Organic chemistry rising to the healthcare challenge

Background

Excellence in synthetic organic chemistry underpins the success enjoyed by the pharmaceutical industry over the last 20 years with at least 10 of the top-selling drugs worldwide (>$1B annual sales at peak) having UK-trained PhD organic chemists as named inventors. In this way, EPSRC–funded organic chemistry research has established an impressive track-record of contribution to UK wealth creation. Furthermore, PhD organic chemists have developed the skills and expertise to enable them to rise to senior positions within pharmaceutical organisations and to have a significant influence over their research strategy and decision-making. Transferable skills acquired during the PhD training have driven subsequent success in a broader setting, such as the pharmaceutical industry. These skills include: creative problem-solving; risk management; treating an unexpected outcome as an opportunity to refine hypotheses; seeking to expand solution space through continual improvement.

Synthetic organic chemistry remains an integral part of medicinal chemistry design, enabling the most carefully designed target compounds to be realised in a rapid and efficient manner. Similarly, powerful synthetic technologies open-up new areas of chemical space introducing new solution options and enabling project teams to identify the very best drug candidates. When synthetic enablement is lacking, we see projects stall, even those with the best biological or clinical rationale.

Recent developments

A key question is how can synthetic organic chemistry best serve the future needs of the pharmaceutical industry[1] where science is moving at an unprecedented pace and multidisciplinary teams work on an ever-expanding range of treatment modalities beyond conventional small molecules.

To address this, we should look back at some historical data. One of the main conclusions from the 2003 review *Chemistry at the Centre* [2] described a view of chemistry as '*small science'*. The report also highlighted *scholarship* as a strength but *innovation* a relative weakness and in response, the EPSRC has introduced funding initiatives such as platform grants and portfolio partnerships. In terms of multidisciplinary research, it is clear from the recent RSC-sponsored Face-to-Face report[3] that although there good examples of collaboration, there is still room for improvement.

More recently, the EPSRC launched the Grand Challenges initiative which sets the priorities for collaborative research across the chemical sciences and engineering for the next 20-40 years. This represents a further shift away from the traditional 'responsive mode' mechanism for funding UK-based research, raising concerns amongst the academic community that access to funding sources will be further diminished and freedom to pursue their chosen areas of scientific investigation will be restricted[4].

Industrial perspective

Senior chemistry leaders across the UK pharmaceutical sector[5] met recently to discuss how we, as scientific partners for the academic community and key customers for the output from PhD programmes (research and skilled scientists) can help bridge the apparent divide. There was broad agreement that the Grand Challenge approach to research funding could represent a key mechanism for retaining a central role for organic chemistry in developing solutions to global problems, rather than becoming a service to other disciplines. At one extreme, the predefinition of priority research areas could stifle the freedom, scholarship and scientific rigor that characterises UK-based research. Indeed, the past record of academic achievement includes plenty of examples where response-mode funded research has led to discoveries with broad utility (e.g. peptide synthesis, C-H activation). However, as long as the themes remain loose enough to accommodate a wide range of academic interests, the Grand Challenges could provide invaluable guidance to researchers, helping to signpost opportunities for collaborative programmes.[6] Equally, sometimes the most transformational solutions can appear to be on the face of it to be incremental and unimaginative and there needs to be licence for such research to continue in order to allow the true potential of existing technologies to be realised in a broader context.

Medicinal chemistry challenges

The Grand Challenges theme *Synthesis, Assembly and Manufacture by Design* recognises the intimate interdependence of design and synthesis expressed earlier. As organic chemists turn their attention to a wider landscape of mechanisms and processes, they will need to call upon an ever expanding range of methodologies to ensure their designs are realisable in a timely, economic and environmentally acceptable fashion. Some examples (by no means exhaustive) are outlined below to illustrate how the Grand Challenges theme can be viewed within the context of medicinal chemistry.

1. To transform the design & synthesis of small molecules to enable interaction with any genomic protein

e.g. expansion of available chemical space through synthetic methodologies/technologies, improvement of 'drug-like' properties of existing agents.

2. To develop the scientific basis of predictive toxicology

Understanding the interrelationship between drug structure, reactivity, metabolism and toxicology and to develop guidelines for predictive design (cf Lipinski for absorption)

3. To support clinical studies with chemical tools

Use of translational chemistry for non-invasive monitoring *in vivo* (e.g. contrasting agents, biomarkers).

4. To discover the next generation of biological drugs

Transform biologics synthesis through integration of small molecule synthetic chemistry with synthetic biology (cf. semi-synthetic natural product synthesis)

5. To develop the scientific basis of drug delivery and selective tissue targeting

Investigating at a molecular level the chemical basis for transport and distribution of drugs and to develop tools to support predictive design

Research skills

From a training perspective, the research skills developed within collaborative programmes will be ever more important in an increasingly multidisciplinary industrial setting where the scientific challenges are becoming less well-defined and the means by which we address the challenges ever more varied and complex.[7] Foremost amongst these skills is the ability to develop partnerships with scientists from other disciplines and to capitalise on such relationships to help identify opportunities for collaboration. Such projects would also be expected to help develop problem-solving and learning skills, cultivate a flexible approach to research and establish an appetite for new challenges.

Conclusions

Postgraduate research training in UK university departments has historically delivered students equipped to succeed in the industrial environment and to contribute to knowledge- and wealth creation. In a rapidly changing environment, the EPSRC Grand Challenges funding strategy could provide a valuable mechanism for signposting areas that would benefit from cross-discipline collaboration. The benefits for organic chemistry of engaging in collaborative research are wide-reaching, both with respect to the types of challenges that can be tackled as well as the research skills that emerge. Key to success is to ensure an effective partnership is maintained across the key stakeholders (academics, funding bodies, professional bodies and industry) through this period of transition.

David Fox, Pfizer
Tony Wood, Pfizer
Paul Leeson, AstraZeneca
David Lathbury, AstraZeneca
David Hollinshead, AstraZeneca
Simon Macdonald, GSK
Phil Jones, Schering-Plough
Luis Castro, Eisai
David Rees, Astex Therapeutics
Keith Jones, Institute of Cancer Research

References

1. It is important to note that this article focuses specifically on the pharmaceutical industry as a partner and customer and that other key industrial sectors will have a different set of challenges and priorities.

2: Chemistry at the Centre: an International Assessment of University Research in Chemistry in the UK
http://www.epsrc.ac.uk/AboutEPSRC/IntRevs/2002ChemIR.htm

3: Face to Face: the UK Chemistry Biology Interface
http://www.rsc.org/ScienceAndTechnology/Policy/Documents/facetoface.asp

4. Refer to article on funding crisis in November issue of Chemistry world
http://www.rsc.org/chemistryworld/News/2008/October/20100801.asp

5. The group included representatives from Astex, AstraZeneca, Eisai, ICR, GSK, Pfizer and Schering

6: This is also the basis behind the complementary Roadmap initiative being led by the RSC
http://www.rsc.org/ScienceAndTechnology/roadmap/

7: See, for example, RSC policy bulletin Issue no. 10 October 2008
http://www.rsc.org/images/Bulletin10_tcm18-134605.pdf