Expanding nature’s chemical repertoire through metabolic engineering and biocatalysis

Editorial overview
Ben Shen and Jon S Thorson

Ben Shen
The Scripps Research Institute, 130 Scripps Way, #3A1, Jupiter, FL 33458, United States
e-mail: shenb@scripps.edu

Dr Ben Shen is a Professor in the Departments of Chemistry and Molecular Therapeutics and the Director of the Natural Products Library Initiative at the Scripps Research Institute. Before joining Scripps Florida, Dr Shen was a faculty member in the School of Pharmacy and Department of Chemistry, University of Wisconsin-Madison (2001–2010) and in the Department of Chemistry, University of California, Davis (1995–2001). His research interests include the chemistry, biochemistry, and genetics of natural product biosynthesis in actinomycetes, natural product discovery from underexplored microorganisms, and natural product-based anticancer and anti-infective drug discovery.

Jon S Thorson
Center for Pharmaceutical Research and Innovation, University of Kentucky College of Pharmacy, 789 South Limestone Street, Lexington, KY 40536-0596, United States
e-mail: jsthorson@uky.edu

Dr Jon Thorson is a Professor in the Department of Pharmaceutical Sciences and the Director of the Center for Pharmaceutical Research and Innovation at the University of Kentucky. Before recently joining UK, Dr Thorson was a faculty member in the School of Pharmacy, University of Wisconsin-Madison (2001–2011) and before that, held an appointment with the Sloan-Kettering Division, Joan and Sanford I. Weill Graduate School of Medical Sciences, Cornell University (1996–2001). His research interests include understanding and exploiting biosynthetic pathways/enzymes, chemoselective chemistries for natural product diversification, and enzyme engineering/evolution.

Natural products have coevolved with proteins that bind them to enable strategies for exquisite control of biological phenomena. It is therefore not surprising that natural products have emerged as a major source for chemical diversity in the context of both chemical genetics and lead structures for modern drug discovery [1–5]. It has been estimated that as many as 50% of marketed small molecule drugs have been derived from natural products [4,5]. Yet, while recent analyses have also revealed natural products to offer a vast range of chemical diversity that is nearly or completely absent from current small molecule-based screening libraries [6,7], the pharmaceutical industry has dramatically de-emphasized natural product-based drug discovery efforts in the last decade citing a range of reasons including difficulties in synthesis/medicinal chemistry due to the often greater structural complexity, low natural abundance, and/or tedious purification. The result has been an increasingly widening gap between the desire for inclusion of natural products and the actual availability of such privileged scaffolds as biological probes, screening tools, and/or drug leads [8]. This thematic issue highlights selections of cutting edge research programs which strive to simplify access to natural product-based chemical entities and merge nature’s and medicinal chemist’s common goal of extending privileged scaffold diversity toward optimization of desired biological outcomes.

A significant challenge to sustaining and expanding natural products discovery programs are strategies to speed dereplication, limit redundancy and expand uniqueness in existing repositories. Toward this goal, Osaka and coworkers highlight the RIKEN efforts to date to combine chemoinformatics and bioinformatics to guide the compilation of the RIKEN NPDepo (a public repository which contains nearly 20 000 natural product-based members). The microbial bioinformatics component of this effort also serves as a basis for studies to understand and exploit biosynthetic pathways and/or enzymes to achieve precursors and/or analogs of novel scaffolds. While these strategies primarily focus upon culturable microorganisms as a source, Brady and collaborators describe the current state of the art for metagenomics in the context of small molecule and biocatalyst discovery. This article highlights both the current technologies/successes and key challenges of using genetic material from uncultured organisms—a remarkable, largely untapped, resource that promises to play an increasingly larger role in bioprospecting.

As the availability of microbial genetic information grows at an exponential rate, the challenge in the context of natural products discovery is how to exploit this information toward generating new chemical entities. Such genetic information serves as a rich source for innovation in both...
Despite current metabolic pathway engineering and biocatalysis toolbox expansion. In the context of metabolic pathway engineering, Khosla and coworkers provide a thoughtful review on the current state of the art in polyketide-based combinatorial biosynthesis and put forth an innovative challenge, reminiscent of the CASP (Critical Assessment of Techniques for Protein Structure) protein structure challenge, to spur the development of new tools and algorithms.

A major bottleneck for translating the information gleaned from an ever growing sequence database into useful tools for the production of novel natural products remains functional gene annotation. This issue highlights recent work that has shed light on a number of new enzyme-catalyzed transformations involved in natural product biosynthesis. Liu and collaborators describe studies to provide definitive proof for enzymes capable of catalyzing pericyclic [4 + 2] cycloaddition reactions — a tantalizing, yet elusive, catalyst in nature that may offer significant potential in chemoenzymatic syntheses. Shen and his team, through functional annotation and database analysis, teach us that bacteria are much more prolific as producers of diterpenoids — natural products historically labeled as plant metabolites. In the context of nonribosomal peptide synthetase (NRPS)-related chemistries, Oikawa and coworkers highlight a remarkable range of reactions, facilitated by the single catalyst SfmC, en route to the tetrahydroisoquinoline saframycin A. An additional cautionary note regarding how the sole reliance upon in vivo genetics can lead to misannotation is highlighted by Rohr and colleagues. This article summarizes recent examples of how multi-enzyme in vitro reconstitution studies helped decipher key steps in aromatic polyketide oxidative rearrangement reactions and novel sugar transformations. In parallel, Bruner and associates point to the value of structural biology in guiding both functional annotation and catalyst engineering and also highlight the importance of applying high throughput structural biology initiatives toward targets found within natural product biosynthetic pathways.

Despite notable progress in the field, continued innovation is required in natural product diversification. Natural product-based discovery programs must deliver novel compounds at a pace that can meet the demands of high throughput functional screening and compete with the speed of alternative library generation strategies such as combinatorial chemistry or diversity-oriented synthesis. One way to begin to achieve this is via chemoenzymatic and/or precursor-directed strategies. Such methods merge a key strength of synthetic organic chemistry (namely, to quickly generate diverse sets of precursors) with the power of enzyme catalysis (specifically, the ability of enzymes involved in natural product biosynthesis to efficiently incorporate these precursors into a highly complex scaffold). As representative examples, Li and coworkers highlight novel recent examples of chemoenzymatic syntheses in the context of glycopeptide antibiotic discovery while Abe highlights the power of type III polyketide synthases in the context of precursor-directed biosynthesis. Innovation can also be found within altering the biocatalysis format. For example, Dordick and colleagues review emerging strategies for in vitro biocatalysis, many of which are specifically designed to directly complement downstream high throughput screening platforms. Last but not least, innovation can be found by stepping out from the confines of conventional biosynthesis paradigms as exemplified via the elegant applications by Suga and coworkers of ribozymes in the synthesis of natural product-like nonproteinogenic-containing macrocycles.

While the work encompassed within this thematic issue is representative of a much broader swath of innovation and discoveries happening every day in the field of natural product-based discovery programs around the world, it clearly points to a vibrant and optimistic future for the field.

References