ACCOUNTS
of chemical research

GUEST EDITORIAL

Modern Molecular Approaches to Drug Design and Discovery

It is an exciting time for chemists to be involved in all aspects of biomedical research. The word "molecular" has always been an integral part of chemistry, but it has gained a new appreciation from physicians and biologists, who have named emerging fields "molecular medicine", "molecular genetics", "molecular biology", "molecular bioengineering", "molecular cardiology", etc. Clearly, "chemistry" or "molecular science" has become the centerpiece of the modern biomedical research.

"Drug discovery" has historically been a stronghold of chemistry, especially natural products chemistry and synthetic organic chemistry. Chemistry is thus inherently well-positioned to have a major impact on drug discovery, since other disciplines cannot create novel small molecules. In other words, "drug discovery and development" cannot happen without chemists.

Classical natural products-based drug discovery, involving extraction, assay-based functional fractionation, isolation, characterization, and target validation has been gradually replaced by molecular target-based drug discovery. High-throughput screening of large libraries of compounds (including computer-based *in silico* screening), lead identification from hits (often using the *in silico* docking analysis of the protein X-ray crystal structures), and lead optimization have been in the mainstream for the last two decades. However, simple random high-throughput screening of a huge number of small molecule libraries generated by combinatorial chemistry has not produced expected results: there has been only one FDA-approved drug (sunitinib for renal carcinoma) from the high-throughput screening of combinatorial chemistry libraries followed by the optimization of hits. Thus, natural products-based drugs (parent compounds, derivatives, analogs, and mimics) are still major entities among the FDA-approved drugs (57.7% of all drugs). Nevertheless, combinatorial chemistry in the form of parallel synthesis or diversity-oriented synthesis (DOS) for the optimization of highly promising lead compounds 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.

Molecular target-based drug discovery with continuous improvement in the quality and diversity of compound libraries has been making steady progress. "Structural biology", "computational biology", "chemical biology", and "chemical genetics" are now fully incorporated into modern drug discovery through target-based approaches. With these modern tools in hand, rational drug design, exploiting combinatorial chemistry for focused libraries, becomes possible. Designing hybrid molecules bearing a dual mode of action is a good example and provides a promising approach to modern drug discovery. Discovery of new generation antimicrobials against multidrug resistant strains of bacteria such as tuberculosis is advancing by extensive use of those modern tools. Natural products chemistry has been re-emerging as a highly promising provider of the sufficiently sophisticated lead structures for drug discovery. A combination of natural products chemistry and focused library synthesis furnishes a powerful approach to drug discovery. The terms "biology-oriented synthesis (BIOS)" and "function-oriented synthesis (FOS)" have recently emerged as a logical evolution in "chemical genetics" for exploring the intrinsic complexity and diversity of the structures of natural products. Moreover, the use of combinatorial biosynthesis, taking advantage of particular gene clusters as a tool for creating a library of highly sophisticated natural product leads, provides another fascinating approach to modern drug discovery.

The critical contributions of chemistry to modern drug discovery are not limited to the identification and synthesis of active drug candidates. Chemistry is also playing a key role in drug delivery, especially targeted drug delivery. Traditionally, "drug delivery" was a specialization in pharmacy for formulations of drugs. However, it is natural that organic, medicinal, materials, and nano chemistry have now become deeply involved in the development of drug delivery systems. These approaches have led to the creation of drug conjugates that are new chemical entities. The use of functional carbon nanotubes as well as designed polymers as a vehicle for drug delivery is a novel approach to drug discovery. Also, the tumor-targeted drug delivery systems, using tumor-specific monoclonal antibodies, vitamins, omega-3 fatty acids, and aptamers as the tumor-target-

Published on the Web 01/15/2008 www.pubs.acs.org/acr
10.1021/ar700158c CCC: $40.75

ing molecules for cytotoxic anticancer drugs with strategically designed linkers cleavable only in the tumor have been emerging as highly promising approaches to efficacious chemotherapy with a minimum of undesirable side effects. Aptamers (synthetic DNAs/RNAs bearing specific affinity to a specific protein) have great potential as the targeting module of drug conjugates for various molecular targets. Targeting mitochondria with scavengers of reactive oxygen species (ROS) may find a range of therapeutic applications. Furthermore, the molecularly engineered nano-biomaterials provide unique extracellular matrices for *in vitro* and *in vivo* models for human diseases, much better than the widely used xenograft models at present. These novel materials and the disease models using them make preclinical evaluation of the efficacy and toxicology of drug candidates much more accurate and predictable for use in humans and contribute significantly to drug discovery.

I hope that this special thematic issue of *Accounts of Chemical Research* provides a perspective on cutting-edge research endeavors in drug discovery. By featuring contributions from leaders in modern molecular approaches to drug design and discovery, I hope to encourage a range of chemists, especially younger generation chemists, to be involved in this challenging but highly rewarding field of multidisciplinary molecular biomedical research.

Iwao Ojima

Institute of Chemical Biology & Drug Discovery, State University of New York at Stony Brook
Guest Editor

AR700158C