ELSEVIER

Exploring the Milky Way of molecular diversity
Combinatorial chemistry and molecular diversity

Editorial overview

Gregory A Weiss

Current Opinion in Chemical Biology 2007, **11**:241–243

1367-5931/$ – see front matter
Published by Elsevier Ltd.

DOI 10.1016/j.cbpa.2007.05.022

Gregory A Weiss

1102 Natural Sciences 2, Departments of Chemistry, Molecular Biology and Biochemistry, University of California at Irvine, Irvine, CA 92697-2025, USA
e-mail: gweiss@uci.edu

Gregory Weiss' research focuses on using combinatorial libraries of proteins and small molecules to develop next-generation anti-viral compounds, soluble membrane protein variants and virus-based electronic biosensors.

As ''continuous as the stars that shine and twinkle on the Milky Way'' (William Wordsworth; 1804. *The Daffodils*), the molecular diversity found in Nature is staggering in its numbers and complexity. However, such an awe-inspiring portfolio has been at least matched by the ingenuity of chemical biologists. The $\approx 10^{11}$ stars in the Milky Way, for example, are surpassed in number by the net diversity of the thousands of phage, yeast, mRNA, bacteria, ribosome, DNA and other molecular display libraries routinely synthesized by chemical biologists. Experiments leverage molecular diversity to understand the wide range of molecules found in biology or to solve problems in chemistry. This issue focuses largely on practical applications of molecular collections, from catalyst discovery to mapping cell-surface carbohydrates.

The theoretical diversity of small-molecule structures can be visualized as a staggering vastness, far exceeding, for example, the number of particles in the galaxy. However, not all chemical diversity space offers the same potential for the development of useful compounds. **Shelat and Guy** plumb this diversity space to map productive areas that generate known functional compounds. The topic, of course, creates tremendous interest amongst drug discovery researchers and many metrics for weighing productivity in chemical diversity have been offered. This provocative review compares measurements used for assessing library quality, and concludes with a clarion call for new small-molecule libraries and approaches. Applying such libraries to cells, **Emre, Coleman and Ding** connect small molecules with stem cells, and describe efforts to target specific cell differentiation pathways in the quest for the discovery of functional small molecules.

Chemists can't help but envy natural evolution. The 'lost in chemical diversity space' problem can be solved quite simply using the natural evolution approach. A productive molecular scaffold can nucleate diversification of combinatorial space, and multiple rounds of mutagenesis followed by selection can optimize function to satisfy any number of complex requirements. **Rozenman, McNaughton and Liu** survey initial attempts by chemists to harness principles of evolution to solve chemical problems. Their wide-ranging report describes spectacular examples of *in vitro* evolution used to uncover new catalysts, synthetic reactions, small molecules and even materials.

Even without the mutagenesis-selection cycles of evolution, molecular diversity offers a vast source of new catalysts. **Revell and Wennemers** describe peptide catalysts, which often require combinatorial techniques to discover, optimize and screen. Though enzymatic catalysis garners most

of the attention in chemical biology, this review describes the impressive range of reactivity and even specificity (stereo, regio and otherwise) accessible to catalysis by short peptides. Significantly, the issues in harnessing molecular diversity to uncover new catalysts for chemical transformations resemble the challenges faced when using similar techniques to examine biological systems. Thus, this review highlights a number of ingenious approaches to solve long-standing problems, which could prove inspirational to researchers in unrelated areas.

One approach to capturing the tremendous potential of natural products in chemical biology simply hijacks the cellular biosynthetic machinery. **Watanabe, Praseuth and Wang** focus on engineering the type III family of polyketide synthases, responsible for the synthesis of aromatic plant pigments by a single-domain ketide synthase. This class of enzyme offers particularly good prospects for the generation of unnatural product libraries. In addition to the relatively small size and single domain of type III polyketide synthases, details of the enzyme mechanism and structure have been elucidated and are reviewed. Such studies set the stage for the development of new unnatural product libraries, though the authors also note the caveats and challenges required to accomplish this goal.

Metal complexes in chemical biology remain a relatively unexplored area of chemical diversity space. **Meggers** charts this space, noting that transition metals can provide a rigid scaffold upon which a variety of different ligands can be hung. Such well-defined shapes can then bind and perturb proteins and other targets usually not considered within the province of receptors for metal complexes. The review concludes with a challenge to the field to leap beyond mere binding to encompass the full range of activities possible with metal complexes — catalysis, condition adaptability and reactivity.

The genome, perhaps the most mined of the biopolymers, offers a diverse set of targets to interact with DNA alkylating agents. **Sturla** suggests that the resultant 'adductome' could fingerprint the complex reactivity and phenotypic effects of multisite-reactive anti-tumor agents, amongst other DNA-damaging compounds. Beyond mere alkylation, DNA offers a rich array of reactive functionalities for covalent modification. The combinatorial possibilities, including sites, reactive compounds and resultant adducts, truly appear endless. In addition, bioorganic chemistry instructors can harvest a rich source of exam questions from this review.

The major focus in chemical biology, characterization of and control over biological function, requires new analytical techniques to fingerprint the carbohydrate-rich surfaces of cells. Such challenges can leverage the molecular diversity of microarrayed recognition scaffolds for Braille-like reading of otherwise intractably complex diverse polysaccharides. **Pilobello and Mahal** describe the latest intersection of mass spectrometry and microarrays to decipher the glycome. A sweet spot for new molecular-diversity-based techniques, the field's recent advances open a window onto a fundamental area of biology, and the future requirements for the field could draw from systems described elsewhere in this issue.

Also highlighting the use of microarrays in chemical biology, **Maynard, Myhre and Roy** examine powerful new protein microarrays used to explore infection and immunity. The increasing complexity of the arrayed species expands the scope of biological questions addressed. For example, a microarray of soluble MHC–peptide molecules (p-MHC) resembles a parade of immunological synapses, complete with the required co-stimulatory molecules and cytokines. The relatively modest numbers of arrayed elements in such examples (seven in the case of the p-MHC array) suggests the nascence of the field. However, given the potential for massive parallelization and insights obtained from other high diversity arrays (e.g. DNA microarrays), the approach seems certain to attract a lot of interest.

Molecular diversity from large collections of RNA and DNA is poised to revolutionize sensor applications. **Fischer, Tarasow and Tok** explore how aptamers can solve problems in biosecurity. Significant progress has been made fusing aptamers that switch conformation upon analyte binding directly into electronic biosensors, but the authors note areas where challenges remain. A microfluidics-based device for rapid selection of binding partners from aptamer libraries could turbocharge the fairly laborious and time-consuming process of fishing winners from combinatorial libraries. Such a device could have enormous impact on all molecular display systems, which face similar difficulties.

Given the practical limitations constraining even the most diverse protein libraries, computational protein design has emerged as a powerful method for focusing the search for new protein functions and properties from combinatorial libraries. **Kang and Saven** describe a wide range of different functions engineered into proteins with guidance by computational techniques. Striking examples include solublization of membrane proteins, and incorporation of non-biological amino acids and cofactors into proteins. Selections and screens for complex protein functions can require manageable diversity numbers, and **Barakat and Love** examine the synergy between selections for new protein function and computational design. **Wright, Heins and Ostermeier** focus on engineering conformational switching into proteins and suggest that proteins are primed to exhibit allostery. Such abilities, both computational and inherent to the proteins themselves, could expand the range of functions selected from protein libraries.

Vast libraries of phage-displayed proteins also offer a test bed for reverse engineering and developing new protein functions. Shotgun scanning, a turbocharged form of alanine scanning, applies diverse libraries of alanine-substituted proteins. Selections for target binding with such libraries can often quickly identify key sidechains required for protein binding. **Sidhu and Kossiakoff** review this powerful approach to protein function mapping. In addition, they examine other protein libraries with restricted diversity. The latter approach promises to simplify receptor engineering and demonstrates the remarkable malleability of molecular recognition.

The wide range of topics covered in this special section illustrates the scope of important contributions to chemical biology offered by experiments leveraging molecular diversity. Notably, this issue also offers a veritable who's who of young chemical biologists, both established and up-and-coming. With important ideas and innovators emerging, the future looks as bright and vast as the Milky Way.