PREFACE

The complexity of drug discovery has increased significantly in the last decade. Years ago, compounds were screened in cellular and animal models without direct knowledge of the molecular target. Subsequent drug design was based upon synthesis of analogs of active compounds and their screening in the key biological model leading to definition of a structure activity relationship. The need to perform rational drug design increased as drug discovery evolved into a mechanism-based strategy. Advances in molecular biology presented the drug discovery scientists with purified proteins - receptors and enzyme targets - in significant quantities. Advances in computer sciences and instrument designs have made available additional technologies to the drug discovery scientist. Now site-directed mutagenesis, protein NMR, X-ray crystallography, and combinatorial chemistry are available to aid in the design of new drugs against increasingly more complex molecular targets.

The focus of this issue is on new drugs designed for treating inflammatory diseases. While arthritis and asthma are usually considered the major diseases in this category, perhaps because of market size, other important disorders may be addressed by drugs emerging from inflammation-based molecular targets, among them inflammatory bowel disease, psoriasis, rhinitis, and transplant rejection.

In this issue, several molecular targets considered important in the inflammatory process are highlighted. In choosing these targets, an effort was made to focus on those in which small molecule inhibitors were identified and in which significant drug design had evolved. One needs to only peruse the literature to note the numerous molecular targets under active investigation by pharmaceutical and biotechnology organizations. The challenge is not only identifying an inhibitor or antagonist of the molecular target being studied, but of equal importance, is the selection of which molecular target is important in disease pathophysiology and at what stage in the progression of the disease. Thus, while it is relatively easy to justify the importance of a given molecular target, the proof of its importance must await not only the identification of suitable inhibitors and antagonists, but also the demonstration of clinical efficacy in an appropriate patient population. And with the impact of health care reforms, it is critical for the new drug to show significant advantages over existing therapies. This issue deals with the first step in the process, the design of drugs suitable for clinical evaluation.

Barry Weichman