chris Abell (University of Cambridge) highlighted some challenges of working with industry and some research areas where chemical biology has had an impact. Mike Hann (GSK) highlighted challenges under each of the workshop's four themes that he thought could be useful to explore with industry. Neil Pegg gave an overview of how CellCentric operated.

Definitions and Barriers to Collaboration

As part of the facilitated discussions at the workshop, the participants explored what Chemical Biology meant to them and were asked to discuss what they saw as the barriers to collaboration between industry and academia.

Some definitions that emerged:

- Where small and large molecules meet.

- Application of new molecular tools and technologies and methods for studying and solving biological problems.

- Chemical probes to elucidate biological problems

- Chemical tools for understanding biology.

- Molecular toolbox for studying biological systems.

- Understanding biological systems in molecular terms

- Application of chemical "technologies" to biology and vice versa

- Complex chemistry

- Quantitative tools. Using better data to inform better hypothesis.

- Using chemistry to create new biology and understand natural biology.

As the list shows, the majority saw Chemical Biology as Chemistry helping us to study biological problems. However, there was support for the idea that biology can help chemistry too.

Barriers to collaboration

In their groups the participants also identified some barriers to collaborating both at the biology-chemistry interface and between academia and users:

- There is a need to understand the languages of each discipline. Joint PhD programmes were cited as a useful way to ensure researchers in different disciplines work together.
- It was felt that the pharmaceutical companies' desire to get a quick return on their investments too early was not helpful to building collaborations.
- It was suggested there is a lack of chemists using chemistry to ask biological questions. And a lack of biologists working in partnership with chemists.
- Where the novelty of the research lies at the interface, it can sometimes be difficult to publish as the single disciplines work is not always seen as exciting on its own. Need to develop innovative chemistry solutions to address fundamental biological problems.
- Material Transfer Agreements (MTAs) could be made easier. Academics would like to have more open access to pharmaceutical companies' compounds. A "molecular library" could be set up where data is loaned on request. This could be done using a Cellcentric model or by donating them to a public body like the Research Councils.
- There was a suggestion pharmaceutical companies could receive tax breaks if they were to release their compounds or probes.
- Chemistry data generated by projects is not always 'open access' or as much as expected in the biology community.

Other general comments captured:

- It was felt that having the NHS in the UK was a strength to the research base.
- Chemistry could evolve like the US e.g. Harvard Chemistry and Chemical Biology. In the UK chemical biology operates within the framework of biological problems e.g. cancer, stem cells etc. as opposed to developing tools out of context or not in partnership with biologists.
- We could make more use of a network group of Molecular Graphic Modellers.
- Continuity of funding for research was seen as vital and the EPSRC Platform grants were cited as a good mechanism that gave this. Also MRC research institutes such as Laboratory of Molecular Biology in Cambridge were mentioned e.g. structural biology of G-protein coupled receptors (Chris Tate, Richard Henderson), crystal structure of the ribosome (Venki Ramakrishnan,), synthetic amino acids and ribosomes (Jason Chin) that can allow better understanding of how antibiotics work and novel ones could be designed (see next point).
- It was felt that the current drug development model was not adequately addressing society needs, e.g. novel antibiotics. There is a need for high-risk speculative drug discovery – but who will fund and absorb the risk?

- The academics felt that more could be done with the failed chemistry and targets that pharmaceutical companies no longer use. However, more open information (e.g. malaria model) may need some shared IP arrangements.

Open space

In discussion with the Research Council's industrial strategic partners four themes (Annex 3) had been identified before the workshop to frame the discussions. The participants selected a theme and were assembled into groups to discuss the research challenges in each of the four theme areas.

The discussions were chaired by one of the participants and facilitated by Research Council staff. This section highlights some of the challenges identified by the groups.

Challenges in Theme 1: Small molecule chemical tools

- Selective molecules that modulate specific receptors.
- Exploit biology to understand chemistry questions.
- How can we change the scale of which we interrogate biology with small molecules?
- How molecules cause toxicity? Polypharmacology.
- How do we define new areas of the chemical space where we are likely to find natural products with the right properties?
- Paradigm shift from proteins to DNA/RNA: Need to focus on compound systems. How to manage complexity? Need new tools for analysing data.
- Novel delivery mechanisms eg RNA to DNA. Identifying small molecules that have non-traditional binding properties.

Challenges in Theme 2: New concepts in target modulation

- Connect physical changes with chemical effect.
- Ask new questions of identified systems especially with temporal components.
- Need homogeneous population of molecules (currently averages).
- Need to encourage cell biologists to make links with chemists.
- Need for mechanistic and structural biology.
- Have pharmaceutical companies been too reductionist? Can gain new insights by looking at more complex systems (e.g. David Spring's work).
- Need much better fundamental understanding through modelling, measurement tools and data.
- Informatics: What can you do with fractional/partial/sufficient data?
- New tools to do biopolymers in living cell.

Challenges in Theme 3: Target deconvolution: proteomics and metabolomics

- Reverse screening of known drugs how promising are they?
    - What technologies enable this?
- Access to molecules.
- Better ways to de-convolute phenotype assays.
- Access to Category 3 facilities (regulation containment facilities).
- Better quantification –MS
    - Better in-vivo tools.

Challenges in Theme 4: The intersection of large and small molecules

- Have a decent assay for endocytosis.
- To see molecules and molecular interaction in real time.
- Real-time molecular imaging.
- Mapping cellular processes.
- Useful nanoparticles.
- Understanding of the dynamics (of molecules).
- Measuring molecular interaction.
- Why and how are different organisms different?
- Metabolic engineering.
- Discovery: Small molecules that are selective, potent, modulate interactions (all desirable, biologically active, useful).
- Small molecules vary in definition.
- Can we manufacture interactions? Is there a biological question?
- Classic pharmaceutical: ligands and active site BUT now other interactions also have effect.
- Locations and other targets.
- Ligation.
- Use a small molecule to define/change functions of large molecule.
- Advantages to combining large and small molecules.

Conclusions and next steps

The open space generated many research challenges under each theme, that academia and industry felt they could tackle together.

There was a sense at the workshop that constructive networking both between disciplines and academia and users would be greatly beneficial to the UK capability in Chemical Biology.

To build on this enthusiasm to network, the Research Councils are planning a call for Collaborative Networks Proposals. We hope these Networks will give academia and industry the opportunity to explore these challenges further and begin to seed ideas for collaborative projects.

Annex 1: Participants list

Professor Chris Abell - University of Cambridge

Dr Rikki Alexander - UCB Celltech

Mr Ross Barnes - EPSRC

Professor Hagan Bayley - University of Oxford

Dr Neil Berry - University of Liverpool

Dr Michael Bodkin - Eli Lilly

Dr Alex Breeze - AstraZeneca

Ms Zoe Brown - EPSRC

Dr Gareth Buchanan - EPSRC

Dr Mark Bustard - bioProcessUK

Professor Stephen Caddick - University College London

Dr Mark Carver - Avecia

Mrs Celia Caulcott - BBSRC

Dr Oscar Ces - Imperial College London

Dr Weng Chan - University of Nottingham

Professor Tim Clark - University of Portsmouth

Dr Andy Cureton - BBSRC

Dr Lloyd Czaplewiski - Prolysis Ltd

Professor Gideon Davies - University of York

Professor Ben Davis - University of Oxford

Dr Fergus Earley - Syngenta Ltd

Dr Clarissa Edwards - BBSRC

Dr Jane Endicott - University of Oxford

Dr Jon Essex - University of Southampton

Dr Ellen Friel - Royal Society of Chemistry

Dr Andrew Furlong - Institution of Chemical Engineers

Dr Peter Gallagher - Eli Lilly

Dr Val Gillet - University of Sheffield

Professor Robert Glen - University of Cambridge

Mrs Eileen Glover - EPSRC

Dr Merlin Goldman - Technology Strategy Board

Dr Ed Griffen - AstraZeneca

Dr Nicolas Guernion - EPSRC

Dr Mike Hann - GlaxoSmithKline

Dr Tom Heightman - University of Oxford

Dr Stephen Hill - University of Nottingham
Professor Rod Hubbard - University of York
Dr Peter Hunt - Novartis Horsham Research Centre
Professor William Hunter - University of Dundee
Dr Sophie Jackson - University of Cambridge
Dr Vicky Jackson - BBSRC
Dr Ruth Jameson - The Wellcome Trust
Dr Paul Jenkins - University of Leicester
Dr Chris Jones - National Institute for Biological Standards
Dr Philip Jones - Merck, Sharp & Dome Ltd
Dr Lyn Jones - Pfizer Ltd
Dr Theo Kanellos - Pfizer Ltd
Professor Douglas Kell - BBSRC
Professor David Klug - Imperial College London
Dr Mike Lant - Syngenta Ltd
Dr Carolina Mailhos - MRC
Ms Carol Marchant - LHASA Limited
Dr Jo Martindale - Royal Society of Chemistry
Dr Theo Meert - Johnson & Johnson
Professor Jason Micklefield - University of Manchester
Dr Ralph Minter - Medimmune Ltd
Professor Adrian Mulholland - University of Bristol
Dr Robert Nash - Phytoquest
Professor Adam Nelson - University of Leeds
Dr John Overington - University of Cardiff
Dolly Parkinson - EPSRC
Dr David Parry - Cyclofluidic Ltd
Dr Neil Pegg - CellCentric Ltd
Dr Trevor Perrior - Domainex Limited
Mr James Phillips - BBSRC
Dr Andrew Pitt - University of Glasgow
Dr John Porter - UCB Celltech
Dr Neil Press - Novartis Horsham Research Centre
Dr Malcolm Rhodes - BioIndustry Association
Professor Alison Rodger - University of Warwick
Professor David Russell - University of East Anglia

Dr Klaus Schneider - GlaxoSmithKline

Dr David Selwood - University College London

Dr Paul Sherwood - STFC, Daresbury

Professor David Shima - University College London

Dr John Sime - Bioscience KTN

Dr Malcolm Skingle - GlaxoSmithKline

Dr David Spring - University of Cambridge

Professor Joe Sweeney - University of Reading

Dr Edward Tate - Imperial College London

Dr David Taylor - Unilever Plc

Dr Peter Varnal - University of Sussex

Professor Ashok Venkitaraman - University of Cambridge

Professor Anthony Watts - University of Oxford

Dr Nick Westwood - University of St Andrews

Dr Mark Whittaker - Evoteck UK

Dr Jonathan Williams - EPSRC

Professor Christine Willis - University of Bristol

Dr Tony Wood - Pfizer Ltd

Annex 2: Case studies Presentations

Adam Nelson – Leeds

- Collaborative project – small molecules, chemical diversity in chem. Bio and med chemistry.
- EPSRC ARF.
- EPSRC/GSK Array Chemistry Call.
- 25M molecules based on 2.5M frameworks – 17% of all compounds based on 30 frameworks, uneven exploration of chemical space.
- Synthetic methods to explore diversity of molecular space.
- Molecular diversity in the context of drug discovery.

Chris Abell – Cambridge

- Does not collaborate with industry – too many obstacles in his view (legal, incl. Material Transfer Agreements (MTAs), overheads, "different missions and ambitions").
- Pure science inadvertently applied.
- Spin-out examples (3 thus far).
- Work on small molecule ligands – fragments – small libraries – no need for screening large chemical space.
- Targeting tuberculosis – neglected diseases (Bill Gates foundation funding).
- Targeting protein-protein interaction (use of fragments for).
- Targeting RNA: riboswitches.
- Assigning function/assessing drug ability – Astex therapeutics (70 people).

Mike Hann – GSK

1) Small molecule chemical tools
    - Avoid molecular obesity – new biophysics needed to detect small weakly binded molecules.
    - Bringing leading UK academics together with compound suppliers – fragment and lead likeness design.
    - Fragment docking.
    - Prediction of binding affinities.
2) Chemogenomics

- Safety/toxicity is biggest cause of attrition in pipeline.
- Public-private partnership – IMI – data in public domain.

3) New concepts in target modulation
   - Where are compounds in tissue and cells?
   - How much compound is in cells?
   - Need better understanding of how to exploit active transport.
   - Prevalence of active transport.
   - In-cell biophysics.
   - Structural biology challenges – IMPs and larger complexes – getting away from reductionist approach.
4) Target deconvolution
   - Deconvolution of phenotypic black box screens (data accessibility).
   - Quantitative proteomics (chemical proteomics).
   - Chemical probes – Stephen V Frye's paper.
   - Chemical probes for epigenetic drug discovery – pre-competitive chemistry.
   - Chemical probes vs. leads for optimisation.

Pharmaceutical companies have to balance the distribution of information in the public domain with the opportunity to make profit out of the work previously carried out by the company.

Neil Pegg – Cellcentric

- Collaboration with academia.
- PI academic network – 30 academic labs around the world.
- Epigenetics – hot, rapidly expanding field in biology.
- PI target identification – Cellcentric: target validation.
- Fundamental biology – pathway delineation.

Q&A session

Comments

- There is a need to focus on fundamental Chemical Biology that can help industry across the board.
- There should be a strategic decision to focus a network on drug discovery rather than techniques and technologies.

- The Cellcentric Network is evolving all the time; scepticism has been replaced by collaborative endeavour.
- There is a tendency to focus on pharmaceutical industries outputs but another benefit is what biology can tell us about the chemistry? Biologically active compounds could help.
- We need to bring chemistry and biochemistry academics into the fold.

Questions

Q1: Wish list needs to translate into coherent plan to take it forward from the Research Councils – how is Chemical Biology is supported is the real issue?

Panel – There are many mechanisms for academia to team up with industry now. How are the pharmaceutical companies influencing TSB and RCUK?

Q2: Are there repositories from industry that could be used in academia. Drug discovery area will become more fragmented - pharmaceutical companies becoming smaller and biotech labs more numerous – is there a clearing house that could be formulated?

Panel – Pharmaceutical companies are diversifying and this should be seen as an opportunity for academics and SMEs. Research will be done differently. A clearing house approach is something to aspire towards even if it is far from being a reality.

- Lists inhibit creativity. The solution is to build networking between academia and industry.

– It was thought networking to be key, especially at a pre-competitive level.

– How do you use biological systems inform chemistry (industrial Biotech)?

Q3: What makes an industry-academia collaboration work well?

Panel – communication, commitment beyond the medium term, mutual benefit, no pre-conceived ideas, enthusiastic behaviours with industry, goals well established (and aligned at start), etc.

- Working together to establish a collaboration that is worthwhile to both parties is important. An academic-industrial collaboration with Unilever was cited as an excellent example.

Q4: Does the panel think that the (funding) landscape is too complicated?

Panel – too complex indeed.

– There are many schemes that be applied for but these can appear complicated for people who have not engaged with industry before.

– more alignment is needed.

Annex 3: Workshop themes

Chemical biology has been described as the study and manipulation of biological systems through the application of chemical techniques and tools. Although the two disciplines are distinct there are many aspects of chemical biology that relate strongly to the challenges of modern medicinal chemistry but may also apply to other industrial sectors e.g. agrifood. We have worked with our industrial strategic partners to identify 4 themes to base the workshop's discussions around:

Theme 1: Small molecule chemical tools

New tools and techniques to discover high quality, biologically active chemical compounds and prevent wasted synthetic effort during development. Techniques may focus on:

- Chemoinformatics (virtual screening): using tailored libraries of compounds to identify successful features of lead compounds for more informed drug design.
- Chemogenomics: using the study of genomic responses to chemical compounds to rapidly identify novel drugs and drug targets.

Theme 2: New concepts in target modulation

Identifying novel modes of action and potential cellular binding partners for small molecules. To achieve this, new techniques should be developed which take into consideration the sub-cellular localisation and the conformational state of the particular protein and/or oligonucleotide target. Biophysical methods need to be developed that use non-invasive label-free measurement protocols (keeping the small molecule and the effector in their native states) that are applicable to whole-cell measurements.

Theme 3: Target deconvolution: proteomics and metabolomics

Investigating new phenotypic screening techniques, such as the use of Activity Based Proteomic Profiling (ABPP): using specific probes to monitor the activity of the enzyme's active site directly. It is anticipated that both proteomic and metabolomic analysis, alongside systems biology, will be employed in the future to identify the targets of such phenotypic effects.

Theme 4: The intersection of large and small molecules

Developing new experimental systems that can measure all the steps involved in recognition, endocytosis and release, by bringing together expertise in particle engineering and medicinal chemistry. Gaining a greater understanding of ligation techniques and carrier protein distribution and function to exploit the use of small molecule-protein conjugates.