Chapter 9

Investment in Biotechnology Applied to Human Therapeutics

"Biotechnology is in a state of evolution. . . the industry is moving away from the technological phase into the clinical phase. "

Peter Drake in ***Chemical Week,***
Sept. 30, 1987, p. 20.

"[there are] not many problems with FDA. It takes a long time to get anything approved, but the delays are not unique to biotech products."

unidentified industry spokesman, ***Bio/Technology,***
December 1987, p. 1277.

"The equation in biotechnology is becoming all too familiar: patent plus patent equals lawsuit ."

(editor) /In The News/ ***Bio/Technology,***
December, 1987, p. 1251.

"We seem to be at a point in the history of biology where new generalizations and higher order biological laws are being approached but may be obscured by the simple mass of data. "

H. Moskowitz and 'l'. Smith
Report of the *Matrix* ***of Biological Knowledge Workshop,*** Santa Fe, New. Mexico
July 13 to Aug. 14, 1987

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INTRODUCTION

The promise of novel pharmaceutical applications has captured most of the attention given to biotechnology in the last decade. Pharmaceutical biotechnology, for the purposes of this report, is defined as the use of recombinant DNA, hybridoma, and related new technologies in the manufacture of human therapeutic products; diagnostics and vaccines are not included under this definition. Although the new biotechnologies have not radically changed the pharmaceutical industry, they have contributed to progress in a number of important product development areas, and have brought about a commitment to research and development (R&D) funding from both public and private sources that greatly exceeds that for any other industry.

Biotechnology has facilitated the development of human therapeutic proteins that are difficult to produce in large quantities by traditional methods such as chemical synthesis or extraction from blood plasma, or tissues. Recombinant DNA technologies to combine DNA from one organism with that of another have been used to clone, or make copies of, genes that produce proteins with therapeutic potential, and to engineer genes to make proteins that are more stable or active than their natural forms. Monoclinal antibodies secreted from hybridomas (the cells resulting from the fusion of immortal tumor cells with antibody producing cells from mouse, rat, or human sources) have been developed primarily as diagnostic reagents, but their ability to specifically recognize foreign substances has made their use as human therapeutics possible. Studies of the basic molecular mechanisms governing cell physiology have been greatly enhanced by the tools of biotechnology, and will likely continue to lead to new drug discoveries and increased understanding of the origins of disease. Enthusiasm for the design of a new pharmaceutical from knowledge of the structure of the molecule (e.g., a cell surface receptor protein) upon which it acts—often called rational drug design—has also been renewed by advances in methods to determine the three-dimensional structures of proteins. Such progress has been spurred in part by the fact that recombinant DNA technology has increased the availability of previously scarce human proteins.

In 1982, the Food and Drug Administration (FDA) approved human insulin as the first recombinant DNA product for clinical use in humans. Scientists at Genentech, Inc. (South San Francisco, CA) devised recombinant DNA methods for producing insulin in bacteria from synthetic insulin genes, and assembling the protein chains into biologically active insulin. Eli Lilly and Company (Indianapolis, IN) subsequently developed and marketed the recombinant DNA version of human insulin, under the trade name Humulin®, as a therapy for diabetes. Since that time, six additional human therapeutic agents produced using biotechnology have been approved for marketing in the United States (table 9-l):

- two recombinant DNA-derived versions of human growth hormone for long-term treatment of children with growth failure due to lack of adequate endogenous growth hormone,
- two recombinant DNA-derived versions of human alpha-2 interferon for treatment of hairy-cell leukemia,
- a recombinant DNA-derived human tissue plasminogen activator protein for treatment of coronary artery blood clots that trigger heart attacks, and
- a mouse monoclonal antibody preparation for preventing acute rejection in kidney transplantation.

These biotechnology products underwent separate testing and clinical trials to receive market approval from the FDA, even though several are

Table 9=1.—Biotechnoiogy-Based Human Therapeutics With FDA Market Approval

Trade Name/Generic Name	Use	Company Receiving Market Approval
Humulin®/Human Insulin	Treatment of diabetes	Eli Lilly and Company
Protropin®/Human Growth Hormone	Treatment of children with inadequate secretion of growth hormone	Genentech, Inc.
Humatrope®/Human Growth Hormone	Treatment of children with inadequate secretion of growth hormone	Eli Lilly and Company
Intron A®/Alpha Interferon	Treatment of hairy-cell leukemia	Schering-Plough Corporation
Roferon-A®/Alpha Interferon	Treatment of hairy-cell leukemia	Hoffman-La Roche, Inc.
Orthoclone OKT*3®/Monoclinal antibody against T-cells	Treatment for reversal of acute kidney transplant rejection	Ortho Pharmaceutical Corporation
Activase®/Tissue Plasminogen Activator	Treatment of cardiac arrhythmia	Genentech, Inc.

[a]First recombinant DNA product to be developad, manufactured, and marketed by a dedicated biotechnology company.

SOURCE: Office of Technology Assessment, 1988.

the same type of protein marketed by different companies for the same therapeutic use.

This chapter assesses the current U.S. investment in biotechnology as it applies to the discovery and development of human therapeutics. The following questions are addressed:

- How is biotechnology being used to discover new or better therapeutic pharmaceuticals?
- What basic and applied research programs related to pharmaceutical biotechnology are being invested in by the public and private sectors?
- How are factors such as gaps in basic and applied research, availability of funds, regulation, intellectual property protection, information access, and availability of trained personnel affecting overall investment in the development of human therapeutics derived from biotechnology?

APPLICATIONS OF BIOTECHNOLOGY TO HUMAN THERAPEUTICS

Biotechnology has become an integral component of many aspects of pharmaceutical research, easing the technical bottlenecks that slow the pace of new human therapeutic discoveries. Biotechnology has brought about significant innovations in methods for isolating and producing human proteins with therapeutic potential in human beings. The following sections summarize the state of the art of research in the development of human therapeutics made using biotechnology.

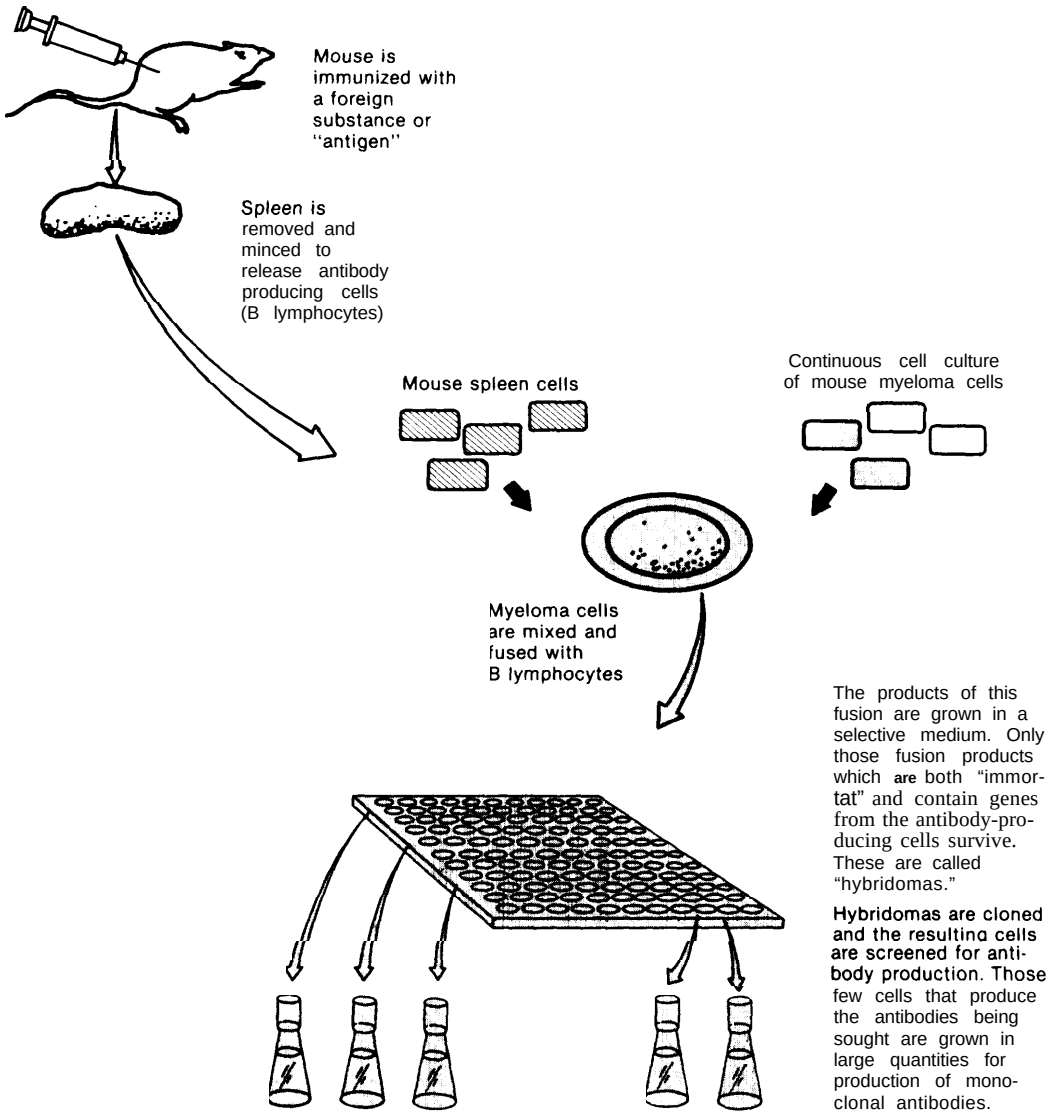
Biotechnology and the Development of Human Therapeutics

Scientific advances in biochemistry, cell biology, immunology, virology, structural biology, and related disciplines over the last 10 to 15 years have yielded an explosion in understanding about the structure and function of infectious agents and the machinery of cells at the molecular level. This substantial progress has been greatly enhanced by the development of methods for DNA and protein sequencing, DNA and protein synthesis, monoclonal antibody production from hybridomas (figure 9-l), recombinant DNA construction, and protein structure determination. Thus, compared to traditional approaches to drug development, biotechnology potentially offers a more rational or targeted strategy that involves an in depth understanding of the complexities of human biol*ogy **(18)24).***

The number of potential human therapeutics is increasing in two general categories because of advances in biotechnology:

- . monoclinal antibodies made from mouse or human hybridoma cell lines; and
- human proteins produced from director engineered copies (clones) of genes.

Figure 9-1.— Preparation of Mouse Hybridomas and Monoclinal Antibodies



SOURCE: Office of Technology Assessment, 1988

Monoclonal Antibody Products of Hybridomas

ORTHOCLONE OKT3® is a monoclinal antibody that targets a subset of the body's white blood cells (T-cells) responsible for acute rejection of transplanted tissue. This therapeutic, manufactured by Ortho Pharmaceutical Corporation (Raritan, NJ), is used to prevent acute kidney rejection. Whereas traditional drugs suppress the entire immune system, resulting in life-threatening infections, the value of OKT3® lies in its specificity for T-cells. At least three biotechnology companics (Centocor (Malvern, PA), Cetus Corporation (Emeryville, CA), and Xoma Corporation (Berkeley, CA)) are developing either mouse or human monoclinal antibodies against the gram-

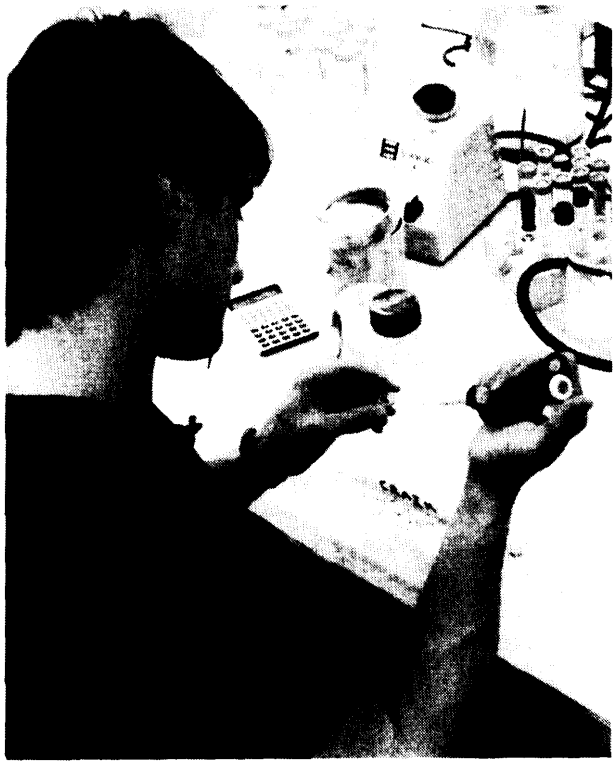


Photo credit: University of California, San Francisco

Molecular biologist preparing for DNA cloning and in vitro mutagenesis experiments.

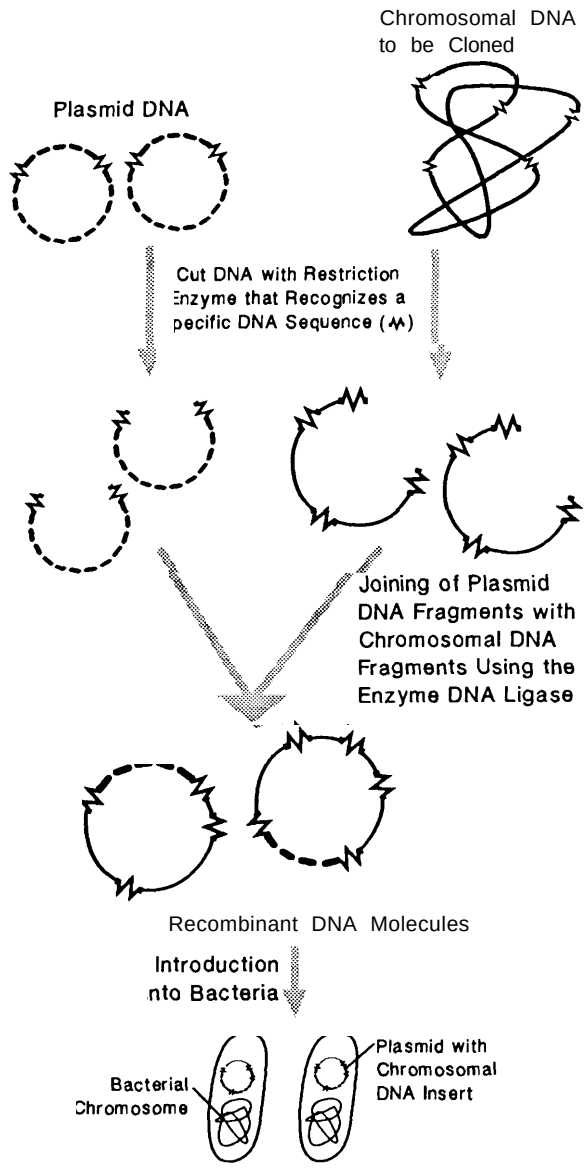
negative bacterial endotoxins that cause septic shock, a life-threatening condition characterized by a severe drop in blood pressure. Other therapeutic monoclinal antibodies under commercial development include those for reducing risks associated with bone marrow transplants, correcting for drug overdoses, and treating various cancers either directly or as targeted carriers of cytotoxic drugs (1,48).

There is also incentive to develop human myeloma cell lines for making human hybridomas. After repeated or long exposures to therapeutic antibodies from rodent sources, humans can become sensitive to the mouse antibodies and respond by making their own antibodies against them (8,26, 34,44). In addition, cell lines derived from mice often release pathogenic viruses that could pose dangers to humans if not removed from the monoclonal antibodies during their purification from mouse ascites fluid (57). An alternative method for producing monoclinal antibodies is to synthesize them from cloned genes in bacteria, yeast, or myeloma cells. Monoclinal antibodies with dual specificities, pre-determined specificities, and additional activities are all possibilities with recombinant DNA technology (69).

products of Cloned Genes

With the exception of the one monoclinal antibody, all of the biotechnology derived human therapeutics presently on the market and most of those in clinical trials are products of genes cloned by recombinant DNA technology (figure 9-2). Brief

Figure 9-2.—DNA Cloning Technology



SOURCE: MedSciArtCo, Washington, DC.

Box 9-A.—Known or Expected Therapeutic Applications of Some Human Gene Products Under Commercial Development

Atrial Natiuretic Factor (ANF). One of the peptide hormones secreted by the heart; acts to regulate blood pressure, blood volume, and water and salt excretion; possible applications in treatment of hypertension and other blood pressure diseases and for some kidney diseases affecting excretion of salts and water.

Epidermal Growth Factor (EGF). A protein growth factor that causes replication of epidermal cells (those cells on the outermost layer of tissues); expected to have applications in wound healing (including burns) and cataract surgery.

Erythropoietin (EPO). A protein hormone growth factor normally produced by the kidney; causes the production of red blood cells; anticipated treatment for anemia resulting from chronic kidney disease; some potential for curing anemias associated with AIDS and other chronic diseases.

Factor VIII:C. A protein involved in blood clot formation; major application in prevention of bleeding in hemophiliacs (deficient in factor VIII) after injury.

Fibroblast Growth Factor (FGF). A protein that stimulates growth of blood vessels; may be useful in wound healing and treating burns.

Granulocyte Colony Stimulating Factor (G-CSF). One of a larger class of colony stimulating factors that stimulates production of the class of white blood cells called granulocytes; could be useful in treating leukemia and AIDS, possibly in concert with other chemotherapeutics.

Human Growth Hormone (hGH). A peptide hormone naturally occurring in the pituitary gland; used as a treatment for childhood dwarfism; expected to have broader therapeutics potential in wound healing or treatment of Turner's syndrome and small stature.

alpha-Interferon (a-INF). A lymphokine protein used as a treatment for hairy cell leukemia; possible broader applications in treatment of venereal warts, Kaposi's sarcoma (associated with AIDS), lymphoma, bladder cancer, and malignant melanoma.

gamma-Interferon (g-INF). A lymphokine protein that activates macrophage cells and interferes with viral replication; potential treatments for various cancers, AIDS.

Interleukin-2 (IL-2). A lymphokine protein hormone that causes immune system responses; potential treatment for various cancers.

Interleukin-3 (IL-3). A blood protein colony stimulating factor that promotes red and white blood cell production at the earliest stages of cell development; potential applications in treatment of white blood cell deficiency in AIDS patients or that induced by radiation and chemotherapy exposures in other cancer patients.

Macrophage Colony Stimulating Factor (M-CSF). A colony stimulating factor that acts only on white blood cells of the monocyte/macrophage type; potential applications are expected for treatment of infectious diseases, primarily parasitic, but some bacterial and viral diseases, possible cancer therapy.

Superoxide Dismutase (SOD). An enzyme that seeks out superoxide free radicals in the blood and prevents damage when oxygen-rich blood enters oxygen-deprived tissue; applications in cardiac treatment and organ transplants.

Tumor Necrosis Factor (TNF). A protein growth factor with possible broad applications in antitumor and antiviral therapy.

Tissue Plasminogen Activator (TPA). A blood protein that activates plasminogen, a naturally-occurring blood protein that breaks down fibrin blood clots; used for dissolving the coronary artery blood clots associated with myocardial infarctions, or heart attacks, with other possible blood clot dissolving applications.

SOURCE: Office of Technology Assessment, 1988.

descriptions of the major recombinant DNA-derived proteins currently under commercial development for use as human therapeutics are given inbox 9-A. Two other OTA reports describe the categories of proteins being developed as human therapeutics (e.g., regulatory proteins including the interferon and lymphokines; blood products; growth factors; and monoclinal antibodies) and the technologies used to make them (51,54).

Recombinant DNA methods can also be used to substitute, delete, or add nucleotides to the DNA that makes up a gene. Such alterations in the DNA lead to changes in the amino acids that makeup its protein product. These biotechnologies for protein engineering have already been used commercially to facilitate protein purification processes, and they show promise for developing the second generation of human therapeutics from biotechnology (see box 9-B).

Biotechnology and the Production of Human Therapeutics

Scale-up and manufacturing technologies for the production of human therapeutics from cells containing recombinant DNA, or from hybridomas, are considered in detail in an earlier OTA report (51) and more recently in other reviews (7,28, 29,70). This section focuses, therefore, on the cells or organisms currently being used for the production of gene products and on some of the tech-

Box 9-B.—Protein Engineering and the Development of Human Therapeutics

The ability to make proteins function more efficiently, to operate under stressful conditions within the human body (e.g., the strongly acidic environment of the stomach), or to create totally new proteins that do not exist in nature are all possibilities of importance to the commercial development of novel human therapeutics. The drugmaker's wish list for "engineered" proteins includes those with enhanced therapeutic effects, those specific for particular disease agents, such as viruses, and those that are stable in the varied biochemical environments of the human body.

Recent advances in recombinant DNA procedures, the chemical synthesis of genes or gene fragments, protein structure determination, and computerized molecular modeling have brought about a new era of *protein engineering*. Protein engineering can be achieved either through direct modification of the amino acid molecules that comprise proteins or by altering the DNA molecules of the genes that produce the proteins. The newer methods for modifying proteins at the DNA level are collectively referred to as *in vitro mutagenesis*, and they have brought new life to the field of protein engineering.

Protein engineering usually involves the substitution of one amino acid for another within a protein. Such procedures can be applied to the development of human therapeutic proteins, either to make more effective therapeutics, or to simplify the process used in their purification. Scientists at Cetus, for example, used in vitro mutagenesis to make amino acid substitutions in b-interferon and interleukin-2, both in advanced stages of clinical trials, to facilitate the process by which these proteins are purified from bacteria. The modification of proteins, by mutagenizing the genes that produce them, has also proved to be a useful tool for testing theories on the relationships between protein structure and function.

Advances in recombinant DNA technology also have made it possible to construct new proteins by substituting or deleting whole portions of genes. A gene made by combining portions of the genes encoding the receptor proteins for two potentially important human therapeutics—interleukin-2 and epidermal growth factor—was constructed in an effort to better understand the biological mechanism by which these growth factors function.

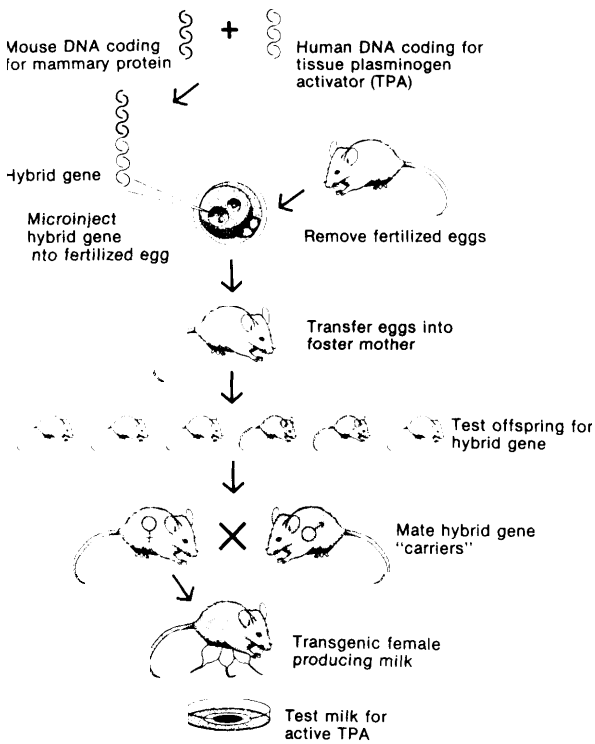
SOURCES: [illegible] Nature 330:347-352, 1987; J.L. Marx, "Protein Engineering," Mosaic [illegible], 1987; [illegible], Cetus Corp., [illegible], CA, personal communication, December 1987; [illegible], "Protein Structure and Design 1987," Cell [illegible], 1987.

nical limitations associated with the use of each source.

Once a human gene is isolated, recombinant DNA methods can be used to make it function in many foreign hosts, ranging from bacteria and yeast cells to insects, mice, and sheep. For human therapeutics made from recombinant DNA technology, vectors (plasmid or phage chromosomes designed to carry extra genes) have been constructed that maximize the expression of the gene product (the protein) in different cell types or organisms. Once synthesized, the cell may need to modify the human protein for proper functioning. These modifications can include the attachment of sugar molecules, by a process called glycosylation, or the removal of some terminal amino acids (45). Therefore, it is necessary to determine the appropriate organism or cell type from which large quantities of a human gene product can be easily purified in a form sufficiently similar to the protein as it is found naturally in human beings.

The choice of host cell or organism for the production of human therapeutics is decided mostly by logistic and economic factors (28), and in many cases, by the particular post-synthesis modification requirements of the protein [29,61). Recombinant DNA-derived insulin, alpha interferon, and human growth hormone–three marketed human therapeutics-are all produced in bacteria. Despite these successes, bacteria are not always able to synthesize human proteins that are similar enough to their natural human counterparts to function adequately. Human proteins that require special chemical modifications, like the glycosylated hormone erythropoietin, are best made in mammalian cell culture where they acquire optimal levels of glycosylation (63). On the other hand, the type of protein glycosylation varies among species and in higher organisms, and also varies from tissue to tissue. In those instances, it may be more economical to synthesize proteins in yeast with partially correct chemical modifications, and then modify the product in vitro (outside of the cell) (28). One alternative to mammalian culture for those proteins that require special modifications is production from the lactating mammary glands of an animal. Isolated genes can be injected into animal embryos (e.g., mouse, goat, sheep, cattle) and incorporated into the germ line where they can function just as the mouse's own genes (figure 9-3) (21). The latter technology is examined in a forthcoming OTA special report on ***Patenting Life.*** The challenge for bioprocess engineers working with human proteins isolated from nonhuman organisms has been to devise methods for retaining protein activity while maximizing yields.

Figure 9-3.—Mouse/Human Hybrid Gene Enables Mice to Secrete Human Therapeutic Proteins



SOURCE: Adapted from Integrated Genetics, Inc., Cambridge, MA.

FACTORS INFLUENCING INNOVATION AND COMMERCIALIZATION

OTA identified six major factors that influence the rate at which biotechnology research will be transformed into commercial products in the area of human therapeutics. These factors, some of which might be considered incentives and others obstacles to product development using biotechnology, were identified in interviews with representatives of established pharmaceutical companies and dedicated biotechnology companies (DBCs), Federal agencies, and from a 1987 OTA workshop on "Factors Affecting Commercialization and Innovation in the Biotechnology Industry" ***(52).*** They are:

- gaps in basic and applied research;
- availability of R&D funds;
- regulation of products made using biotechnology;
- protection of intellectual property;
- access to information generated in biomedical research; and
- availability of trained personnel.

The availability of funds for ***basic research is*** the factor of central concern to those involved in developing new human therapeutic products. Nevertheless, each of these elements factor into the R&D process, and taken together, they influence the overall level of investment (including monetary, personnel, and other types of resources) in applications of biotechnology by the pharmaceutical business sector.

Gaps in Basic and Applied Research

Despite significant advances in recombinant DNA technology and the development of efficient protein production systems, major bottlenecks, or gaps in knowledge, remain in research ultimately applicable to the development of new human therapeutic agents. This section focuses primarily on the major research needs in the identification, isolation, engineering or chemical synthesis of new drugs, including new approaches for:

- **isolating** human proteins and genes;
- establishing relationships between protein structure and function;
- determining how proteins fold into active three-dimensional structures;
- developing animal models useful for elucidating the physiological roles of previously uncharacterized proteins;
- understanding mechanisms of protein maturation and export from cells; and
- administering protein drugs.

Isolating Human Proteins and Genes

There are probably over 50,000 proteins in the human body (11). Only a few hundred of the human genes that produce these proteins have been isolated, however, so many more human genes will be needed before the full impact of recombinant DNA on the discovery of potential human therapeutic proteins is realized. Currently, most scientists target specific genes and gene products for study, often using information from small amounts of the natural human protein to isolate the corresponding gene (53). A National Research Council panel urged that additional resources be given to scientists for developing the DNA mapping technologies necessary for identifying and isolating the entire set of human genes (40).

Establishing Relationships Between Protein Structure and Function

Regardless of the method used to isolate a human gene, the function of the corresponding protein product is rarely obvious from the structure of the gene. Studies aimed at determining the potential of human proteins as therapeutic agents depend on knowing how the proteins function in the human body. In the absence of experimental evidence for the function of a particular protein, scientists often attempt to predict the protein's function from its structure. From the DNA sequence of a gene, the genetic code can be used to predict the amino acid sequence of the corresponding protein. The next step is to predict from the amino acid sequence the three-dimensional structure of the protein. The final step, the prediction of a protein's function, is less straightforward. At the molecular level, the "structure-function problem" refers to the difficulty scientists have in determining the relationship

between the presence of a particular stretch of amino acids in a protein, and the activity or function of those amino acids (38).

A standard approach of biologists to the structure-function problem is to compare the structure of a protein with unknown function to a protein or proteins with known functions (figure 9-4). If structural similarities exist, then experimentally testable predictions can be made on possible functions of the uncharacterized protein. Computer methods for identifying amino acid sequence similarities among proteins, or DNA sequence similarities among genes, are available (16), as are methods for three-dimensional structure prediction and comparison (5). These tools need to be further developed for predictions of protein structure and function from sequence data to become more practical. In addition, in vitro mutagenesis techniques for engineering genes to produce modified proteins (protein engineering–see box 9-B) have advanced, but are still in need of further development (30). These techniques are important for making detailed molecular models of how specific protein structures correlate with particular functions.

Understanding How Proteins Fold Into Active Three-Dimensional Structures

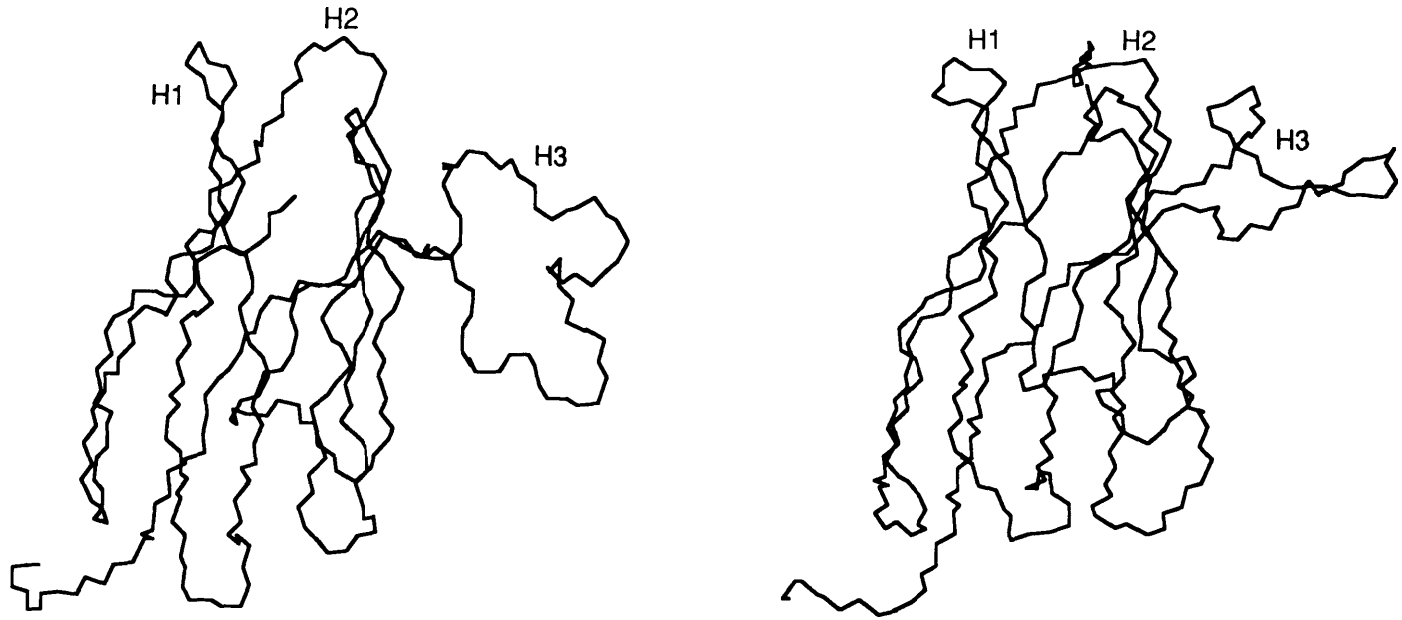
"protein-folding is the genetic code expressed in three dimensions" (19). How does the linear sequence of amino acids in a protein code for its structure? How does the three-dimensional conformation of a protein drive its function? Sometimes the amino acid sequence of a protein with an unknown function is similar to that of a protein with a known function; in many such cases, the similarity is a valid indicator of comparable jobs. In other cases, the three-dimensional structure of a protein (the amino acid sequence folded into the actual structure of the protein) gives more reliable clues about function. At present, scientists cannot predict with certainty how the linear sequence of amino acids in a protein will fold into the protein's three-dimensional structure—thus the protein-folding problem. As more DNA sequences of genes are obtained, the problem will take on even greater significance. In a recent report, the National Academy of Sciences stated that protein folding is "the most fundamental problem at the chemistry-biology interface, and its solution has the highest long-range priority" (38).

The protein products of cloned human genes can be produced in and purified from other organisms or cells, but in the process, they often become improperly folded, inactive molecules. The human factor VIII blood clotting protein required by hemophiliacs (see box 9-A), for example, has posed significant problems for protein chemists trying to purify the recombinant DNA version from non-human sources (32). Because of such problems, it is important to develop a better understanding of how the chemical and physical properties of a protein guide it to become a properly folded, active structure under normal physiological conditions.

Most predictions of three-dimensional structure are based on theories of the behavior of amino acids in certain chemical and physical environments and on information gleaned from viewing the atomic structures of proteins through x-ray diffraction (5). X-ray diffraction of protein crystals is an important tool in the field of structural biology-the study of protein and other macromolecular structures. It is the most important technique for determining the three dimensional structures of large proteins at the atomic level. Advances in x-ray crystallographic (15,65) and other biophysical technologies are needed so that more protein structures can be determined to give a solid foundation for further development of protein-folding theories.

Experimental evidence suggests that certain structural domains serve similar functions in a number of different proteins. Thus, it is the combination of domains that gives a protein its unique overall function (figure 9-4). Protein structure predictions have recently been used to propose a possible structure for Interleukin-2 in an important step toward understanding the interaction of this protein with its receptor during the immune response in humans (13). Once the protein-folding problem is solved, and methods for correlating structure with function are further developed, the road going from the DNA sequence of a gene to the function of its protein product will be considerably shortened, and in some cases, will pave the way for the development of promising new human therapeutic products.

Figure 9-4.—Structural Similarities Between the Doma ns of Different Proteins



	(a)		(b)	(H1)	(c)		(c')	(H2)	(c")	(d)		
IgG	EVQLVQSG	GGVVQPGRSL	RLSCSSS	GFIFSS	YAMYWVRQA	PGK	GLEWVAIIW	DDGS	DQHY	ADSVKGR	FTISR	NDSKN
CD4	QGKKVV	LGKKGDTV	ELTCTAS	QKKS	IQFHWKNSN	QIK	ILGNQG	SFL	TKGP	SKLNDRA	DSRRS	LWDQG
identities	Q -	+ - G-&+	-L&C&&S	S	+ + W -	K	++&		-	&- -	&	-

Seq.1

	(e)		(f)	(H3)	(g)	
IgG	TLFLQMD	SLRPEDT	GVYFCAR	DGGHGFCSSASCFGPD	YWGQGTPVTV	SSAS
CD4	NFPLIIK	NLKIEDS	DTYICEV	EDQKEEVQLLVFGLTANSDTHL	LQGQSLTLTL	ESPP
identities	+ L +—	L- ED&	Y+C	- + & &=	+ GQ& &+T+	S&&

Seq.2 Seq.3

identities
Seq.1 : 75 %
Seq.2 : 57 %
Seq.3 : 79 %

An illustration of the three-dimensional structure of the CD4 receptor domain 3; CD4 is the membrane protein that is the cellular binding site for one of the proteins of the AIDS virus. The three-dimensional, computer-generated model for CD4 domain 3 was constructed by comparison with a known antibody structure (IgG). At bottom are shown the amino acid sequence comparisons between the two protein domains, illustrating the fact that proteins can be structurally similar even though they have few amino acid sequences that match directly.

SOURCE: Ernest Feutmans and Robert Fletterick, University of California, San Francisco, CA.

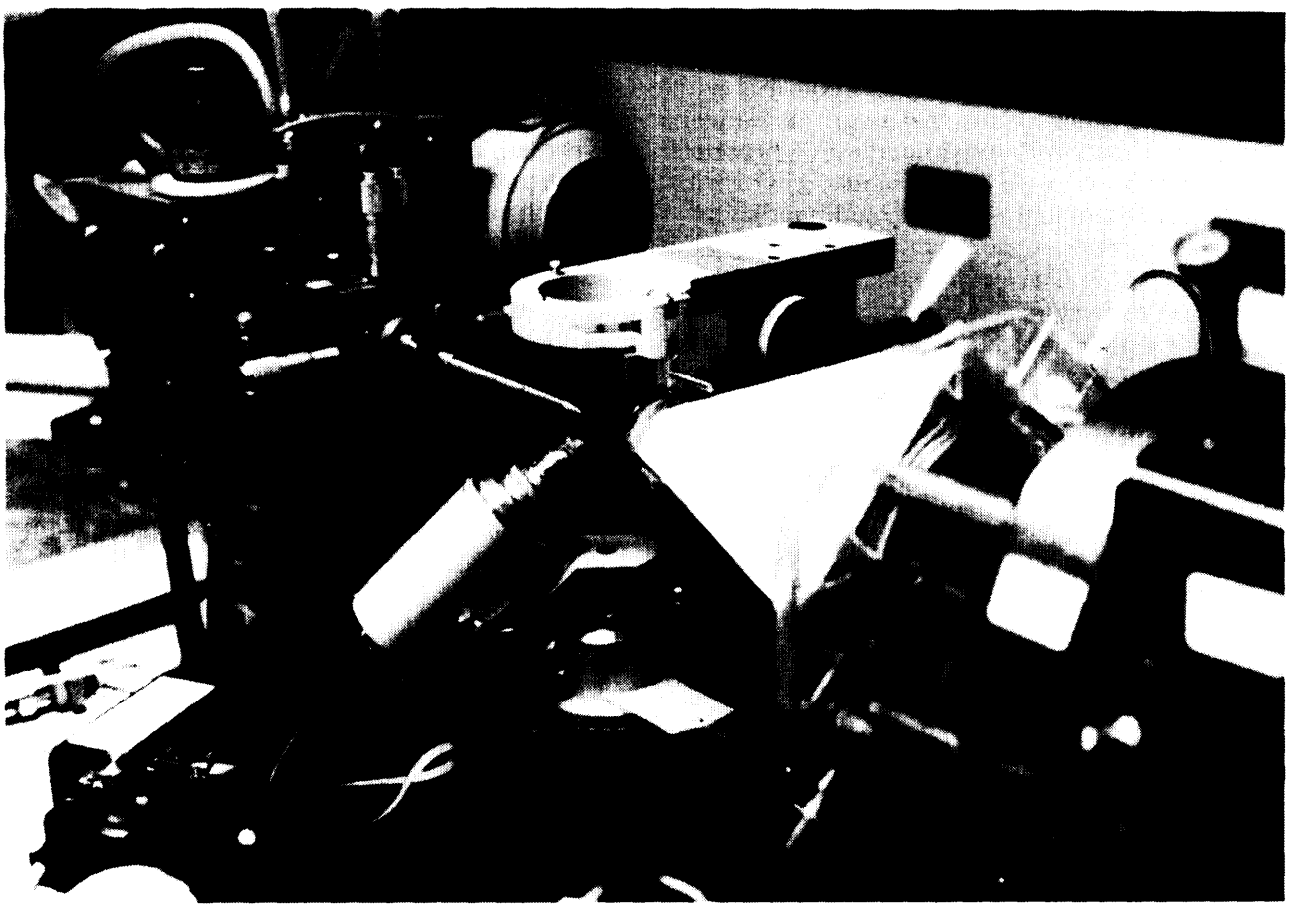


Photo credit: University of Texas Health Sciences Center, Dallas

Instrument for x-ray diffraction analysis of protein crystals used in three-dimensional structure determinations

Developing Animal Models for Studying the Function of Human Proteins

The therapeutic potential of any newly isolated human protein can only be ascertained once its function in the body is known. With current technology, it is faster to clone a human gene than to establish the function of its protein product. As already described, there are theory-based tools for extracting functional information about a protein from both its amino acid sequence and its three-dimensional structure. The most direct method is to experimentally determine the role of a particular human protein under the physiological conditions of the human body. However, experimentation with untested protein products on humans is necessarily prohibited to protect human subjects. In animals, advances in recombinant DNA technology have made it possible to introduce human genes into germ lines shortly after the egg is fertilized (41). An example of such a transgenic animal is the mouse whose milk produces tissue plasminogen activator protein (21) (see figure 9-3). For transgenic animals to be useful in the analysis of human genes whose functions are not known, methods must be devised for directing genes to specific sites in the genome, and for assaying the physiological effects of introducing human genes into animals (53).

Understanding Mechanisms of Protein Maturation and Export From Cells

For many proteins, mammalian cell culture can produce a human protein with greater similarity to proteins isolated from natural human plasma or tissue than can bacteria or yeast cells. There are many problems, however, with the use of large-

scale mammalian cell culturing for the production of human therapeutics, including: high costs; technical difficulties; infection of cultures with viruses and other agents that might be dangerous to humans; and contamination of products with proteins secreted from the host cells or with proteins present in the culture medium that may cause an immune response or be otherwise toxic to humans (7)9). The levels and types of contaminants in the final preparation of a human therapeutic is a major concern of both producers and Federal regulators, and a great deal of effort needs to be directed at finding technical solutions to these problems. In addition, since bacteria and yeast have proven to be commercially valuable systems for the production of human proteins from recombinant DNA, it is important to continue developing an understanding of the process of protein maturation (e.g., how and why certain chemical modifications occur) and export from these cells, so that better production methods might be devised.

Methods for Administering Protein Drugs

One of the greatest challenges to the development of proteins for use as human therapeutics is the requirement of special delivery mechanisms for proteins—both those derived from recombinant DNA and those extracted from human tissue and blood. Protein drugs are often ineffective if ingested, because they are rapidly broken down by enzymes in the gastrointestinal tract. When they do survive in such harsh environments, the large sizes of proteins can inhibit their absorption through the intestinal wall. Consequently, protein drugs are usually administered by subcutaneous, intramuscular, or intravenous injections, but even these delivery routes are associated with problems. Dosage is also a problem unique to protein therapeutics; many proteins, particularly hormones, must be released continuously at a controlled rate over a period of weeks or even months (25). In addition, prolonged exposure to incompletely processed human proteins can induce allergic responses.

Manufacturers of biological therapeutics are beginning to address these problems with a variety of innovative approaches. Protein engineering, for example, could potentially be used as a tool for more effective drug delivery. Industrial researchers used recombinant DNA and computer graphics-assisted molecular modeling to engineer a version of insulin that, when injected daily, is reported to behave more like the body's own insulin than do earlier versions of recombinant DNA-derived human insulin (49). While intravenous and subcutaneous delivery have been standard procedures for many years, methods for administering protein drugs through mucosal routes are now being developed. California Biotechnology, Inc. is developing Nazdel®, a nasal delivery system, as an alternative to insulin injections. Other protein therapeutics such as human growth hormone and a hormone secreted by the heart (atrial natiuretic factor, or Auriculin®), are also under study for intranasal delivery (2).

Photo credit: University of California, San Francisco

Scientist illustrating the use of computer modeling in protein engineering.

Research and Development Funding

Biomedical research encompasses a large number of disciplines, including biochemistry, virology, immunology, genetics, neurobiology, and cell biology. Research in these fields serves as the foundation for innovation in the pharmaceutical industry. The tools of biotechnology are now so intimately woven into each of these fields that it is difficult to differentiate between funding dedicated to biotechnology-based research and that going to more traditional technology. The National Institutes of Health (NIH), the National Science Foundation (NSF), the Department of Defense (DoD), and the Department of Energy (DOE) are the government agencies funding the greatest amount of biomedical research that underlies applications of biotechnology to the development of human therapeutic products.

The contributions of Federal agencies, the States, and U.S. industry to biotechnology research are covered in detail in chapters 3, 4, and 5, respectively. In this section, examples of notable biotechnology projects funded by Federal agencies supporting the greatest portion of biomedical research are identified. Investment by industry and philanthropic organizations in biotechnology research with implications for the development of new drugs is also discussed.

Federal Agencies

The National Institutes of Health (NIH). With the exception of the National Institute of General Medical Sciences (NIGMS), each institute of the NIH has as its principal mission the support of research on a range of diseases. NIGMS supports research and training in the basic biomedical sciences fundamental to understanding health and disease. Its primary function is to support U.S. and international research projects that can serve as the basis for the more disease-specific research undertaken by the other, categorical NIH institutes. The NIH has two categories of biotechnology research: basic research directly related to or using the new techniques that comprise biotechnology; and a larger science base of free-ranging research underlying biotechnology. The more applied areas of research fall under the first category.

The NIH estimates that 38 percent of its $6 billion fiscal year 1987 budget was devoted to biotechnology research. The National Cancer Institute (NCI), the NIGMS, and the National Institute for Allergy and Infectious Diseases (NIAID), were the three lead institutes for biotechnology funding, spending $645, $356, and $297 million, respectively (see table 3-2). NIH funds a number of biotechnology research grants that are pertinent to drug discovery and development. Particularly relevant to the discovery of human therapeutics are relatively new programs aimed at developing therapies for Acquired Immunodeficiency Syndrome (AIDS), stimulating research in protein structure determination and other areas of structural biology, and developing techniques for mapping and sequencing genomes. These projects often fund multidisciplinary research teams.

Under its Small Business Innovation Research (SBIR) grants program (see ch. 3 for further discussion) in fiscal year 1986, NIH funded $44.5 million worth of research at small companies, with nearly 40 percent awarded to companies using biotechnology in their research. Research on delivery systems for protein drugs, production methods for human therapeutic proteins, and other applications of biotechnology is also being funded by NIH at dedicated biotechnology firms and pharmaceutical companies (see table 9-2).

The National Science Foundation (NSF). The funding of basic research grants in genetics, cell biology, and biochemistry is the major mechanism of NSF for supporting biotechnology research with long-term applications in human therapeutics. However, while NIH contributes the greatest share of basic research funds to independent investigators, other agencies, such as NSF, are making significant contributions to the discovery of novel pharmaceuticals by funding large multi-investigator projects in applied research. NSF funds an Engineering Research Center (ERC), called the Biotechnology Process Engineering Center, at the Massachusetts Institute of Technology (see box 3-A). The Center has programs in genetics and molecular biology, bioreactor design and operation, product purification, and biochemical process engineering systems.

Table 9-2.–Representative Biotechnology Small Business Innovation Research (SBIR) Program Grants Funded by the National Institute of General Medical Sciences in Fiscal Year 1987

Biotechnology Firm	Title of Research Grant
Radiation Monitoring Devices, Inc. Watertown, MA	Improved gel electrophoresis for medical research
Genelabs, Inc. San Carlos, CA	Rapid approaches for production of genomic DNA probes
Collaborative Research, Inc. Lexington, MA	Analysis of yeast glycosylation of a human glycoprotein
Biosym Technologies, Inc. Rockville, MD	Computer-assisted protein design
Biotech Research Laboratories, Inc. Rockville, MD	Porous microcarriers for growing cell cultures
Litron Laboratories, Ltd. Rochester, NY	Genetic Toxicology Testing by high-speed flow cytometry
Applied Sciences Consultants, Inc. San Jose, CA	Computer folding of RNA using Monte Carlo method
Biogen Research Corporation Cambridge, MA	Production of recombinant proteins in milk
TSRL, Inc. Ann Arbor, MI	Technology for oral delivery of first pass drugs
Genex Corporation Gaithersburg, MD	Bacillus hosts for pharmaceutical protein secretion
Electrocell Buffalo, NY	Electrofusion and electropermeation of cells
Verax Corporation Lebanon, NH	An improved system for mass culture of human hybridomas
Stratagene Cloning Systems San Diego, CA	New chromosomal jumping vectors for gene mapping

SOURCE: The National Institute of General Medical Sciences, 1988.

The NSF, the North Carolina Biotechnology Center, and several corporations jointly fund the Monoclonal Lymphocyte Technology Center. The Center supports research at several North Carolina universities in genetic engineering, lymphocyte biology, immunochemistry, and bioengineering as they apply to the production and use of monoclonal antibodies. The major goal of the programs supported by the Center is to stimulate university-industry cooperative research in areas with good potential for commercialization.

The Department of Energy (DOE). The Office of Health and Environmental Research (OHER) is the component of DOE with a mission in biomedical research. The primary mission of OHER is to study sources of radiation, pollution, and other environmental toxins (particularly those related to the generation of energy), to trace them through the environment, and to determine their effects on human health and the environment. DOE's commitment to funding a major initiative to map the DNA in the human genome (the entire set of human chromosomes) could be particularly relevant to the application of biotechnology in the pharmaceutical industry. This commitment stemmed from the work of the DOE national laboratories on developing technologies to isolate human chromosomes and examine their structure. An outside advisory panel to OHER recently proposed that DOE request $20 million in additional funds for fiscal year 1988, $40 million in fiscal year 1989, and $200 million in funds by fiscal year 1993 for mapping the human genome at both academic and National Laboratories (55). DOE spent $4.7 million on projects related to mapping genes on human chromosomes in fiscal year 1987, and received an appropriation of $11 million in fiscal year 1988 to expand their gene mapping efforts.

The Department of Defense (DoD). While biological research is not the main mission of DoD, some areas of biotechnology research are supported by its various components. Each military service, especially the Army and the Navy, conducts some research related to the health needs of military personnel or to defenses against chemical and biological warfare. Over $2 million per year is being spent by DoD through its Defense Advanced Research Projects Agency (DARPA) program on university research aimed at protein structure determination and solving the protein folding problem. Biotechnology R&D at the U.S. Army's Medical Research and Development Command Laboratories, such as the unclassified research at the Institute of Infectious Diseases (USAMRIID), has led to the development and testing of a number of internationally important vaccines. USAMRIID spent about $20 million in fiscal year 1987 for applied medical biotechnology research.

Joint Agency R&D Funding. Besides large contract research such as GenBank®—a DNA sequence database funded primarily by NIH and DOE–the joint funding of multi-investigator biomedical research programs by NIH, NSF, and other Federal agencies is uncommon. Joint agency research funding might, in certain instances, bean appropriate mechanism for accelerating the ap-

plication of biotechnology to neglected areas of biomedical research.

The States

The States have few programs directed solely at pharmaceutical biotechnology applications (see ch. 4). The Center for Advanced Research in Biotechnology (CARB) based in Shady Grove, MD is one State-supported biotechnology research program with emphasis on human therapeutic design. Protein engineering and rational drug design are the focus of CARB (see box 9-C). The North Carolina Biotechnology Center, funded in part by the State of North Carolina, is contributing approximately one-third of the funding for a new Engineering Research Center at Duke University that will use emerging technologies to develop treatments for cardiovascular disease.

Industry

Setting up the infrastructure and facilities for developing and manufacturing biotechnology derived human therapeutics is expensive. Established corporations can support these initial costs from profit on sales revenues from traditional drugs, whereas dedicated biotechnology companies (DBCs), in general, continue to rely on capital from contract/collaborative research agreements with large companies, and private and public stock offerings.

Box 9-C.—Center for Advanced Research in Biotechnology (CARB): A Research Facility for Protein Engineering and Rational Drug Design

The University of Maryland, the National Bureau of Standards (NBS) and Montgomery County, MD have established a joint venture called the Center for Advanced Research in Biotechnology (CARB). The aim of this research organization is to make the State of Maryland a national leader in biotechnology by inspiring collaborative research among local academic, government, and industrial scientists.

CARB researchers are currently housed at NBS, but are expected to relocate by the end of 1988 to CARB's future headquarters at a 40,000-square-foot facility in Rockville, MD. The venture's founders hope that having CARB's research facility in close proximity to the National Institutes of Health, the Food and Drug Administration, the Department of Agriculture research headquarters, and a number of commercial biotechnology firms will greatly enhance its chances for success.

The Center has a singular biotechnology research goal that greatly complements the needs of the pharmaceutical industry: to use genetic engineering, computerized molecular modeling, and biophysical techniques to radically reduce the time and effort required to determine the atomic structure of proteins and to effectively model and predict their properties. It is expected that meeting this objective will help build the foundation for the emerging fields of protein engineering and rational drug design. Additional areas of related research include protein separations, biosensors, and biothermodynamics.

Officials at CARB are putting together a multidisciplinary team of scientists and engineers and providing them with state-of-the-art biotechnology instrumentation and facilities. From NBS, CARB hopes to derive expertise in physical and chemical measurement technologies that are relevant to macromolecular structure determination and analysis. University of Maryland scientists and a group of visiting academic and industrial scientists are also to be housed at the CARB facility. Training for graduate students and postdoctoral scientists is anticipated as well.

CARB is the furthest along of four proposed research centers established in the Maryland Biotechnology Institute by the University of Maryland Board of Regents in 1984. CARB received a one-time allocation of $9.5 million from Montgomery County. The Maryland General Assembly appropriated approximately $1.4 million to CARB for fiscal year 1988 for personnel salaries and equipment. The NBS will also contribute $1.5 million to the Center's operating budget in fiscal year 1988.

SOURCES: CARB, Shady Grove, MD, promotional pamphlet, 1987. Walter Plosila, Montgomery County High Technology Council, Rockville, MD, personal communication, April 1988.

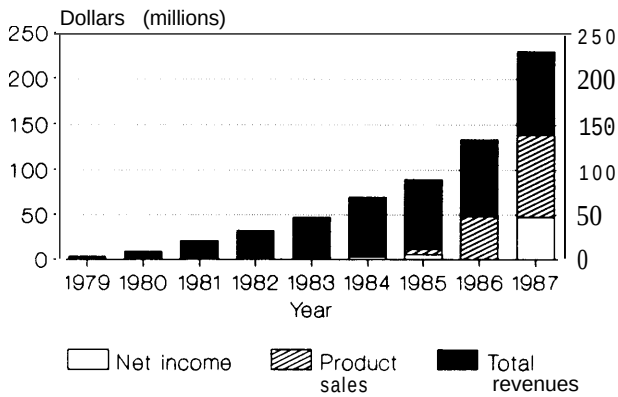
OTA surveyed 296 DBCs in Spring 1987; of these, 63 firms (21 percent) had a primary research focus in human therapeutics. The mean R&D budget of biotechnology companies dedicated to therapeutics was $9 million in 1986 (compared to a mean of $4 million for all DBCs), and a total R&D investment of $0.6 billion.

Fifty-three large, established corporations were surveyed in July 1987; of these, 14 corporations (26 percent) had a primary biotechnology research focus in human therapeutics. These pharmaceutical corporations had a mean biotechnology R&D budget of $16 million in 1986 (compared to $11 million for all established corporations), and a total biotechnology R&D investment of $0.2 billion, or 33 percent as much as the DBCs. The total R&D budget of the large corporations with a primary focus in human therapeutics was $3 billion in 1986, making biotechnology R&D only 7 percent of their total R&D expenditures.

More than for any other business sector, applications of biotechnology to the pharmaceutical industry are moving from the technology development phase to the clinical phase. Contributing to this transition, among other factors, is that between 1983 and 1986, the top management of many of the DBCs changed from the early scientist/entrepreneurs to professional managers, often from the larger, established corporations (33). Nevertheless, over the next several years, revenues from biotechnology product sales will be a reality for only a few firms specializing in human therapeutics. Profit from sales of more traditional pharmaceuticals (e.g., products of chemical synthesis) is still the primary source of biotechnology R&D funds for established companies, while even the most successful DBCs continue to rely on revenues from contract/collaborative arrangements and other outside sources (see ch. 5).

The long-term independence of the DBCs depends upon their ability to continue to raise the capital needed to become fully integrated pharmaceutical companies. A fully integrated company invents, develops, and markets products independently. In the view of most industry analysts, Genentech, Inc. is the only DBC, thus far, that has achieved the goal of becoming a fully integrated pharmaceutical company (figure 9-5). As discussed

Figure 9-5.-The Financial Maturation of a Dedicated Biotechnology Company



* Net income loss of $352.2 million.
SOURCE: Genentech, Inc., 19S8.

in chapter 5, the primary source of capital for companies striving for independent growth must change from venture capital, private or public equity investments, or contract research revenue, to revenues from product sales. Becoming a fully integrated pharmaceutical company is not the goal of each of the DBCs that specializes in human therapeutics, however, and it is an unlikely option for the majority.

Philanthropic organizations

Biomedical research, including that involving biotechnology, enjoys the greatest level of private funding of all the sectors considered in this report. Endowments used to fund biomedical research are provided by numerous foundations, ranging from disease-specific foundations, such as the National Huntington's Disease Association and the Cystic Fibrosis Foundation, to very large organizations targeting research at diseases affecting large numbers of Americans, such as the American Cancer Society.

In the last several years, the Howard Hughes Medical Institute (HHMI), a medical research organization with an endowment of over $5 billion, has emerged as a major source of funds for researchers in a number of biomedical fields that involve biotechnology research. The Institute has increased its biomedical research funding dramatically over the last decade, from

about $15 million in 1977 to over $168 million in 1987 (10).

HHMI operates three main research programs. The first and largest sponsors research in 27 laboratories in medical centers throughout the United States. Research funded by the Institute focuses on five main areas: genetics, neurobiology, cell biology, immunology and structural biology. The second major program includes the human genome program for international data collection and coordination of genome mapping projects, and the Cloister project, a joint effort with NIH to encourage medical students to pursue careers in medical research by enabling them to spend a year at NIH. The third program is the Institute's newest, and focuses on three main areas: graduate training fellowships; research resources grants; and undergraduate science education. Programs for promoting public understanding of science and for evaluating biomedical ethics issues are also being evaluated for this program. The Institute will dedicate at least $500 million to this third major program over the next 10 years (10).

Leaders of the HHMI professed a desire to address gaps in the NIH basic research program at a NIH Director's Advisory Committee meeting in June 1987 (43). The Institute's Director also expressed interest in working with NSF to ensure a strong national program of training grants for doctoral students in biomedical research disciplines (10). The influx of HHMI funds in biomedical research, much of which involves biotechnology, is an important supplement to government funding, but deficiencies in basic research funding could arise if such private investments are considered as substitutes rather than supplements to Federal funds.

Regulation of Pharmaceutical Biotechnology

For DBCs participating in the high value-added human therapeutics industry, the renewal of funds for R&D and ultimately the survival of those companies depends on the incentives and barriers along the path to market approval of their products. The regulatory component of the human therapeutic development process is perceived by both entrepreneurial and established companies as the major factor influencing the time required to develop a pharmaceutical product.

The debate over the rigorous and lengthy drug regulatory process has gone on for years. Arguments have been made that when too strict, regulation becomes prohibitive to pharmaceutical development. Overly stringent regulation could impede international competitiveness, and compromise human health by reducing the availability of therapeutic products. On the other hand, the private sector and the general public continue to stress the importance of protecting public health from unsafe or ineffective drugs. As a background for analyzing regulatory issues relevant to biotechnology products, this section describes the mechanisms currently employed in the United States for regulating human therapeutics. The Food and Drug Administration (FDA) is the regulatory agency with purview over the development of therapeutic products.

Biotechnology Regulatory Policy at FDA

An underlying policy question addressed by the White House Office of Science and Technology Policy (OSTP) in the Coordinated Framework for Regulation of Biotechnology was whether the regulatory mechanisms that pertained to products developed by traditional techniques were sufficient for regulating products produced using recombinant DNA and other new biotechnologies (51 F.R. 2331 O). **Congress gave FDA** authority, under the Federal Food, Drug and Cosmetics Act (FFDCA) and the Public Health Service Act (PHSA), to regulate products regardless of how they are manufactured. These laws authorize the FDA to monitor the testing of a new drug for safety and efficacy before it can be marketed for human use in the United States. The FDA has determined that there is no need for new administrative procedures and regulations specific for products made by biotechnology. In its final policy statement, the FDA indicated that it would not classify products of recombinant DNA or hybridoma technologies any differently from those produced by traditional techniques, and that such products are already covered under existing statutory provisions and regulations for drugs and biologics for human use.

The New Drug or Biologic Approval Process

The general process for obtaining new drug approval includes four main stages: preclinical (animal) studies; clinical investigation; application approval to market the new product; and postmarketing surveillance.

Investigators planning to conduct clinical investigations on human subjects with new products must file a Notice of Claimed Investigational Exemption (IND). The IND must contain information on drug composition, manufacturing data, data on experimental controls, results of animal testing, the training of investigators, intended procedures for obtaining the consent of subjects and protecting their rights, and an overall plan for human clinical studies. Detailed records of clinical investigations are required by the Center for Drug Evaluation and Research before a New Drug Application (NDA) for marketing approval will be considered. The Center for Biologic Evaluation and Research also requires such documentation for biologics (e.g., blood proteins). In addition, each biologic product lot must be characterized, and an establishment license for the production facilities must be obtained before a Product License Application (PLA) for marketing approval will be considered (56). Proteins with therapeutic potential fall under the purview of one or the other of the two Centers.

Special "Points to Consider" bulletins have been issued by FDA for products made using recombinant DNA and hybridoma processes. These include information to assist manufacturers in developing and submitting to FDA applications for approval of such biotechnology products for investigation or marketing, The FDA has requested assistance from product developers in the continuing development of the "Points to Consider" documents (53 F.R. 5468).

FDA Approval of Human Therapeutics From New Biotechnologies

Seven human therapeutics made using recombinant DNA or hybridoma technologies have thus far been approved for marketing by the FDA. To date, the mean time spent by companies taking their biotechnology products through clinical trials and regulatory review at FDA (i.e., from the filing of an IND to the approval of an NDA or PLA) has been five years, significantly less than the **10-** to 16-year average estimated for conventional drugs (67).

For some of these therapeutics, clinical data on their counterparts, or on close analogues prepared from human plasma or tissues by non-biotechnological methods, were available. For example, substantial information already existed on the effectiveness of human growth hormone for dwarfism and on porcine insulin for diabetes-each prepared by conventional techniques (31). A key component of clinical trials for some of the seven biotechnology products now on the market was thus to demonstrate that the biotechnology products are as safe and effective as products prepared by conventional means.

The lack of previous preclinical or clinical studies on a potential protein drug has not, however, appeared to slow the regulatory approval process for biotechnology products at the FDA. Genentech, Inc.'s tissue plasminogen activator protein (Activase®) was approved for marketing only four years after the IND was filed, even though the manufacturing method was modified in the process (47), and there were no prior clinical studies with the protein (32). On the other hand, some biotechnology products, such as interleukin-2, have been in clinical trials for substantially longer times. Over the last several years, there has been considerable controversy surrounding the degree to which the effectiveness of this protein as an anti-cancer agent balances with its toxicity in human beings (1,35). Biotechnology products do not have a monopoly on the "fast-track" at FDA (3). For example, the NDA for azidothymidine (AZT), a non-protein drug that is not a product of biotechnology, was approved in March 1987 for treatment of AIDS symptoms, only 4 months after it was filed, and only two years after the IND was submitted (27), Therefore, therapeutic products whose effectiveness can be demonstrated easily, and for which an efficient production method and dosage form can be readily determined, are likely to be approved in a timely manner, while others will require more extensive clinical studies.

In addition to the seven biotechnology products already approved for marketing by the FDA, there are nearly 400 human therapeutics (produced either by cells that express cloned genes or by hybridomas) in some stage of clinical trials (32). Compared to the total number (25,000) of active INDs for all drugs and biologics currently on file at the FDA, the number of biotechnology products is small—representing only about 2 percent of potential therapeutics in some stage of human clinical trials (32). Nevertheless, in 1986 alone, 20 new human therapeutics were approved, of which four were products made using either recombinant DNA or hybridoma technologies. INDs for products made using the new biotechnologies are currently being filed in the Center for Biologic Evaluation and Research at a rate of about 125 per year, corresponding to nearly 50 percent of the total new INDs for 1987 (32). Meanwhile, the number of FDA personnel available to review the data from the relevant clinical studies has not increased proportionately (32, 71). The FDA Commissioner reported that these factors, combined with the recent emphasis at the FDA on speeding the review of applications involving drugs and biologics that are potential AIDS therapies, could cut into the Agency's resources for processing biotechnology product applications aimed at other therapeutic uses. Despite these concerns, the relatively short time required to obtain market approval of human therapeutic products made using the new biotechnologies, and the high proportion of biotechnology products approved, should help sustain the current high level of public and private R&D funding for the application of biotechnology to human therapeutics in the near term.

Recent Legislative Actions

Since the 1984 OTA report on commercial biotechnology (51), Congress acted in at least two areas involving drug regulation that influence the level of industrial investment in biotechnology-based human therapeutics: orphan drugs and drug exports.

The Orphan Drug Act.—Prior to 1983, pharmaceutical companies had little incentive to invest research funds and personnel in developing drugs likely to yield only limited financial profit. Small biotechnology companies developing innovative new techniques were even less likely to invest any of their limited R&D budgets in unprofitable human therapeutics. Drugs for such rare afflictions as Huntington's disease and Turner's Syndrome, that affect only a small population, were thus commonly known as "orphan drugs, " In 1983, Congress amended the FFDCA with the "Orphan Drug Act" (Public Law 97-414) to provide incentives for developing drugs for rare diseases that would otherwise not be developed because the anticipated financial rewards were insufficient. A 50 percent tax credit for the cost of conducting clinical trials and 7-year market exclusivity were the key incentives provided in the Act. The 7-year market exclusivity provision of the Act was designed to protect companies selling dregs that were ineligible for product or use patents, were off patent, or had little patent term outstanding. Such companies could not otherwise be protected from competition from firms that were already marketing the drug for other therapeutic applications, and thus would not be able to recoup their costs in developing the product for an orphan application.

The Act has been amended twice. A 1984 amendment (Public Law 98-551) defines a rare disease or condition as that which affects fewer than 200,000 persons in the United States, or more than 200,000 persons for which it is clear that the cost of developing the drug will not be recovered by sales of the drug in the United States. A 1985 amendment (Public Law 99-91) authorizes seven years of exclusive marketing approval for all orphan drugs regardless of their patentability, with the intention of encouraging private pharmaceutical companies to invest more in orphan drug development (50). In addition, the amendment reauthorizes grants and contracts for clinical testing of orphan products, authorizes grants and contracts for preclinical testing, and establishes a National Commission on Orphan Diseases.

More than one company can receive the orphan designation for a particular use of a product, entitling them to the tax credit incentive for conducting clinical trials. However, in the cases where several sponsors seek marketing approval at the same time, only the first sponsor

to receive approval is awarded the 7-year market exclusivity for that drug approved for that particular use. The approval of all others is delayed until the end of the 7-year period. The provisions of the Orphan Drug Act have stimulated new commitments to orphan drugs by both research-oriented pharmaceutical companies and DBCs (50,59). As of December 1987, a total of 179 drugs and biologics had been given an orphan designations for specific therapeutic uses (50). Of these, there were eight cases in which more than one company had initiated development of the same drug.

The awarding in 1985 and 1986 of 7-year market exclusivity rights to two companies for the use of their recombinant DNA-derived human growth hormones as a treatment for a rare form of childhood dwarfism has spurred substantial controversy (14,20,37,42). The second version of human growth hormone differed from the first by one terminal amino acid, and may cause less of an immune response in human beings. By approving the second product, the FDA indicated that they considered it a different, and presumably a more effective product, than the first. Other companies are also developing versions of recombinant DNA-derived human growth hormone, and view their own products as having therapeutic advantages as well (66). Analysts predict a potential annual market of over $150 million for human growth hormone, which is one likely reason for the competition among firms for exclusive marketing rights. Human growth hormone is only one of several biotechnology products that have received ‘(orphan” designation from the FDA that are expected to yield substantial revenues. other products include erythropoietin, epidermal growth factor and superoxide dismutase (see box 9-A). Each of these also show potential for additional, non-orphan therapeutic uses and greater long-term profitability.

Competition among U.S. companies for access to future market shares of a few of the same “orphan” biotechnology products is already evident, leading some observers to question whether a highly profitable drug, or one with broad potential applications outside the particular rare affliction warranting its orphan designation, should be eligible for special regulatory status (17,42,50). The market exclusivity provision in the Orphan Drug Act was not intended to be applied unless it is a necessary incentive for innovation. The Committee on Energy and Commerce in the U.S. House of Representatives reported their concern that there will be a sizeable number of drugs developed using the new biotechnologies that will be sponsored by more than one company. The primary reason, in the view of the Committee, is that these companies are not confident about the patentability of their products, and believe that the 7-year market exclusivity provision of the Act is an excellent alternative (50).

Drug Export Amendments Act of 1986.--Until 1986, the United States banned the export ***for sale*** of drugs and biologics not yet approved by the FDA. (Prior to the Act, unapproved drugs could be exported for investigational use only.) The FFDCA was amended in the 99th Congress to establish conditions for the commercial export of new drugs and new animal drugs and biologics manufactured but not yet approved for sale in the United States. The new provisions are referred to as the “Drug Export Amendments Act of 1986” (Public Law 99-660).

Commercial biotechnology trade groups were major advocates of this legislation, arguing that previous export restrictions on drugs and biologics not yet approved by the FDA put them at a competitive disadvantage by forcing them either to build plants abroad or to license their valuable technology to potential competitors. The Drug Export Amendments Act allows, under certain conditions, U.S. pharmaceutical manufacturers to export for commercial purposes drugs and biologics to any of 21 developed countries provided that the drug or biologic has been approved for sale by the importing country (2 I U.S.C. Sec. 382(b)(l)). The exporting company must have an effective IND exemption allowing testing on human subjects, and be actively pursuing final product approval. If a listed country has not approved the product for sale, it may still receive the product for purposes of export to another country on the list in which the drug has been approved.

The Drug Export Amendments create a new export category for the sale of semi-processed)

or biological intermediate products (e.g., a strain containing a recombinant DNA molecule). Under the law, a partially processed biological product that will be used as a therapeutic can be exported for sale upon FDA approval. To obtain FDA approval, the exporter must show that the product is manufactured in compliance with Good Manufacturing Process regulations; the product is labeled appropriately; and there must be certification from the importing company that the finished product is approved or approval is being sought. The provision for partially processed biological products could be particularly important to entrepreneurial companies, such as the DBCs, with budgetary constraints that preclude them from building facilities abroad.

The new drug export laws might benefit DBCs seeking new markets more than large, established corporations using biotechnology. Many established pharmaceutical companies have licensing agreements with international affiliates, or with foreign companies to manufacture their products locally. In contrast, less established biotechnology companies do not want to license out all of their technologies to foreign competitors, but they cannot generally afford to build facilities in several countries. The new Drug Export Amendments lessen the likelihood that the DBCs will lose their share of a product in foreign markets—where the drug could be approved first–by the time FDA approves the drug for marketing in the United States.

Opponents of the new drug export legislation voiced concern that products not yet rigorously tested would be eligible for export. In their view, once an unapproved drug leaves the United States, the FDA will have great difficulty monitoring problems such as mislabeling or illicit shipment to other nations, especially those with little or no regulatory restrictions. It is still too early to establish whether these concerns have been substantiated by FDA actions.

Intellectual Property Protection

The legal protection of intellectual property is a necessary factor for encouraging investment. Reliable patent protection stimulates innovation and reduces the focus on developing analogs or modifications of drugs that have already been proven effective. When intellectual property laws are unclear, the companies developing important new products, such as human therapeutics, **are forced** to invest valuable resources in expensive and time-consuming litigation. In the case of human therapeutics made using recombinant DNA technology, the litigation has involved all types of patents, including those for the products themselves, the processes used to manufacture and purify them, and their various uses.

Broad Scope of Patent Claims

A widely held view of industrialists is that the scope of the patent claims for biotechnology-based human therapeutics is too broad (52). An example of litigation over broad patent claims is that involving the tissue plasminogen activator protein (TPA). A British court revoked a TPA patent that Genentech, Inc. had been awarded in the United Kingdom. The court ruled that the claims in the patent were too broad upon a challenge by the Wellcome Foundation (England) (22). Genentech, Inc.'s U.S. patent for TPA is still pending. Genetics Institute (Cambridge, MA) was awarded broad process patent coverage for a purification method for erythropoietin (EPO) from ***any*** source. This decision is being challenged by Amgen (Thousand Oaks, CA), which has product and process patents pending for EPO (1,22).

Effects of Infringement Suits on Wall Street

Infringement suits between companies producing human therapeutics by recombinant DNA technology have, at the very least, temporary effects on the investment community. On September 12, 1986, for example, Genentech, Inc.'s stock plunged 10.5 points based on the news that Hoffman-La Roche, Inc. (Nutley, NJ) had sued for infringement of their patent covering synthetic human growth hormone. Likewise, the issuance of Genetics Institute's patent on EPO sent Amgen stock down $6.75 per share from $38.25, and Genetics Institute's stock up $4.75 per share from $31.25 on the day of the announcement, July 1, 1987, This oscillating investment activity reflects, in part, the lack of case law histories for biotech-

nology patent infringements. There is a long case law history for patents on traditional pharmaceuticals, but there is little information investors can use to determine the potential outcome of litigation over patents on human therapeutics derived from biotechnology. The creation 4 years ago of the Court of Appeals of the Federal Circuit has resulted in a strong presumption of patent validity for all classes of patents (46).

What Is Patentable?

The U.S. Patent and Trademark Office has four main criteria for patentability of an invention: it must be novel, possess utility, be nonobvious, and the patent must enable others in the field to use the invention (64). Products of biotechnology are complex proteins that must maintain a certain three-dimensional structure, and in many cases acquire certain chemical modifications, in order to function at their full potential, Thus, depending on the organism used to produce the protein, and the process used to purify it, two recombinant DNA-derived versions with identical amino acid sequences could fold into three dimensional structures with different levels of activity. This leads to questions on whether the patent on one protein product excludes the rights to patent all other versions. Another question regarding biotechnology patents relates to the nonobviousness criteria. Once a protein is discovered, is it obvious to produce it using recombinant DNA technology? For these and other reasons, some industry analysts believe that second and third generation recombinant DNA-based human therapeutics will be more easily protected under existing patent laws (1,22). Second generation protein products made using biotechnology can be those modified by protein engineering to have enhanced activity, or those made by a sufficiently different process than the first generation product. The patent protection of these products is uncertain, but the number of companies developing such products reflects high hopes (see ch. 5). There are at least five companies competing for second generation tissue plasminogen activator protein, for example.

Alternatives to Patent Protection

Pharmaceutical companies trying to protect their human therapeutic products may use patents, trade secrets, or copyrights. Recombinant DNA technology offers the pharmaceutical industry new methods for producing proteins that already exist in nature. As long as it does not naturally occur in pure form, and the purification process is not obvious, a therapeutic protein can be patented by the first individual or individuals to create a purified version. Recombinant DNA-derived insulin and human growth hormone were not patentable because purified forms had been prepared in the past using conventional techniques. However, the non-recombinant DNA-derived human alpha interferon was patented (46).

Although patents are the strongest protection and most favorable, there are certain circumstances under which trade secret protection could be preferable (see ch. 6). Process patent protection is not as broad and enforceable as product patent protection can be, so it is sometimes desirable to make innovative processes trade secrets. The advantages of trade secrets are that they do not have to be published, nor do they have to meet the patent requirements of novelty and nonobviousness (51).

Other Intellectual Property Issues

Another issue of intellectual property protection that can influence the level of investment in pharmaceutical applications of biotechnology is the infringement of U.S. process patents by developing and newly industrialized countries. Emerging biotechnologies are particularly vulnerable to weaknesses in process patent protection because it is often the only protection available for a human gene product isolated or produced using biotechnology. A forthcoming OTA report on ***Patenting Life*** will examine these process patent issues, as well as those surrounding the patenting of whole animals engineered to produce human gene products with therapeutic potential.

Access to Biotechnology Information

Rapid advances in recombinant DNA and other biotechnologies have caused an information explosion in the biological sciences, The relentless pace of new developments in biotechnology parallels that of information processing, storage, and retrieval. The combination of developments from these two high-technology sectors could lead

to even greater advances. Access to information generated by biotechnology is crucial to innovation. Organization of the data generated in biotechnology research is necessary for researchers in the participating scientific disciplines (e.g., microbiology, biochemistry, immunology etc.) to build on their individual contributions. Biotechnology information access and organization has implications in several areas of national policy, such as:

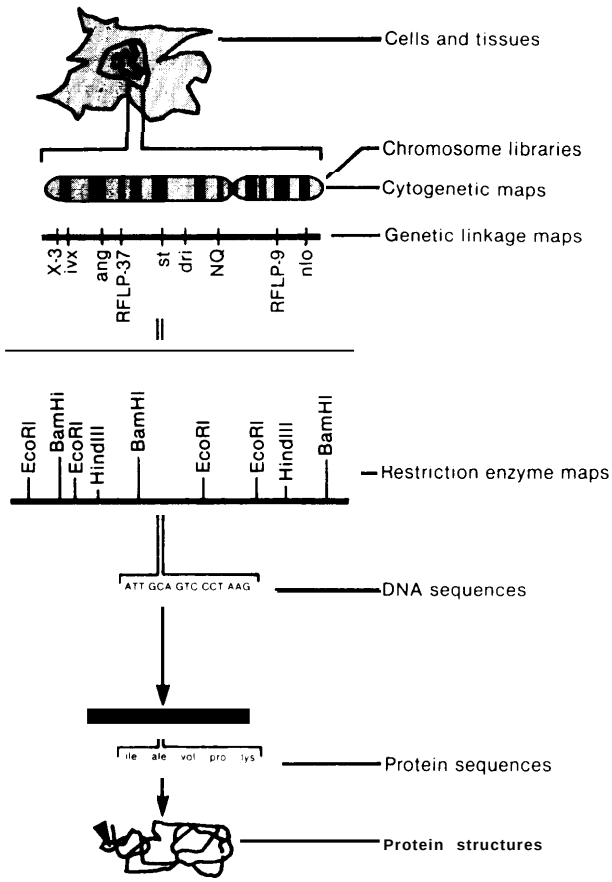
- regulation of commercial products of biotechnology;
- support of biotechnology research and development;
- public perception and awareness of biotechnology;
- intellectual property rights; and
- coordination among Federal agencies (39).

This section focuses on how information access and organization is vital to continued advances in the application of biotechnology to medicine.

A National Research Council report (39) urged that Federal agencies supporting biotechnology research continue to fund or initiate funding in activities concerning biotechnology information. These efforts could range from developing relevant computer software to national centers for information networks. Another recommendation was that the National Library of Medicine (NLM) at the National Institutes of Health coordinate a "database of databases" for biotechnology information and expand its role as an information resource center. Implementation would require an expansion of the current NLM directory of information sources (DIRLINE) and would include a cross-referencing system and a thesaurus for biotechnology. The users of these facilities would not only be the researchers in the multiple scientific disciplines involved, but regulators, patent attorneys, and other officials needing information on biotechnology. Congress appropriated $3.83 million in fiscal year 1988 for the NLM to initiate work on the proposed database of databases.

There are more than a hundred different databases—some more frequently used than others—maintained as sources of data for researchers in the various biological sciences (12). There are databases containing the nucleotide sequences of cloned genes, the amino acid sequences of proteins, the structures of organic molecules, locations of genes on chromosomal maps, pedigree data from families with genetic diseases, and three-dimensional atomic coordinates of protein structures (figure 9-6). Computer software has been developed that allows a researcher to analyze his or her own data relative to that stored in the databases. The Division of Research Resources at NIH funds a national computer resource, called BIONET, that offers sophisticated analytical software for use by government and academic researchers (industry only has access to the BIONET information network). Databases of structures of nonbiologic drugs with established activity can be used together with those containing three-dimensional structure data on proteins in rational drug design strategies. Research on the structure of one of the family of viruses that cause acquired

Figure 9.6.—Databases in Biotechnology



SOURCE: The National Library of Medicine and Office of Technology Assessment. 1988.

immune deficiency syndrome was made feasible by the BIONET resource (60).

In 1987, a group of government, academic, and industrial scientists met in Santa Fe, NM to develop a strategy for making biological information accessible to all users. Their goal is to create an expert system, called the Matrix of Biological Knowledge, by interconnecting available databases in ways that will interpret the scientific questions of investigators from any one of a number of diverse fields in biology and chemistry (36). The NLM database of databases would be only one component of the system. Through the Matrix system, a pharmaceutical scientist would be able to communicate on-line with the data from the work of agricultural scientists, for example. Certain task groups have been set up to initiate small projects that would demonstrate the efficacy of Matrix, with the hope of gaining additional support for the project (68).

The transfer of information from proprietary sources to the public domain is an important public policy issue. For example, scientists from both the public and private sectors are conducting research aimed at elucidating the structure and function of human genes and gene products. Ready access to information, as it evolves, is essential for maintaining the current pace of innovation in areas of biotechnology that could improve human health and prevent disease. This will require the timely entry of information (proprietary and otherwise) into public databases (53).

Availability of Trained Personnel

The availability of trained personnel has been indispensable to the dominant position maintained by the United States in pharmaceutical biotechnology. There is a wide variety of scientific and administrative personnel who perform the work involved in applying biotechnology to the discovery and commercialization of human therapeutics. Scientists who carry out basic research, process engineers responsible for product scale-up, pharmacologists and clinicians who perform studies in animals and humans, legal and regulatory administrators who must apply existing law to the products and processes of biotechnology, and marketing personnel are all involved. Chapter 8 covers the general scientific training and personnel needs of both academia and industry. Chapter 6 addresses the problems in obtaining and keeping highly trained scientific personnel in the various government agencies. This section summarizes the research disciplines from which highly trained scientists must continue to emerge to fill the existing gaps in biotechnology research along the path to development of new human therapeutic products.

In a recent report, the National Academy of Sciences (NAS) (38) requested increased Federal attention to the need for interdisciplinary training in biology, chemistry, and physics for graduate students and postdoctoral personnel. The new generation of structural biologists, those who will be primarily responsible for advances in protein engineering and rational drug design, must be trained in the basics of protein chemistry, molecular biology, and biophysics. An increasing number of large corporations and dedicated biotechnology companies have set up programs to study the three-dimensional structure of large molecules such as proteins and DNA. These programs require expertise in such biophysical methods as x-ray crystallography, nuclear magnetic resonance spectroscopy (NMR), theoretical molecular modeling, and computer graphics. While the fields of molecular and cellular biology are well populated (38), academia and industry (especially pharmaceutical companies) are competing for scientists trained in structural biology (23).

As the number of cloned human genes rises, and the ability to purify their protein products increases, there will be a growing need for scientists trained to determine how these proteins work in the human body, and to assess their potential as human therapeutics. This would require researchers from the traditional fields of human physiology, pharmacology, and toxicology, but with experience that extends beyond traditional synthetic drugs to include protein drugs.

In assessing personnel and training program needs, it is important to emphasize that as biotechnology becomes fully integrated into biomedical research, and new research tools continue to be developed, the types of scientific expertise re-

quired will also evolve. Therefore, scientists with solid training in the general areas of biology, chemistry, and computer science will likely be the best prepared to meet the changing needs of biomedical R&D in both academia and industry.

FUTURE APPLICATIONS OF BIOTECHNOLOGY TO HUMAN THERAPEUTICS

Some scientists believe that the use of biotechnology will actually contribute more to studies aimed at understanding the basic processes underlying cellular physiology than to the production of novel human therapeutics. In other words, once the mechanisms directing normal cellular functions are known, conventional drugs (e.g., pharmaceuticals made by chemical synthesis) may be designed more intelligently (or rationally) because the chemical characteristics of their target sites and their mechanism of action will be better understood (6). Biotechnology has stimulated the interest of pharmaceutical companies in rational drug design, but research in this area is expensive, requiring multidisciplinary research teams and costly instrumentation and computers for designing molecules. Despite the renewed enthusiasm in this area, computers and molecular modeling have led to very few rational drug design successes (43)62). Therefore, for the time being, these methods are more likely to remain in academic laboratories and a few large pharmaceutical companies, than in the smaller companies dedicated to biotechnology.

One strategic challenge posed by human therapeutics made using biotechnology is that new methodologies are constantly being developed that improve product purity, stability, and production efficiency, and manufacturing processes must be modified accordingly, For example, Genentech, Inc. modified its manufacturing protocol for TPA during clinical trials, making it necessary to ascertain any effects unique to the product manufactured by the new process (47,7 I). In such circumstances, the sponsor is faced with the obvious benefits of rapid advances in molecular biology and the desire to design a superior product against the financial and regulatory burdens incurred by altering manufacturing processes during development (4). In contrast to the scenario for conventional drugs where manufacturing records establish the criteria for product purity, for human therapeutics made using biotechnology, the process also plays a role in defining the regulatory guidelines for the products (57,58). For therapeutic applications in which biotechnology is not the only option for product development, these factors will continue to influence the choice between biotechnology and more conventional routes.

ISSUES AND OPTIONS

ISSUE 1: Should action be taken to ensure that the development incentives provided in the Orphan Drug Act are being used for their intended purposes?

The objective of the Act was to provide incentives for developing drugs for rare diseases that would not otherwise be developed because the anticipated financial rewards were insufficient. The simultaneous development of an orphan product by multiple companies implies either that the potential commercial value of the product is high enough that it would be developed even without the Orphan Drug Act incentives, or that the companies are unaware of each other's development activities. Therefore, if Congress takes measures to amend the provisions of the Act to prevent improper use of its objectives, it should do so taking care not to remove incentives for the majority of sponsors who are developing drugs that are truly orphans.

Option 1.1: Take no action.

The Orphan Products Board reported a significant increase in orphan drug development, including a substantial number of products made using biotechnology (over 10 percent of the total) in the five years since the Act. Dedicated biotechnology companies have limited resources to invest, and they generally aim their R&D budgets at potentially profitable drugs. If the existing incentives for R&D investment in orphan drug applications were altered, the dedicated biotechnology companies might be less likely to participate in orphan drug development than would the large, established corporations. However, the smaller companies have contributed much to innovation in the development of biotechnology products, and for some orphan diseases, these could prove to be the only effective products. Congress could thus determine that the tax credit and 7-year market exclusivity incentives of the Act are, for the most part, being used as designed, and that no further action is necessary.

Option 1.2: Amend the Orphan Drug Act to discourage sponsors from using orphan drug status as a means of achieving market exclusivity for drugs that they would likely develop without the incentives of the Act.

The 7-year market exclusivity provision of the Act was intended to assure orphan drug developers that they would recoup their development costs, even though there was little commercial value and inadequate patent protection for the product. Concern has been raised that in the face of uncertainty over the validity and scope of patent protection on many biotechnology products, the developers are viewing the Act market exclusivity provision as a patent substitute. Therefore, in keeping with the legislative intent of the Act, measures could be taken to ensure that its incentives are not abused by sponsors who stand to make substantial financial gains on orphan products. One or a combination of any of the following options could be used by Congress to amend the market exclusivity provisions of the Orphan Drug Act:

- Orphan drug sponsors with pending patent applications, or holding patents with lifetimes that will not expire soon after market approval, could be excluded from 7-year market exclusivity rights.
- Any company willing to carry out all of the necessary testing of a drug identical to or similar to one already approved for the same disease could market their product during the 7-year protection period afforded to the company that originally developed the drug.
- A 7-year term of market exclusivity could be granted to all companies that had filed NDAs or PLAs for the same therapeutic use of the orphan product by the time market approval was granted to the first company. Congress might find that this option balances the need to continue proven incentives for orphan drug development with both the equitable treatment of codevelopers of a particular drug and competition in the major markets that can support it. If market exclusivity is shared only by companies that have already filed an NDA or PLA at the time the first application is approved, then companies only days away could be excluded, even though they had made significant investments in orphan drug development.
- The market exclusivity provision could be removed. Congress could determine that the low profitability of drugs marketed for orphan uses offers a natural market exclusivity to the original developer in most cases, thereby superseding the need for such a provision. Without the provision, however, there would be no assurance that the sponsor of a product that is either off patentor unpatentable, could offset some or all of the development costs by recouping all possible revenues from the sale of the drug. Moreover, exercising this option would remove incentives for all orphan product developers, even though only a few products, such as recombinant DNA-derived human growth hormone and erythropoietin, could yield substantial revenues.
- Sponsors receiving revenues from sales of orphan drugs for rare disease applications that exceed a fixed ceiling could lose their market exclusivity rights. Congress could find that this approach is the most direct one for discouraging the use of the development incen-

tives offered by the Act for drugs with anticipated profitability.

ISSUE 2: Should Congress act to facilitate access to information generated by biotechnology-based research with potential applications to human health?

Rapid advances in recombinant DNA, hybridoma, and other biotechnologies have led to an explosion of information in the biological sciences. Organization of the data generated in research based on biotechnology is necessary for building on individual contributions and furthering innovation. Databases exist in government and academic laboratories for a wide variety of biological information; some of the databases, such as those containing DNA and protein sequences, are heavily used, while others are used by individuals in more specialized fields. In some cases, databases are used to indicate the availability of and to describe certain types of biological materials. The users of biotechnology information are not only academic, government, or industrial researchers, but regulators, patent attorneys, and other officials needing data.

Option 2.1: Take no action.

The National Institutes of Health, through the Division of Research Resources and other categorical institutes, maintain over 100 informational databases, and fund research for managing and understanding large amounts of biological information. Congress could conclude that these NIH activities, and those of other Federal agencies are sufficient to meet the major needs in biotechnology information management. However, many scientists view the existing resources for assimilating and analyzing the rapidly accumulating biotechnology information as insufficient to meet the needs of the community of users.

Option 2.2: Increase funding levels for existing programs or initiate funding in new activities concerning biotechnology information management.

The development of computer software to link the large number of different databases in a way that will allow researchers to better analyze their own data, and to avoid unnecessary duplication of research, is a major goal of all researchers using biotechnology. Congress could authorize Federal agencies that support biotechnology research to fund more activities related to the development of new systems for managing biotechnology information. These efforts could range from developing relevant computer software to national centers for information networks. The designation or creation of a center or centers for biotechnology information analysis and management could assist in the development of new communication tools and serve as centers for the distribution of biological information.

The National Library of Medicine (NLM) is one possible location for a biotechnology information center. The NLM has made a catalog of human genetic loci, called Mendelian Inheritance in Man, available on line through its Information Retrieval Experiment (IRX) program, and has linked the data in this volume to the information available in GenBank® and the Protein Information Resource databank (funded primarily by NIH), to important databases for researchers in molecular biology. The NLM has also begun an experimental program for linking molecular biology databases, using researchers at NIH to test the system's effectiveness.

SUMMARY

The pharmaceutical industry enjoys the highest level of biotechnology R&D investment from both public and private sources. In fiscal year 1987, the National Institutes of Health, with its research mission inhuman health and disease prevention, provided about 20 times the amount of any other Federal agency on biotechnology R&D. Companies developing human therapeutics based on biotechnology had R&D budgets higher than those financed by any other industrial sector in the 1986/1987 fiscal years. Human therapeutics make up the primary R&D effort of 21 percent

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of dedicated biotechnology companies and 26 percent of the larger, established corporations using biotechnology. Because the application of biotechnology to the development of human therapeutics has only recently begun to make the transition from new technology development to successful clinical applications, the availability of funds for basic and applied research will be important in sustaining the current pace of product development.

The rate of human therapeutic product development could be substantially increased if greater effort were given to developing new methods to isolate genes and proteins for research; establish relationships between protein structure and function; determine how proteins fold into active structures; study the physiological roles of human proteins in model systems; analyze the mechanisms of protein maturation and export from cells; and deliver human therapeutic proteins to the appropriate targets in the human body. Despite its successes in the area of human therapeutics, however, biotechnology will likely only complement more traditional methods of isolating or synthesizing pharmaceuticals.

The new biotechnologies are now an integral part of research in the development of human therapeutics at dedicated biotechnology companies and at larger, more established pharmaceutical corporations. Biotechnology is now being applied by the pharmaceutical industry as a tool for developing therapies for many different human diseases and afflictions. A company's success in applying biotechnology to the development of human therapeutics will now be measured not just by its research capabilities, but also by its strengths in meeting drug approval requirements, protecting intellectual property rights, and new product marketing. There is no longer a clear advantage of the dedicated biotechnology companies **over** the pharmaceutical industry giants in the development of new products and processes. On the other hand, the large, established companies can no longer claim a substantial lead in the management end of product development.

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