Journal of
Medicinal
Chemistry

Volume 51, Number 9 May 8, 2008

Miniperspectives: Natural Products in Drug Disovery

Modern Natural Products Chemistry and Drug Discovery

Iwao Ojima[†]

Department of Chemistry and Institute of Chemical Biology & Drug Discovery, State University of New York at Stony Brook, New York 11794-3400

Received October 14, 2007

Historically, natural products chemistry and synthetic organic chemistry have been the driving force for drug discovery. Natural products chemistry has provided impressive "chemical diversity space". The secondary metabolites of diverse life forms have potent biological activities and have provided lead compounds in drug discovery for the treatment of cancer, microbial infections, inflammation, hypercholesteremia, and tissue rejection in organ transplantation. Also, these natural products have provided a number of extremely useful tools to molecular pharmacologists and cell biologists.

However, classical natural products-based drug discovery through extraction, assay-based functional fractionation, isolation, characterization, and target validation has been gradually replaced by molecular target-based drug discovery. This "modern approach" by means of high-throughput screening of large libraries of compounds, lead identification from hits, and lead optimization has become the main stream in the past 2 decades. The modern drug discovery also exploits computational biology and structural biology, i.e., in silico screening and in silico docking analysis of protein X-ray crystal structures.

It is surprising, however, that over the past 20 years there has been only one FDA-approved drug (sunitinib for renal carcinoma in 2005) resulting from high-throughput screening of combinatorial chemistry libraries followed by the optimization of hits. Thus, natural products-based drugs (parent compounds, derivatives, analogues, and mimics) are still major entities among the FDA-approved drugs (57.7% of all drugs). Nevertheless, the use of combinatorial chemistry or parallel synthesis for the optimization of highly promising lead compounds arising from more traditional drug discovery processes around "privileged structures" has been successful in many drug discovery and development cases. The focused library approach is especially beneficial for clearing ADME/Tox (absorption, distribution, metabolism, excretion and toxicology) requirements. Consequently, the molecular target-based drug discovery with continuous improvement in the quality and diversity of compound libraries has been steadily advancing. Along this line, modern natural products chemistry has been re-emerging as a highly promising provider of the adequately sophisticated lead structures for drug discovery. A combination of natural products chemistry and focused library synthesis furnishes a powerful tool for drug discovery. Also, it should be noted that "structural biology", "computational biology", "chemical biology", and "chemical genetics" are now fully incorporated into the modern drug discovery. With these modern "tools" in hand, it is a natural evolution in "chemical genetics" to promote structure-based rational drug design, exploring the diverse structures of natural products.

Moreover, the "combinatorial biosynthesis" and "gene mining" would provide fascinating approaches to modern drug discovery. Studies on cyanobacterial natural products have made it possible to access an unusually large number of mixed nonribosomal peptide synthetase/polyketide synthase (NRPS/PKS) systems, leading to the finding that the corresponding metabolic systems are comprised of complex multifunctional proteins that can generate structurally complex molecules via a modular multistep process. The detailed genetic and biochemical understanding of such biosynthetic pathways will eventually lead to the development of engineered NRPS/PKS systems that efficiently generate novel structures with significant potential as therapeutic agents. Furthermore, rapid development in

[†] Contact information. Phone: 631-632-1339. Fax: 631-632-7942. E-mail: iojima@notes.cc.sunysb.edu.

10.1021/jm701291u CCC: $40.75
Published on Web 04/05/2008

genomics has made quite a large amount of DNA sequence data available from a wide variety of organisms in publicly accessible databases. The "gene mining" approach exploits such data to characterize human physiological processes, to identify and validate new drug targets in human pathogens, and to discover new chemical entities from natural sources. Thus, this new gene technology would play a significant role in finding natural product-based new chemical entities (NCE) and lead compounds for drug discovery. In fact, "combinatorial biosynthesis" and "gene mining" are emerging as new technologies, which may bring about a significant paradigm shift in drug discovery.

This Miniperspectives series on natural products in drug discovery was made possible by Dr. William Greenlee, the Perspectives Editor of the *Journal of Medicinal Chemistry*, who asked me to select appropriate topics and authors for a special issue, following the very successful two-session symposium on the "Modern Natural Products Chemistry and Drug Discovery" at the 231st National Meeting of the American Chemical Society in Atlanta, GA, March 2006, sponsored by the Division of Medicinal Chemistry and the Division of Organic Chemistry.

Biography

Iwao Ojima received his Ph.D. from University of Tokyo, Japan in 1973. He was a Senior Research Fellow at the Sagami Institute of Chemical Research (1973–1983). At the Department of Chemistry, State University of New York at Stony Brook (1983−), he is a Distinguished Professor since 1995 and was Department Chairman in 1997–2003. In 2003, he became Director, Institute of Chemical Biology & Drug Discovery (ICB&DD). The following are some of his accomplishments. Publications: >650 (SciFinder), >350 papers and reviews, >150 patents and patent applications, 6 books. Awards & Honors: Arthur C. Cope Scholar Award (1994), Emanuel B. Hershberg Award (2001), Hall of Fame, Division of Medicinal Chemistry (2006) (American Chemical Society); The Chemical Society of Japan Award (1999); Outstanding Inventor Award (2002) (Research Foundation of the State University of New York); Fellow of the J. S. Guggenheim Memorial Foundation, the American Association for the Advancement of Science, and the New York Academy of Sciences.

JM701291U