Editorial

Special Series: Natural Products at the Core of Drug Discovery

Over the past century, the plant kingdom as well as the marine and microbial worlds have provided scientists with a plethora of small molecules. With their unique and diverse structural scaffolds, these natural products have inspired chemists, biochemists, biologists, and microbiologists alike and not only provided the mankind with life-saving antimicrobials, but also contributed to the development of new chemical and biochemical tools. The broad range of biological properties has also kept Nature's small molecules at the core of the drug discovery process.[1] With many more natural products to be discovered,[2] chemically or chemoenzymatically modified, or genetically engineered,[3] this remains an active area of research. In these exciting times where the ever expanding genomic information,[4] high-throughput and bioinformatics[5,6] capabilities, mass spectrometry, X-ray crystallography, and NMR are widely accessible and getting more and more sophisticated, one can easily envision a variety of novel directions for future natural product research.

In this Special Series, experts in the fields of natural product synthesis, biosynthesis, isolation, identification, and production, provide the latest updates and discoveries in the study of natural products. These molecules can be divided into two classes: (i) the non-templated natural products that include alkaloids,[7–9] oligosaccharides,[10] and aminoglycosides[11] and (ii) the templated natural products that comprise the fatty acids (FAs),[12] polyketides (PKs),[13,14] and nonribosomal peptides (NRPs).[15,16] In this issue, a special attention is given to molecules that belong to the latter class. The fascinating modular biosynthetic logic utilized by fatty acid synthase (FAS), polyketide synthase (PKS), and nonribosomal peptide synthetase (NRPS) enzymes for the production of these structurally unique and diverse molecules has been and continues to be the focus of many research programs. Despite decades of extensive investigations directed towards the understanding of these complex machineries, multiple questions remain to be answered. Only recently, thanks to the power of X-ray crystallography, a clearer molecular picture of how these multi-enzyme complexes function has emerged.[17] In the years to come, it is predicted that a new trend in merging scientific disciplines related to natural product research will enable the development of new chemical, biochemical, and genetic tools as well as the discovery of novel natural products and analogs with potential therapeutic applications.

While navigating this Special Series, the reader should keep in mind the following questions: (i) where do natural products come from? (ii) what new tools are currently being developed for their study? (iii) how can one use what has been learnt to produce novel analogs of these compounds as potential therapeutics? and finally (iv) what is the future role of natural products in drug development and discovery? There are most definitely multiple good answers to these questions, and many more questions can come to mind.

In parallel to the extraordinary diversity of publications in the field of natural products, the manuscripts in this Special Series are intended to provide an overview of the latest and future trends in this ever-growing area of research. This issue of Biopolymers features three review articles that highlight the recent advances in our understanding of three different classes of polyketide and nonribosomal peptide natural products. Campbell and Vederas provide a thorough overview of the biosynthesis of the cholesterol lowering agent lovastatin and its related metabolites, whereas Du and his colleagues contribute an in-depth analysis of the polyketide-derived mycotoxins. Together, these reviews elegantly summarize the current knowledge associated with fungal iterative PKS enzymes. Garneau-Tsodikova and coworkers introduce us to the world of nonribosomal peptides with a comprehensive discussion on bisintercalator natural products, their biosynthesis, the novel strategies for the production of their analogs, and insight into bacterial resistance. This Special Series also features five research articles describing some of the latest discoveries in the field. Moon and Van Lanen present the exciting characterization of a unique adenylation enzyme with dual specificity and dual function involved in the biosynthesis of the dipeptide antifungal antibiotic nikkomycin. With their study of the tyrosine aminomutase *Sg*TAM, Cooke and Bruner nicely demonstrate how a combination of

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biochemical and structural studies can provide useful insights into the mechanism of action of enzymes. Following a conceptually similar approach, Campopiano and coworkers with their study of the serine palmitoyltransferase from *Sphingomonas wittichii* RW1 propose an interesting link between fatty acid and sphingolipid metabolism. Finally, two fascinating and insightful manuscripts by Heide and coworkers and Brady and coworkers describing novel methodologies for heterologous production of natural products demonstrate the future directions in the study of these molecules.

Overall, beyond the specific and complementary findings presented in the individual articles of this Special Series, we hope that other experts working on natural products will be inspired by these studies, and that readers that are new to the field will be encouraged to learn more about it and maybe even find their own niche of research in this amazing and continuously evolving resource of compounds that Nature provides us with.

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