THE LAST WORD

by Peter D. Lomedico
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BIOTECHNOLOGY AND DRUG DEVELOPMENT

How will biotechnology affect the future of pharmaceutical research and drug discovery? Recombinant DNA and monoclonal antibody technologies are exceedingly powerful tools for the analysis and large-scale production of biologically active polypeptides, peptides, and antibodies. However, the initial optimism concerning direct therapeutic use of proteinaceous materials has faded somewhat, and we feel that only a limited number of such substances will be successfully developed into widely used pharmaceuticals. We believe, instead, that the new biotechnologies will prove more useful in the generation of research tools necessary for a detailed understanding of physiological processes. Manipulation of these unique tools will ultimately aid in the design of novel, non-proteinaceous therapeutic agents.

The basic premise underlying this point of view is that proteins play a critical role in the regulation of all physiological processes, and that the pharmacological modulation (either agonism or antagonism) of endogenous protein function will be an effective therapeutic goal. In some cases, the protein-regulated process may be directly involved in disease etiology, while in other cases intervention may be desired to affect disease symptomatology. Hence, proteins (enzymes, hormones, cell-surface receptors, etc.) are attractive targets for specific drug development. Using genetic engineering and hybridoma techniques, it is now possible to characterize and produce these natural protein effector molecules that previously were difficult—if not impossible—to manipulate experimentally. Unlimited quantities of protein and neutralizing antibodies makes available powerful probes in confirming and, in many cases, in extending our understanding of the molecular basis of relevant physiological processes. Armed with this knowledge, one can confidently embark on a research effort which is heavily dependent on the new biotechnologies to discover agents that pharmacologically modulate these processes.

To illustrate these concepts, one can consider a chronic disease like rheumatoid arthritis for which novel, disease-modifying drugs are needed. The traditional pharmaceutical research approach is to screen compounds in relevant animal models. Interesting leads identified by this method are then manipulated by the medicinal chemist and subsequently evaluated to identify analogs with enhanced potency, improved duration of action, and/or reduced toxicity. Historically, this approach has been very successful, often in the absence of an understanding of the biological basis for the lead compound's activity.

In contrast, the biotechnology approach to the problem is to attempt to develop some recently cloned protein (e.g. one that mediates an anti-inflammatory state) as a new therapeutic entity. The new breed of "medicinal chemists" (i.e. genetic engineers and synthetic peptide chemists) would proceed to manipulate this protein to increase its biological half-life and solve its delivery problems.

Our vision of the future is a synthesis of these two strategies whereby traditional medicinal chemists synthesize non-proteinaceous compounds, capitalizing on the research tools and leads generated by the molecular geneticists and protein chemists. For instance, consider the scenario where the genetic engineers clone a gene coding for a poorly studied polypeptide hormone which appears to contribute to inflammation and connective tissue destruction in the rheumatoid joint. Recombinant protein and specific antibodies against this protein represent research tools that can be used to verify the importance of this protein's role in pathology, and also to extend our understanding of the underlying mechanism. At this point, one can begin in earnest to search for antagonists using both rational and random approaches. Recombinant protein can be used in receptor binding assays and specific bioassays to screen for simpler compounds that block the protein's activity; these leads can in turn feed into the traditional medicinal chemistry/pharmacology approach. In parallel with this traditional approach, the molecular geneticists and protein chemists can extend their technologies to dissect structure-function relationships by creating genetically engineered analogs, synthetic peptides, and site-specific antibodies. One can envision the identification of a research lead (e.g. a peptide that blocks binding of the protein to its receptor) in this matter. These efforts, when combined with the power of protein X-ray crystallography and molecular modeling techniques, provide information for the medicinal chemist to begin the design of non-proteinaceous peptidomimetics. These molecules can be refined to yield novel, highly specific pharmaceuticals.

The approach we have outlined is not entirely novel: witness the development of ACE inhibitors. However, we feel the marriage of traditional medicinal chemistry with the new biotechnologies adds extra dimensions—not only in terms of speed, but particularly in the ability to approach problems of considerably greater complexity and broader applicability—in the quest for innovative therapeutic agents that modulate physiological processes.

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