

## Natural Products and Production Systems: Opening Comments

Natural products have served an unquestioned role in providing new therapeutic drug compounds. Several studies have emphasized the impact natural products have had in producing antibiotic and anticancer therapies.<sup>1,2</sup> However, while these represent perhaps the most significant bioactivities associated with natural products, other medicinal outlets include cholesterol-lowering, immunosuppressant, and antifungal activities. In summary, there is no doubt that natural products have paid dividends in current medicine, and there is also no doubt that their medicinal properties continue to drive current research.

However, there are several challenges associated with realizing the medicinal potential of natural products. At one level, there are fundamental questions related to the origins, cellular regulation, and biosynthesis of natural products. Such fundamental knowledge, once gathered, then supports more applied efforts at natural product production. Production efforts are also fraught with issues that include isolating and successfully culturing the biological sources responsible for natural products, scaling processes based upon natural product biological sources, applying both process and metabolic engineering for enhanced production, and isolating and producing new compounds predicted to exist in nature. These issues are key research areas that are crucial for further unlocking or expanding the potential of natural products.

Adding to the challenges of studying natural products are the range of natural product systems and sources under study. Terpenoids (and isoprenoids), polyketides, nonribosomal peptides, and flavonoids have emerged as natural product classifications with both established and potential therapeutic impact, yet, each system is uniquely defined by its own characteristic molecular architectures and biosynthetic mechanisms, making it difficult for researchers within a particular niche of the natural products field to be fully updated on each system and even more challenging for the nonspecialist. Closely related to the diversity of natural products are the natural hosts that produce them. Ultimately, all natural products can be traced back to natural environments, and within those environments are the organisms responsible for natural product biosynthesis. More noted sources include plants, bacteria, and fungi with the soil and marine environ-

ments recognized as consistent locations for the isolation of medicinally relevant natural compounds.

With a growing understanding of the types of medicinal natural products made available through nature and their respective natural sources, both research and production efforts were launched in an attempt to provide significant amounts of natural compounds to be used in clinical settings. The efforts were complicated by the complex molecular architectures associated with many natural compounds, limiting economic chemical—synthetic routes to many of the compounds of interest and prompting production options that instead relied on native biological sources for natural product biosynthesis. However, many plant, bacterial, or fungal sources were difficult to culture and/or manipulate for the maximal production of a desired natural compound. The potential of natural products was then tempered by the practical challenges of mass-producing such compounds for widespread therapeutic use. These same limitations also tempered both industrial and academic enthusiasm for research and funding related to natural products.<sup>3</sup>

Yet, natural products were still considered promising candidates for new medicinal drugs and a recent re-emergence of fundamental and applied studies have opened new avenues for effective production. This issue then serves two purposes: (1) to highlight this re-emergence and detail the primarily recent advances in accessing medicinal natural products and (2) to provide a comprehensive overview (to both the specialist and nonspecialist) on natural products and the biological options for their production. In so doing, the issue will highlight the potential and therapeutic range associated with four important classes of natural products (terpenoids, flavonoids, polyketides, and nonribosomal peptides) and also detail emerging biological production options for these natural product classifications that feature bacterial, fungal, and plant host systems.

Several experts have contributed to the issue with articles that detail the four natural product classifications to be profiled, often in the context of the author's own specific research area. Dr. Michael Thomas has provided an excellent overview on nonribosomal peptides using a historical perspective to explain biosynthetic schemes and clinical use. Dr. Clay Wang provides an overview on polyketides with emphasis placed on those produced through fungal sources. Dr. Gregory Stephanopoulos offers an article on terpenoid

(1) Newman, D. J.; Cragg, G. M.; Snader, K. M. Natural products as sources of new drugs over the period 1981–2002. *J. Nat. Prod.* **2003**, 66 (7), 1022–37.

(2) Newman, D. J.; Cragg, G. M. Natural products as sources of new drugs over the last 25 years. *J. Nat. Prod.* **2007**, 70 (3), 461–77.

(3) Koehn, F. E.; Carter, G. T. The evolving role of natural products in drug discovery. *Nat. Rev. Drug Discov.* **2005**, 4 (3), 206–20.

natural products and recent advances by his laboratory on heterologous production options. And, finally, Dr. Mattheos Koffas describes flavonoids and recent work associated with their biological production options.

Meanwhile, a second subset of authors will focus more on the biological options for natural product production. Dr. Susan Roberts highlights the use of plant cells as options for production. Likewise, Dr. Dirk Hoffmeister reviews recent advances in fungal host systems used for natural product production. Finally, Dr. Blaine Pfeifer has prepared an article summarizing the use of bacteria as hosts for production purposes. These articles highlight both the native and heterologous biosynthetic potential of three popular host systems for natural product mass-production. Each host system has particular advantages and disadvantages related to natural product biosynthesis, and when used as heterologous host systems, these advantages and disadvantages can often be correlated to the type and origin of the natural product pathway to be reconstituted.

To summarize, this issue is meant to offer a comprehensive view of natural products and their production options. In so doing, individual articles will highlight the medicinal impact and potential associated with natural products as well as the challenges associated with accessing this medicinal range.

Readers, both familiar and unfamiliar with the natural products field, will find articles describing four significant classifications of natural products and three additional articles describing biological production options. At one level, the issue then offers a wide-spanning summary of the natural products field, again, applicable to readers who study a small subsection of this field and desire a better understanding of other classifications and/or production options and also to readers outside the natural products field who desire a comprehensive review of current fundamental and applied knowledge and research. At another level, the issue will feature an up-to-date account of renewed success in understanding and exploiting the medicinal potential of natural products and an echoed sentiment that these compounds have had and will continue to have a significant impact on the production of medicinal therapies.

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