Chem Soc Rev

Dynamic Article Links

Cite this: *Chem. Soc. Rev.*, 2011, **40**, 4269–4270

www.rsc.org/csr

EDITORIAL

Small molecules in biology†

Ali Tavassoli,[a] Andrew D. Hamilton[b] and David R. Spring[c]

DOI: 10.1039/c1cs90028e

We live in the post-genomic era, with ever-increasing information on the components of living systems being continuously uncovered and reported. Simultaneous advances in analytical and biophysical techniques have enabled the structure and function of many of these newly identified systems to be deciphered. To bridge the gap between this newly uncovered information and new therapies and therapeutics, a detailed understanding of chemical processes and the ability to prepare a multitude of small molecules is essential. Multidisciplinary research at the interface of chemistry and biology, and the utilization of chemical tools and small molecules to probe biological systems are therefore key to delivering on the promise made by the recent advances in biology. This issue focuses on a number of significant recent topics that illustrate the above.

Protein–protein interactions are increasingly considered to be important points for intervention in the development of novel therapies for a variety of diseases. The discovery of small molecule inhibitors of these interactions by high-throughput screening has recently been a key issue. Heeres and Hergenrother (DOI: 10.1039/B923660K) review emerging technologies, including photonic crystal biosensors, that can be used to develop new high-throughput screens to discover protein–protein interaction modulators.

[a] *School of Chemistry, University of Southampton, Southampton, SO17 1BJ, UK*
[b] *Department of Chemistry, University of Oxford, Mansfield Road, Oxford, OX1 3TA, UK*
[c] *University of Cambridge, Department of Chemistry, Lensfield Road, Cambridge, CB2 1EW, UK*

† Part of the themed issue on small molecules in biology.

Ali Tavassoli

Ali is currently a Reader in chemical biology at the University of Southampton, jointly appointed to the School of Chemistry and the Cancer Research UK Centre at the Faculty of Medicine. Ali started his scientific career with a BSc in Chemistry (1995) at Bristol University, and a PhD at Reading University (1999) with Professor Joe Sweeney, followed by a postdoctoral fellowship at Sussex University (1999–2001) working with Professor Douglas Young. He then moved to the Pennsylvania State University (2001–2006), to work with Professor Stephen Benkovic on a variety of projects, including the development of compounds that inhibit de novo purine biosynthesis. In 2006 he joined the University of Southampton as a lecturer in chemical biology, being promoted to a Readership in 2011. Ali is the recipient of the silver medal for European Young Chemist (2008) from the European Association for Chemical and Molecular Sciences, and a Cancer Research UK Career Establishment Award (2008–2013). His research spans the interface of chemistry and biology, using chemical tools and biological methods to probe, understand and target the cellular protein interaction network for therapeutic purposes. His research group is also active in the field of synthetic biology, developing approaches for the chemical synthesis of genes and genomes.

Andrew D. Hamilton

Andrew D. Hamilton is currently the Vice-Chancellor and Professor of Chemistry at the University of Oxford. His research interests lie at the interface of organic and biological chemistry, with particular focus on the use of synthetic design for the understanding, mimicry and potential disruption of biological processes. Professor Hamilton, read chemistry at the University of Exeter. After studying for a master's degree at the University of British Columbia, he received his PhD from Cambridge University in 1980 and then spent a post-doctoral period at the Université Louis Pasteur in Strasbourg. In 1981 he was appointed Assistant Professor of Chemistry at Princeton University then in 1988 served as a department chair and Professor of Chemistry at the University of Pittsburgh. In 1997 he became the Benjamin Silliman Professor of Chemistry and Professor of Molecular Biophysics and Biochemistry at Yale University, where he was Chair of the Chemistry Department from 1999 to 2003 and was Provost of Yale from 2004 until October 2008. In 2009 Professor Hamilton became currently the Vice-Chancellor and Professor of Chemistry at the University of Oxford.

Metabolism in microorganisms and animals relies on B_{12}-derivatives for a variety of important processes. Gruber, Puffer and Kräutler (DOI: 10.1039/C1CS15118E) illustrate the structure and reactivity of B_{12}-derivatives and describe their numerous interactions with proteins and nucleotides.

Molecular methods that enable the selective functional control of biological components are excellent tools and also of potential therapeutic benefit. Beharry and Woolley (DOI: 10.1039/C1CS15023E) describe the use of azobenzene as a photoswitch in biological systems through its ability to drive functional change in peptides, proteins, nucleic acids, lipids and carbohydrates. Højfeldt, Van Dyke and Mapp (DOI: 10.1039/C1CS15050B) explore the rational design of small molecules that can be used to activate or repress specific genes at the transcriptional level.

Peptides are critical in biology. Synthetic versions and mimetics have a huge potential in that they can be designed and avoid limitations of biological production. Boyle and Woolfson (DOI: 10.1039/C0CS00152J) review the building blocks used in *de novo* peptide design and the subsequent materials that have been produced such as hydrogels and virus-like particles. Ko, Liu and Burgess (DOI: 10.1039/C0CS00218F) discuss the concepts of minimalist and universal peptidomimetics and highlight their advantages in the discovery of biologically active agents.

Teratogenic small molecules have been effectively used to study developmental biology. Sakata and Chen (DOI: 10.1039/C1CS15019G) provide an overview of the chemical tools involved, and outline the current challenges and possible future directions for the research.

The hypoxia response network and the hypoxia inducible factor play vital roles in cancer, which has led to their being targets for small molecule intervention and potential therapeutic design. Nordgren and Tavassoli (DOI: 10.1039/C1CS15032D) discuss the system and describe the development of small molecules that disrupt the pathway and their potential as anticancer drugs.

Boron containing small molecule therapeutics represent an increasingly important area, not least due to the impact of the boronic acid drug Velcade®. The use of boron in the inhibition of enzymes is discussed by Baker, Tomsho and Benkovic (DOI: 10.1039/C0CS00131G).

2-Oxoglutarate dependent oxygenases are involved in numerous processes such as fatty acid metabolism, DNA repair, RNA modification and hypoxic sensing. The development of small molecule modulators of 2-oxoglutarate dependent oxygenases is a rapidly developing area. Rose, McDonough, King, Kawamura and Schofield (DOI: 10.1039/C0CS00203H) review the field, focussing on small molecule inhibitors as chemotherapeutic agents.

Genetic information for all organisms is stored in DNA and RNA, which can be damaged by UV irradiation commonly resulting in bipyrimidine formation. Heil, Pearson and Carell (DOI: 10.1039/C000407N) provide an overview of the synthesis and biological effects of such oligonucleotides.

Chemical genetics is the study of biological systems using small molecule intervention, instead of only genetic intervention. Selective and cell-permeable small molecules can potentially be used to perturb protein function rapidly, reversibly and conditionally with temporal and quantitative control in any biological system. O' Connor, Laraia and Spring (DOI: 10.1039/C1CS15053G) introduce the field and highlight recent developments.

The interface of chemistry and biology, as led by scientists with a chemical background, is an exciting place for research. This issue should be a useful introduction to the area and provide inspiration and encouragement for further reading and involvement.

Finally, we would like to express our appreciation to the authors, for their expert contributions and cooperation with this project. Also, we wish to acknowledge the Editorial board members for support, and especially the Editor Robert Eagling and Deputy editor Joanne Thomson for their help and guidance with the production of this issue.

David R. Spring

David R. Spring is currently a Reader at the University of Cambridge within the Chemistry Department and a Fellow of Trinity College. He gained his BA (Hons) and MA in Chemistry (1995) from the University of Oxford, where he also achieved his DPhil (1998) for work on the proposed biosynthesis of the manzamine alkaloids under the supervision of Sir Jack E. Baldwin. He then moved to Harvard University to work with Stuart L. Schreiber as a Wellcome Trust Postdoctoral Fellow and Fulbright Scholar (1999–2001), after which he joined the faculty at the University of Cambridge as a BBSRC David Phillips Fellow (2001–2006) and an EPSRC Advanced Fellow (2006–2011). He was promoted to a University Lectureship in 2006, to a Senior Lectureship in 2008 and to a Readership in 2011. Dr Spring's research spans the disciplines of chemistry and biology through the synthesis of small molecules, which are applied to problems in the life sciences. In particular, he has focused on diversity-oriented synthesis, new synthetic methodologies and chemical biology in order to discover new antibiotics and anticancer drugs. In addition, he has developed microarray technologies for high throughput small molecule synthesis and screening.

