Academic Preparation for Modern Drug Discovery

Norman Uretsky, Larry Robertson

Norman J. Uretsky, Ph.D., and Larry Robertson, Ph.D., are professors emeritus at the Ohio State University College of Pharmacy in Columbus, Ohio.

ScienceCareers.org, 12 March 2004
American Association for the Advancement of Science

Recent advances in understanding disease development and in technology have markedly facilitated the process of drug discovery. The discovery of new drugs to treat disease has become a multidisciplinary undertaking, involving biochemists, physiologists, pharmacologists, medicinal chemists, computer analysts, clinicians, and others. No one area of study can prepare an individual to specialize in all phases of the drug discovery process. However, individuals, preparing for a career in drug discovery might consider becoming familiar with various areas involved in the drug discovery process.

A demanding and interdisciplinary process

The drug discovery process is responsible not only for the introduction of many new drugs to the market place but also for marked improvements in the therapy of many diseases. These include drugs to treat diseases such as cardiac disease, stroke, bronchial asthma, rheumatoid arthritis, diabetes, bacterial and viral infections, and neurological and psychiatric diseases. Traditionally, the discovery of new drugs has been based on observations of a useful biological effect produced by a natural product, usually obtained from a plant or microorganism, or a synthetic chemical compound. If the biological effect of a chemical antagonized the symptoms of a disease and the adverse effects were minimal, it would be considered as a potential drug to treat disease.

This approach is helped by studying the mechanism of action of substances that produce effects on biological systems, as detected by screening a large number of compounds in animal models. If the effects produced by these substances were sufficiently potent and selective at a target site, they could be used as lead or reference compounds for the development of more potent agents. To accomplish this result, the chemical structure of the substance had to be clarified and analogs synthesized. The effects of the analogs and the reference compounds would then be compared at the molecular, cellular, and organ system level. The goal is to find a compound with high potency and selectivity and low toxicity, or, in other words, a high therapeutic index.

Advances in the molecular nature of drug action and in technology have produced new approaches to the discovery and development of drugs. Our expanded understanding of disease development and progression has made it possible to describe diseases in molecular terms. Many different endogenously formed substances have recently been found to play a role in the pathology and symptoms of a disease. These substances are frequently macromolecules, usually proteins, including receptors that reside in membranes, intracellular receptors, intracellular enzymes, signal transduction pathways, and sequences of RNA or DNA, among others. Various chemical agents have been studied for their ability to interact with these molecules with the goal

of reversing the disease state. Thus endogenous molecules can be considered as targets, or even candidates, for potential drugs.

Expanding scope, including new research technologies

The target may be identified by a variety of techniques, including descriptions of abnormal genes and proteins responsible for the pathological state. In rational drug design, knowledge of the chemical nature of the target may be used as a guide in determining the type of chemical compound that can interact with it. For this purpose, chemical agents are screened for their ability to interact with the target, and agents that can interact with the target have the potential of modifying the disease process. Computer-assisted analysis of the structure of both the target site and the chemical substances that can interact with the target can help identify the optimal structure of compounds that potently interact with the target.

Improvements in the technologies involved in screening of drugs for target sites, including the use of high-throughput screening procedures, recombinant DNA techniques, combinatorial chemistry, and new computing methods, have markedly increased the number of compounds that can be tested for their ability to bind to the target. Once a chemical is found to have suitable properties, it can be used as a lead or reference to develop analogs that will further enhance the potency and selectivity for interaction with the target. Potential drugs should be able to selectively produce beneficial changes that will antagonize or reverse the disease state.

One should note that all drugs produce effects on more than one system. Effects at sites other than the target site are one source of toxic adverse effects. In this case, adverse effects depend upon the relative potency of the compound at the target site and at sites outside the target. The eventual development of potential drugs for therapy involves extensive screening of the drugs for effects throughout the body. This requires evaluations of drug effects on organ systems and in the whole animal for effectiveness, selectivity, and toxicity. Only after a drug can pass an extensive preclinical evaluation can it be tested in humans for effectiveness and toxicity.

Thus, the search for new drugs to treat disease is a multidisciplinary undertaking. It involves scientists from a variety of fields including biochemists, physiologists, pharmacologists, medicinal chemists, computer analysts, clinicians, and others. Thus no one individual can be an expert in all phases of the drug discovery or drug development process. So how does a student interested in drug discovery become adequately prepared for a career in this challenging field?

Extensive academic preparation recommended

Undergraduate: As an undergraduate interested in drug discovery, a student must be well-grounded in science-based courses. This grounding would include not only the standard science courses, such as physics, general chemistry, organic chemistry, qualitative and quantitative analysis, biology, and biochemistry, but also courses, if offered, in physiology, molecular biology, and pharmacology. Computer education courses would also be helpful as computer programs are used more and more frequently to assist in constructing the three-dimensional structures of chemical agents to determine whether they bind optimally to a defined target.

Graduate: Those who aspire to a career in drug discovery research should plan to go to graduate school to attain a Ph.D. degree in a biological science-related discipline. This includes such

fields of specialization as pharmacology, medicinal chemistry, molecular biology, biochemistry, or psychobiology. Pharmacology is a particularly useful discipline in this regard because it includes studying drug action on the molecular, cellular, organ system, and whole animal levels. In many graduate programs, pharmacologists work together with medicinal chemists to design compounds that will interact with target sites.

The tools of biotechnology are becoming increasingly important in all phases of drug discovery, including identification of potential molecular targets, the production and identification of new compounds as leads, and the development of new leads into useful drugs. Therefore, students will have to be knowledgeable concerning new techniques in biotechnology. Ideally, the student's faculty mentor should be cognizant of the changes that occur in drug discovery research, particularly as new approaches in drug discovery and research are introduced.

Postdoctoral research: Postdoctoral training is recommended for students to further enhance their education. Postdoctoral researchers trained in these programs should use these opportunities to perform interesting and important work in drug discovery. Students may want to select a postdoctoral experience that will add a new dimension to their knowledge base. In selecting from among graduate programs and postdoctoral training sites, students should ask where graduates from these programs are currently working. The responses will provide good indicators of the quality and relevance of their preparation.