Biotechnology and Managed Care

by August J. Salvado and Grant D. Lawless

OBJECTIVE: To present an overview of the biotechnology industry, with a discussion of newer techniques and their relationship to drugs that are either in the testing phase or approved for human use. Future trends in biotechnology are cited.

DATA SOURCES: Presentations given by the authors at a Blue Cross Blue Shield National Medical Management Forum in Dallas, TX, on October 26, 1999; MEDLINE literature searches using biotechnology, gene therapy, monoclonal antibody therapy, signal transduction inhibition, matrix metallopro-

teinase inhibition, antisense oligonucleotide therapy, and angiogenesis inhibition.

CONCLUSION: The potential impact of biotechnology on disease detection, diagnosis, prevention, and other areas of medical significance is enormous. Recent findings and technical developments are likely to spawn commercial applications in the next 3 to 10 years. Developments in biotechnology are emerging at too rapid a pace for any one individual to keep current.

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The twentieth century witnessed an explosion in human inventiveness, including aviation, wireless communication, and the development of the semiconductor and digital computing. Although each of these technologies continues to have profound effects on human existence, none will do so in a greater variety of ways than biotechnology. Virtually everything that is important to health care practitioners and patients will be fundamentally transformed by the current revolution in biotechnology and genetic medicine.

Biotechnology is the application of biology to the development of products and services that use naturally occurring molecules created to restore biologic processes.¹ Biotechnology has evolved dramatically during the past 50 years, beginning with the discovery of deoxyribonucleic acid (DNA) and its structure in the 1950s, the identification of its genetic code in the mid-1960s, and the cloning of the first human gene, somatostatin, in 1977 (see Figure 1, opposite).² In the early 1980s, the ability to manufacture DNA using recombinant technology opened up many commercial possibilities. In 1982, for example, recombinant human insulin was approved for use in refractory diabetics.³ Since then, biotechnology has progressed exponentially.

This article presents an overview of the biotechnology industry, with a discussion of new techniques and their relationship to drugs that are in the testing phase or approved for human use. We also look at future trends in biotechnology.

The Current Biotechnology Industry

Enthusiasm for the development of biotechnologic techniques and products led to substantial funding of the biotechnology industry in the late 1980s and early 1990s. However, the late 1990s saw a decline in this funding, based on the perception that ventures were too risky, slow, or difficult. Despite variable patterns of success, the biotechnology industry has grown into a significant economic force, worth more than \$13 billion in annual revenue and encompassing more than 1,300 companies.¹ Collectively, these biotechnology companies have 2,200 products in development; 1,700 of these products are in clinical trials, and more than 300 products are in late clinical trials (see Table 1, opposite).⁴ About one-third of the products in these trials are oncology-related. Other therapeutic categories most likely to benefit from biotechnology include hematology, infectious disease, immunology, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), rheumatology, and gastroenterology.

The Food and Drug Administration (FDA) has facilitated more rapid availability of biotechnology products in the marketplace—over the past decade, FDA new drug application

FIGURE 1 Evolution of Biotechnology

(NDA) review periods for biotechnology products decreased from more than 30 months to less than 12 months. This trend in accelerated regulatory review and approval time of biotechnology products is expected to continue.

New Drug Discovery

Some conventional therapies, such as cancer chemotherapy, are inadequate because of the lack of selectivity between dysfunctional and normal cells. The discovery of novel agents that will selectively target dysfunctional cells without causing toxicity to normal tissues has been fueled by the unveiling of a host of potential molecular targets through the application of molecular biology methods. These methods have also encouraged the investigation of these potential targets for drug discovery by allowing functional expression or production of the targets for use in high-throughput screening assays of natural and synthetic molecule libraries. Molecular biology techniques have also allowed the production of sufficient quantities of target proteins for x-ray crystallographic studies that provide pertinent three-dimensional structural information about the targets and their interaction with ligands/inhibitors for structure-based rational drug design. Interesting and creative approaches to treating diseased or dysfunctional cells have emerged.

Genomics

Gene therapy, the most important emerging area of biotechnology directly related to human health, may revolutionize modern medicine.¹ This facet of biotechnology is based on genomics—the study of genes and how they affect the human body. Although the term genomics is used broadly to categorize several types of biological methods for research and drug development, in its most restricted definition it refers to the sequencing of DNA.² The entire human genome (i.e., the full set of genes in an individual) is thought to consist of 50,000 to 150,000 functional genes. A complete genome sequence contains the code for every structural protein and enzyme required for the synthesis of cellular components.⁶ The Human Genome Project, a

TABLE 1 Number of Pivotal Trials by Disease Control

Disease Category	Phase II/III Phase III
Infectious diseases (includes vaccines)	30
Cancer	78
Neurology (includes Alzheimer's disease)	17
Dermatology	8
Diabetes	5
Endocrinology/ metabolic diseases	9
Gastrointestinal	6
Hematology (includes blood substitutes)	11
Hepatitis	14
AIDS	16
Nephrology	5
Cardiovascular	13
Osteoporosis	13
Rheumatoid arthritis	7
Sepsis	5
Wound healing	10
Miscellaneous	66
Total	313

Sources: Goldman-Sachs & Co., Bio World Financial Watch, Ernst & Young, LLP

government-funded consortium, recently completed a draft for the entire sequence of the human genome. This effort will allow researchers to sort the entire code of 3.15 billion nucleotide base pairs and help efforts to identify disease-relevant genes.

To date, two biotechnology firms have sequenced more than 85% of the nucleotide base pairs. Computerized database searches for sequence similarities among gene sequences have yielded important discoveries, and the role of genetics in many diseases has become more apparent.⁷

Historically, genomics involved a time-consuming process of biochemical purification of protein products designed to identify and characterize proteins associated with a particular disease state or tissue. Once a protein was determined to have potential relevance, scientists worked backward to identify a gene sequence. In contrast, a more contemporary process

involves the use of gene sequences to screen tissues or proteins for the presence of molecules with similar or identical gene sequences. Once a promising gene is determined to be relevant for treatment of disease, its function is best determined by placing it in a transgenic mouse; interesting phenotypic expression in the animal suggests that the gene is a good target for a pharmaceutical product. Conversely, phenotypic expressions that are hidden when a specific gene is inactivated also suggest new molecular targets for drug therapy.

Bioinformatics combined with other technologies, such as combinatorial chemistry against pure molecular targets and high-throughput screening, enables researchers to identify novel peptides, proteins, or small molecules that target specific genes or proteins. Combinatorial chemistry is the process of testing cellular targets against large libraries of peptides or oligonucleotides to identify compounds that chemically interact with the targets. High-throughput screening is an automated process that rapidly sorts large compound libraries to identify potential therapeutic candidates. Computational structure-based drug design, utilizing x-ray crystallographic information, helps probe for mechanisms of action and potential toxicity profiles of these novel agents.

Gene therapy applies the principles of genomics to the search for improvements in disease diagnosis, treatment, and prevention. Generally, gene therapy is characterized by the transfer of genetic information in the form of nucleic acid (usually DNA, which encodes for a therapeutic protein) into the cells of a patient for amelioration of disease.⁸ The goal of gene therapy is twofold: (1) to repair underlying genetic defects responsible for a number of disorders (e.g., hemophilia, cystic fibrosis); and (2) to overcome limitations, including low bioavailabilities, inadequate pharmacokinetic profiles, and high manufacturing costs, often associated with the administration of traditional therapeutic proteins.⁹ These goals are achieved by the discovery and development of therapeutic antibodies, proteins, or small molecules that target a specific genetic abnormality, which are devoid of toxicities commonly encountered with today's pharmaceuticals. Of the therapeutic opportunities for genetic intervention, oncology holds the most promise; cancer gene therapy accounts for approximately 65% of gene therapy clinical trials.⁹ Other potential uses for gene therapy are in hematology, immunology, pulmonology, and cardiology.

With few exceptions, the impact of genomics and other new technologies on pharmaceutical discovery has not been fully realized. However, the drug discovery process involving genomics is expected to evolve as more molecular drug targets are extracted from gene sequencing data. New technologies are being developed to help bridge the gap between poorly characterized gene sequences and well-characterized proteins.⁵ These technologies, collectively referred to as functional genomics, are designed to monitor gene expression patterns as a step in excerpting genes of interest and will hasten the genomic-based

drug discovery process.

■ Therapeutic Applications of Biotechnology

Monoclonal Antibodies

Monoclonal antibodies (MAbs) are specialized forms of protein, designed to target other proteins, enzymes, or receptors that are elevated during disease. MAbs are used to facilitate delivery of drugs or toxins to pathologically altered cells and to carry enzymes to tumor surfaces to activate pro-drugs. Radiolabeled MAbs are used for site-directed delivery of radioisotopes.

MAbs were first described in 1975 by Köhler and Milstein, and mass-scale production of MAbs for clinical investigation followed.¹⁰ The development of MAbs as therapeutic agents was costly and time consuming, however, and generation of human MAbs was difficult.¹¹ These limitations led to the use of new technologies to redesign MAbs, which resulted in smaller, recombinant MAbs that closely resembled human immunoglobulins and retained the antigen-binding characteristics of the original murine MAbs.¹¹ These redesigned MAbs allowed for more adequate tumor penetration and elimination of immunogenicity problems.¹¹ Over time, the production of unlimited quantities of highly specific MAbs has facilitated their use for many diagnostic and treatment purposes.

MAbs are prepared by various methods: (1) introducing a foreign antibody into an animal, which results in the formation of antibody-producing lymphocytes; (2) harvesting B lymphocytes from the spleen; (3) fusing antibody-producing B lymphocytes to cancer cells to impart the continuous reproductive characteristic of cancer cells; and (4) separating and cloning the hybrids to produce individual cell lines that secrete MAbs.¹²

The first MAB clinical trials began in the late 1970s, primarily in patients with hematologic malignancies. Therapeutic applications of MAbs have been particularly useful in oncology, with MAB use representing significant advancement compared with conventional methods of cancer therapy in the treatment of breast, gastrointestinal, and colorectal cancers; melanomas; and non-Hodgkin's lymphomas.¹³ MAbs have also been used for imaging and in cancer therapy.

The remarkable efficacy of MAbs in the treatment of cancers in animals is the basis for continued research in human cancers. Two MAbs were recently approved by the FDA: rituximab (Rituxan; Genentech, Inc. and IDEC Pharmaceuticals) and trastuzumab (Herceptin; Genentech, Inc.). Rituximab is used for the treatment of relapsed or refractory low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma. Trastuzumab is an anti-HER2 MAB used as monotherapy for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their

metastatic disease are candidates for trastuzumab in combination with paclitaxel. Other MABs currently undergoing evaluation in phase II and III trials hold the promise of being approved and marketed in the next five years.¹¹

Signal-Transduction Inhibition

Recently, a better understanding of the molecular basis of cellular communication indicates that a number of diseases result from a malfunction of intracellular signaling. The activity of a particular signal-transduction pathway is often enhanced or inappropriately active in the diseased cell; study results suggest that blocking a signaling element that is overactive in a tumor cell but essential for normal cell function is a promising therapeutic approach.¹⁴ Signal-transduction malfunction results in proliferative diseases, such as cancers, atherosclerosis, and psoriasis, as well as inflammatory conditions, such as sepsis, rheumatoid arthritis, and multiple sclerosis.¹⁴ Signal transduction may be inhibited using reagents, such as small molecules, antibodies, DNA proteins, antisense RNA, and target-specific RNA ribozymes; in particular, this approach to therapy has been developed for protein tyrosine kinases (PTKs). PTKs, essential to normal cell growth, play a role in proliferative diseases when overexpressed. They function in signaling, and their enhanced activity leads to a cellular abnormality, such as activation of genetic mutations or persistent stimulation of cell division by growth factors.¹⁵ Major pathways of PTK-related signal transduction have been unraveled in recent years and serve as useful targets for signal-transduction interception. Natural PTK inhibitors serve as models for the development of other synthetic inhibitors. Development of drugs that interfere with the catalytic functions of PTKs will undoubtedly be relevant in the treatment of allergic diseases, autoimmunity, transplantation rejection, and cancer.¹⁶ Additionally, success with PTK blockers in cell and animal models suggests promise for the treatment of restenosis (an advanced form of atherosclerosis), psoriasis and other skin conditions, and certain inflammatory conditions.

Matrix Metalloproteinase Inhibition

Matrix metalloproteinases (MMPs) are a gene family of at least 15 structurally related enzymes responsible for the degradation of extracellular matrix components associated with angiogenic and metastatic processes. The proteolytic activity of MMPs is normally regulated by the tissue inhibitors of metalloproteinases (TIMPs); disturbance of the MMP/TIMP balance can result in pathologies such as rheumatoid arthritis, osteoarthritis, and atherosclerosis, as well as tumor growth and metastasis.¹⁷ MMP overexpression has been shown in prostate, lung, breast, and colon cancers and is five times higher in low-graded kidney tumor tissue than in normal tissue.¹⁸

Advances in molecular research led to a greater understanding of metastatic processes, including the role of proteinases that are required for basement membrane penetration by invad-

ing tumor cells. These proteinases have become targets for novel cancer therapies in the form of MMP inhibitors.¹⁹ The so-called first-generation MMP inhibitors showed poor oral bioavailability and offered little advantage over the natural TIMPs.²⁰ Refinement in the design of these compounds, in the form of low-molecular-weight MMP inhibitors with good oral bioavailability, represents an important stride in the area of MMP inhibitor drug development and research. Several MMP inhibitors are being evaluated as oral treatments for cancer, inflammatory bowel disease, and rheumatoid arthritis.

Antisense Oligonucleotides

Antisense oligonucleotides are a novel class of therapeutic agents used in the prevention and treatment of gene-mediated disorders. This class of compounds was developed on the premise that inhibiting the process and translation of messenger RNA (mRNA) blocks the expression of target genes involved in pathologic processes. Gene expression is inhibited by hybridization of an oligonucleotide to sequences in the mRNA target by base-pairing rules. These base-pairing rules govern the interaction between the antisense oligonucleotide and the target, allowing the design of these compounds to target any gene of a known sequence.²¹ Several types of antisense approaches have been developed: one uses antisense DNA and the other uses RNA. Different antisense compounds act at various stages in the synthesis of a biologically active target protein.²² Advantages of antisense approaches over conventional pharmacotherapy include extremely high specificity of antisense DNA and RNA for their target, ease of design, and requirement of information only on the nucleic acid sequence encoding a given protein.²²

The concept of antisense technology was considered relatively simple, although development of antisense oligonucleotides with therapeutic applicability proved difficult. The mechanisms by which oligonucleotides interact with nucleic acids are complex and numerous, and little is understood about the factors that may be involved after oligonucleotides bind to their receptor sequences.²³ Pharmacokinetic, toxicity, and manufacturing issues had to be resolved before developing a biologically effective oligonucleotide.²¹

Antisense oligonucleotide therapy is being applied to oncology and hematology, and to cardiovascular, infectious, and viral diseases.²⁴ The first antisense-based drug marketed in the United States, fomivirsen sodium, has been approved for local treatment of cytomegalovirus retinitis in patients with AIDS. Phosphorothioate oligonucleotides are being evaluated in phase I and II trials for the treatment of cancer and viral infections and have demonstrated acceptable pharmacokinetic and safety profiles.²⁴

Angiogenesis Inhibition

Realization that tumors depend on a blood supply to grow and metastasize fueled research for a method to eliminate the vasculature required to nourish growing tumors. The strategy

behind angiogenesis inhibition represents a promising and unique breakthrough in cancer research. Tumor angiogenesis involves a number of complex processes, beginning with the production and release of angiogenic factors by tumor cells or their surrounding matrix, which activates endothelial cells (ECs) and culminates in a highly vascularized tumor.²⁵ Angiogenic growth factors produced by tumor cells and the surrounding matrix are key modulators of EC function. Thus, the interruption of growth-factor binding or signaling pathways in ECs is an appropriate strategy for inhibiting tumor-induced angiogenesis. Vascular endothelial growth factor (VEGF) is a potent EC-specific prototypic protein produced and secreted by many tumors, rendering it a prime target for antiangiogenic therapy. VEGF acts as both an angiogenic factor and a vascular survival factor, which may explain why VEGF deprivation may lead not only to inhibition of further angiogenesis but also to tumor vessel regression.²⁶ Two strategies that appear to be promising for antiangiogenic therapies are modulation of VEGF activity by MAbs to the ligand or its receptor and small-molecule inhibition of the VEGF receptor tyrosine kinase.²⁵

Future Trends in Biotechnology

Over the next two decades, discoveries in biotechnology and advances in gene therapy will transform the practice of medicine—the traditional treatment concepts of palliation, cure, and prevention will move toward human enhancement and capability. The drug-discovery process will be even more accelerated, and new drugs will be developed based on the biologic cause or pathway of human disease. Development of gene chips containing the DNA representative of all the human genes will facilitate individual gene profiling and analysis of distinctive disease-specific gene patterns. These chips will allow clinicians to make more accurate diagnoses and recommend particular therapies with much greater certainty. Health care will evolve to a more sophisticated level of customization, enabling therapeutic selection precisely tailored to an individual's biochemistry. The advances expected to occur through biotechnology in the coming decade will have far-reaching effects on patients, clinicians, and payors, and will redefine the concept of medical practice in the new millennium.

Conclusions

The managed care pharmacist is charged with being responsible not only to employers and health care plans but also to the general public. Redeveloping partnerships between managed health care organizations and practicing clinicians or health care facilities will undoubtedly create mutual opportunities for all parties. Moreover, creating strategic clinical networks between key pharmaceutical and biotechnology product manufacturers will allow greater opportunities for on-site research and critical input regarding the products most needed in clinical care.

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CE EXAM

Biotechnology and Managed Care

Upon completion of this article, the successful participant should be able to:

1. Define genomics and list two goals of gene therapy.
2. Describe the proposed or defined anticancer mechanism of action for monoclonal antibodies, signal transduction inhibitors, matrix metalloproteinase inhibitors, antisense oligonucleotides, and angiogenesis inhibitors.
3. List three disease categories whose prevention and treatment are likely to be revolutionized by biotechnology.

SELF-ASSESSMENT QUESTIONS

1. The disease category for which the majority of new biotechnology agents or therapies are being investigated is:
 - a. infectious diseases.
 - b. hematology.
 - c. oncology.
 - d. cardiovascular disease.
2. The estimated number of biotechnology products in development is:
 - a. 2,200.
 - b. 13 billion.
 - c. 1,300.
 - d. 1,700.
3. A goal of gene therapy is to:
 - a. repair underlying genetic defects.
 - b. transfer genetic information between cells.
 - c. define how genes affect the human body.
 - d. all of the above.
4. The entire human genome (i.e., the full set of genes in an individual) is thought to consist of approximately:
 - a. 5,000–15,000 functional genes.
 - b. 50,000–150,000 functional genes.
 - c. 3,000–30,000 functional genes.
 - d. 30,000–300,000 functional genes.
5. Monoclonal antibodies are currently Food and Drug Administration–approved for which of the following indications?
 - a. metastatic breast cancer patients whose tumors overexpress the HER2 protein
 - b. relapsed or refractory low-grade or follicular, antigen CD20-positive, B-cell non-Hodgkin's lymphoma
 - c. relapsed or refractory CD34-positive acute myelomonocytic leukemia
 - d. a and b
6. Protein tyrosine kinases are the primary target for:
 - a. monoclonal antibodies.
 - b. signal-transduction inhibitors.
 - c. matrix metalloproteinases.
 - d. angiogenesis inhibitors.
7. Enzymes responsible for the degradation of extracellular matrix components associated with angiogenic and metastatic processes are:
 - a. signal-transduction inhibitors.
 - b. matrix metalloproteinases.
 - c. angiogenesis inhibitors.
 - d. antisense oligonucleotides.
8. Inhibiting the process and translation of mRNA by inserting base-pair sequences into a target mRNA describes:
 - a. genomics.
 - b. gene therapy.
 - c. antisense oligonucleotide therapy.
 - d. angiogenesis inhibition therapy.
9. Vascular endothelial growth factor is a:
 - a. signal-transduction inhibitor.
 - b. matrix metalloproteinase.
 - c. angiogenesis inhibitor.
 - d. antisense oligonucleotide.
10. Fomivirsen sodium was the first antisense-based drug marketed in the United States and is indicated for:
 - a. metastatic breast cancer.
 - b. acquired immunodeficiency syndrome (AIDS).
 - c. cytomegalovirus retinitis.
 - d. non-Hodgkin's lymphoma.

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CE Exam

DEMOGRAPHIC INFORMATION *(not for scoring)*

11. In what type of setting do you work?
(Leave blank if none of the responses below applies.)
- HMO
 - PPO
 - Indemnity insurance
 - Pharmacy benefits management
 - Other
12. Did this program achieve its educational objectives?
- Yes
 - No
13. How many minutes did it take you to complete this program, including the quiz? *(Fill in on answer sheet.)*
14. Did this program provide insights relevant or practical for you or your work?
- Yes
 - No
15. Please rate the quality of this CE article.
- Excellent
 - Good
 - Fair
 - Poor

INSTRUCTIONS

This test affords 1 hour (0.10 CEU) of continuing pharmaceutical education in all states that recognize the American Council on Pharmaceutical Education. To receive credit, you must score at least 70% of your test answers correctly. To record an answer, darken the appropriate block below. Mail your completed answer sheet to: Academy of Managed Care Pharmacy, 100 N. Pitt Street, Suite 400, Alexandria, VA 22314. If you score 70% or more, a certificate of achievement will be mailed to you within eight weeks. If you fail to achieve 70% on your first try, you will be allowed only one retake. The ACPE Provider Number for this lesson is 233-000-00-005-H01. This offer of continuing education credit expires October 31, 2001.

	A	B	C	D	E
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3.	☐	☐	☐	☐	☐
4.	☐	☐	☐	☐	☐
5.	☐	☐	☐	☐	☐

	A	B	C	D	E
6.	☐	☐	☐	☐	☐
7.	☐	☐	☐	☐	☐
8.	☐	☐	☐	☐	☐
9.	☐	☐	☐	☐	☐
10.	☐	☐	☐	☐	☐

11. ☐A ☐B ☐C ☐D ☐E
12. ☐Yes ☐No
13. Minutes _____
14. ☐Yes ☐No
15. ☐A ☐B ☐C ☐D

Participant Identification: Please type or print.

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CITY

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State & Lic. No.: _____

STATE

LICENSE NO.

Member Type:

☐ Active

☐ Supporting Associate

☐ Student

☐ Nonmember

Signature: _____

I verify by my signature above that I have completed this examination independently.