Focus on chemical systems biology

Chemical biologists are exploring biological phenomena of greater complexity and systems biologists are increasingly adopting chemical tools. At the same time, both fields have begun to investigate, often with different techniques and perspectives, the potentially pleiotropic biological effects of small molecules. In this issue, we highlight a number of exciting areas at the emerging interface of systems and chemical biology.

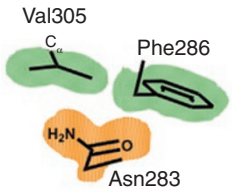
Understanding the components and dynamics of cellular networks is essential for a global view of cellular function. Russell and Aloy [**Review, p. 666**] discuss interaction networks and the ways in which these maps are currently being exploited for applications from biomedicine to synthetic biology. For a few well-studied prokaryotic systems, computational modeling of large collections of genomics data has been used to successfully predict the dynamic response of the organism to genetic or environmental perturbations. Bonneau [**Perspective, p. 658**] describes computational methods for deciphering regulatory networks and discusses the outlook for extending these approaches to metabolomic and proteomic data and across a wider range of species. The importance of integrating multiple levels of omics data is highlighted by the significant differences observed between quantitative proteomic and RNA interference data in *Drosophila melanogaster* [**Research Highlights, p. 657**]. Proteomic approaches are contributing to a better understanding of apoptosis with two reports doubling known caspase substrates [**News & Views, p. 651**].

Chemical tools, with their potential for rapid and dose-dependent action, are proving to be important for systems-wide approaches to understanding biology. Simon and Cravatt [**Commentary, p. 639**] highlight chemical methods, including global approaches for profiling post-translational modifications and enzyme activity, that are particularly promising chemical parts in the systems biology toolbox. Zamir and Bastiaens [**Commentary, p. 643**] describe how chemical perturbations can be combined with quantitative detection and a recently developed mathematical approach to gain new insights into the dynamics of intracellular signaling pathways. Lehár, Stockwell, Giaever and Nislow [**Review, p. 674**] describe how combinations of chemical-genetic or chemical-chemical perturbations can advance chemical genetics from investigating protein function to probing pathway structure. "Systems chemistry" is also contributing to our understanding of molecular interaction networks at the chemical level [**News & Views, p. 654**].

A systems-level understanding of biology can provide new approaches for targeting disease and for understanding drug action. For instance, metabolomics approaches have recently been used to identify palmitoleate as a new adipose lipid hormone with an important role in regulating systemic metabolism and, in a separate study, to implicate fatty acid synthesis as a potentially broad-spectrum antiviral target [**Research Highlights, p. 657**]. Hopkins [**Review, p. 682**] puts forth the case for targeting perturbed disease networks rather than disease-causing genes and describes the new chemical challenges that emerge in seeking to design small molecules that act on multiple targets. In a step towards rational polypharmacology, Apsel *et al.* [**Article, p. 691; News & Views, p. 648**] design compounds that selectively target Src, a tyrosine kinase, and PI(3)K, a lipid kinase, and then investigate the biological effects of these dual inhibitors. Finally, Peterson [**Commentary, p. 635**] proposes that chemical biologists could benefit from embracing a systems biology perspective and moving away from a one molecule–one target mindset towards an 'integrationist' view of small-molecule action.

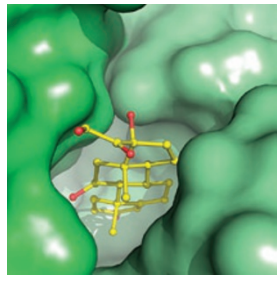
We hope that these articles highlight the exciting advances at this interface, and we look forward to seeing more 'chemical systems biology'. *JK*

Second-shell selectivity



Nitric oxide (NO) is an important signal in several biological processes, including thermoregulation and neurotransmission, and must be carefully controlled *in vivo* to avoid mild to severe physiological consequences. NO is produced by one of three nitric oxide synthase (NOS) isoforms, each of which has distinct physiological roles. The selective inhibition of these enzymes has been complicated, however, by their significant sequence conservation. Now Garcin *et al.* determine multiple NOS-inhibitor cocrystal structures, the analysis of which indicates that variable second- and third-shell residues differentially allow the conformational rearrangements of conserved active site residues. The authors use this information to develop a new, iNOS-selective inhibitor using an 'anchored plasticity' approach in which binding energy is gained from interactions with a core chemical structure but specificity is determined by substituents that rely on unique second-shell residues to control protein motions. [**Article, p. 700**] *CG*

Potentiated potassium channels



The voltage-gated Shaker channel, Kv1, opens in response to membrane polarization, releasing K^+ ions and restoring ion balance. The Kvβ subunit gates Kv1 channel openings through a 'ball-and-chain' mechanism, in which binding of the 'ball' blocks the pore of the channel, thereby limiting the duration of action potentials. Although this functional coupling requires that Kv1 and Kvβ be intimately associated (and indeed their disassembly has not been observed), Pan *et al.* report their serendipitous discovery that cortisone can dissociate the Kv1-Kvβ complex. Cortisone-dependent dissociation prolongs Kv1 pore opening and increases the intensity of action potentials. X-ray crystal structures reveal that Kvβ contains two cortisone binding sites. Mutagenesis and channel recordings indicate that one site, located at the protein-protein interface, is the relevant target site. It is unclear whether cortisone reaches sufficient concentrations *in vivo* to modulate Kv1 channel activity, but this report demonstrates that disruption of channel subunit assembly may be a mechanism for physiological regulation and drug intervention. [**Article, p. 708; News & Views, p. 650**] *AD*

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