COMMENTARY ON BIOPHARMACEUTICALS JACQUELINE SIEGEL

Good science doesn't guarantee good drugs

Many of the problems that have surfaced among biotechnology firms in recent years have their genesis in the notion that an understanding of the basic biology of a molecular disease area should translate to identification of a target disease or a therapeutic molecule. This is not always the case.

In the beginning, biotechnology companies were founded to make therapeutic proteins from gene-cloning or monoclonal-antibody technologies. A critical aspect of these approaches was that the end products—such as human growth hormone (HGH) or insulin—had often been identified prior to the start of the drug-development process. The markets at that time were obvious and attractive. The clinical trials often had extensive precedents, and the regulatory reviews were relatively simple. We know that the hurdles faced in commercializing genetically engineered proteins were daunting, since the products had to be manufactured to levels of purity and scale never imagined in the research laboratory. At the end of the day, however, the technical breakthroughs involved engineering advances rather than scientific advances.

The success of certain products—particularly Genentech's (S. San Francisco, CA) HGH and Amgen's (Thousand Oaks, CA) erythropoietin—masked certain critical issues that have come to the forefront over the past few years. In particular, companies are currently functioning close to the edge of the scientific frontier. As a result, potential products are often identified by interesting properties that suggest that they may be useful in certain broad disease categories. In addition, very complex diseases, such as cancer or inflammation, often seem approachable at the molecular level because scientists have been able to identify certain biochemical mechanisms associated with a disease. Yet target diseases are often difficult to define or to understand when a candidate molecule is not well understood.

Two old, but good, examples of this problem are α-interferon and interleukin-2.α-interferon was one of the first proteins targeted by fledgling biotechnology companies and their strategic partners, including Biogen (Cambridge, MA) and Schering-Plough (Madison, NJ), as well as Genentech and Hoffmann-La Roche (Basel). The protein was cloned, expressed, and manufactured in bulk. However, the identification of a clinical target proved difficult. Early thoughts had been that α-interferon would be a potent anticancer and antiviral agent. Yet most trials in humans did not support this early optimism, and the drug was ultimately approved for hairy cell leukemia, a relatively uncommon cancer. In recent years, though, sales of α-interferon have actually exceeded early speculations, because the drug has been approved worldwide for treating a wide range of tumors, viral infections, and HIV-associated diseases. By contrast, the early promise of interleukin-2 as a cancer treatment has not yet been achieved, largely due to the serious side effects associated with therapeutic doses.

The biological activities of both drugs were intriguing, and scientists reasoned that clinical targets would be easier and less costly to identify and to develop than was the case. Cytokine biology was a young science 10 years ago, and these assumptions seemed valid. Many of the recent problems that have surfaced among biotechnology companies are, in part, due to a similar rationale, namely, that an understanding of the basic biology of a molecule or a disease area should translate directly to identification of a therapeutic molecule or a target disease. As we have seen in the sepsis and wound-healing debacles, as well as in many other cases, good scientific reasoning may not translate directly into successful drug development.

In passing, we note that the molecule in question need not be a protein. In today's world of biotechnology, proteins are more often used as tools to discover smaller therapeutic chemicals, rather than as stand-alone drugs. The application of molecular biology to small-molecule discovery is leading to more rapid and sophisticated screens for new drug activities. But the issue is still the relationship between the basic science and the drug-development process. The success rate will depend on both the maturity and breadth of the scientific foundation, as well as on serendipity. The more we know about a disease area, the more likely we are to identify promising candidates and conduct the right clinical trials. ///

Jacqueline Siegel is senior director at Mabon Securities (New York).

Understanding of the basic biology of a molecule or a disease area doesn't always translate to identification of a therapeutic molecule or a target disease.

COMMENTARY ON THE ENVIRONMENT RUSS HOYLE

BST off to a fast start, despite early stumbles

Shortly after the Food and Drug Administration (FDA, Rockville, MD) approved bovine somatotropin (BST) and issued its controversial voluntary labeling guidelines last February, signs sprung up almost everywhere milk was sold, especially in dairy states, touting "BST-free" milk. Never mind that the FDA has bent over backward to assure consumers that milk from BST-treated cows is no different than milk from cows that produce the hormone naturally. Legally, the FDA opened up a loophole large enough to drive a dairy truck through that was intended to appease critics and inform consumers by allowing milk retailers to make a distinction in the marketplace that scientists were unable to make in the lab. As long as they did not say that milk from BST-treated cows was bad, retailers could say