

Introduction

The biotechnology industry is growing rapidly and is likely to have dramatic impacts on business and society throughout the foreseeable future. Drug development efforts are already affecting human health care significantly, although many difficult issues, such as the ethics of stem cell therapy and the ownership of biologically based intellectual property, remain problematic. As these issues are resolved, the development of drugs and other therapeutic products may well accelerate, improving the quality of life and health for hundreds of millions of patients. Yet, the potential and implications of biotechnology extend far beyond health care.

Understanding the biotechnology industry—and the basic biology that underlies it—is essential. We as citizens will want to participate effectively in the public debate and make informed decisions about how best to use this technology. But there are further reasons why businesspeople should deepen their understanding. Many companies operating outside of the healthcare industry may soon find themselves interacting with biotechnology companies in unexpected ways:

- A furniture maker may be invited into a strategic alliance with a biotechnology company that grows plastic materials as a crop in a farmer's field.
- An airplane manufacturer may discover that the most effective way to assemble its products is through logistical guidance from algorithms calculated in a DNA-based biological computer.
- A grocery store may begin distributing edible vaccines for infectious diseases that are genetically engineered into its food products.

These examples illustrate why businesses will need to recognize the potential for such interactions as early as possible, and have strategies for leveraging opportunities as they arise. This will require a basic literacy about both the science and the technology that most businesspeople have yet to develop.

This publication begins to address that gap by providing an overview of the biotechnology industry, the science underlying the technology, some of the most promising developments in both domains, and a framework for thinking about current and emerging opportunities. Biotechnology is both a powerful tool and a catalyst for the future; understanding the possibilities today will translate into real opportunities tomorrow.

AN OVERVIEW OF THE BIOTECHNOLOGY INDUSTRY

The biotechnology industry is relatively young. Its first company, Genentech, was founded in 1976 by Bob Swanson and Herb Boyer in South San Francisco, California.

In 1980, the first biotechnology IPO was carried out, again for Genentech, and two years later, its first product—insulin protein—entered the market. Today, with a market capitalization of \$29 billion, Genentech is still one of the largest biotechnology companies, second only to Amgen, which has a market capitalization of \$79 billion. The industry is growing rapidly within and beyond the United States, even though most companies are small, privately held, face barriers to financing, and lack product-based revenues. Still, the level of innovation and commercial potential are enormous across a wide range of applications.

Financial Growth of the Industry

From that singular beginning just over 25 years ago, the industry has grown to more than 1,400 biotechnology companies operating worldwide. Of these, 380 are publicly traded, while 1,000 are private companies. However, most of these publicly traded companies are considered relatively early stage, with less than 10 percent (32) operating at profitable levels last year. The rest still lack product sales-based revenues, and focus primarily on research and development. Indeed, global product sales for the biotechnology industry were \$18.1 billion in 2001, a 12.6 percent increase from the previous year, with total revenues of \$25 billion in 2001. However, total R&D expenses were \$14 billion, and the industry is still operating in the red, with an overall net loss of \$5.8 billion.

Operating in a profitable mode can be very lucrative for investors: 25 biotechnology companies have market capitalizations greater than \$5 billion each, and these companies are the same ones that are operating most profitably. At the other end of the spectrum, the smallest 70 biotechnology companies have an average market capitalization under \$70 million; these companies are operating in the red and mostly lack significant product sales-based revenues.

To fuel the growth of the emerging biotechnology industry, total financing reached \$32.7 billion last year, including 56 IPOs in 2000. The aggregate market capitalization of all the publicly traded biotechnology companies is about \$350 billion.

Even so, entrepreneurship is still a risky business. For a new company, the probability of survival without an additional cash infusion is not high; the average biotechnology company can survive about three years without additional financing. Today more than 100 small biotechnology companies have less than one year of cash reserves, and for those that are public, this instability has resulted in an average market capitalization of around \$100 million. In 2000, only 143 companies had more than five years of cash reserves in the bank, and 12 percent had three to five years' worth of cash.

Fundamentals of Raising Capital

Success as an entrepreneur in the biotechnology industry requires an understanding of the intellectual property at the core of most companies, the strategy driving an often-long product-development cycle, technical milestones that may impact company growth and valuation, the funding sources available at each stage of the company's growth, and an understanding of the scientific regulatory framework surrounding the product development process. These factors are interdependent, posing a substantial barrier to entry for most emerging companies.

Biotechnology ventures often form around a core set of intellectual property, typically developed over several years at a research institution such as a university or medical center. The intellectual property is licensed to the new venture, often for a share in the company as well as for royalties and upfront payments. The founders are typically scientists, and most potential investors assume the technology base is sound. Investors base their decisions on the people involved in the company, both from a scientific and engineering perspective as well as from a management perspective. A newly-formed company may begin operations with a relatively small amount of seed funding, perhaps several hundred thousand dollars, often from private investors. This funding is usually sufficient to secure the relevant intellectual property rights and to begin the process of recruiting the key management and scientific team.

Growing a biotechnology venture often occurs in discrete stages, where headcount growth and other company expansion is staged through several serial investments, each of which is typically associated with the achievement of particular technological or scientific milestones. The first professional investment in a biotechnology company usually ranges from \$3-\$10 million and involves the investors purchasing a sizable portion of the company's equity. When this stock is issued, it is referred to as "Series A." Later investments can range from a few million dollars to more than \$50 million; with each successive round of investment, a progressively

greater portion of the company is sold off, diluting the ownership percentage of the original founders. The subsequent rounds of investment are labeled with a successive letter, e.g., Series B, Series C, and so forth. Several rounds of funding are typically required to support a biotechnology venture to the point where it is economically viable as an independent entity. Several rounds often take place in a time frame of five years or more.

When a company's pre-money valuation exceeds \$250–\$300 million, it is potentially positioned to “go public,” in which an initial public offering (IPO) is carried out to sell a significant portion of the company to the public. Investment banks typically do not initiate the assignment of analysts to track that company until its total valuation exceeds the \$250–\$300 million threshold; analyst time is so scarce that it is not economically feasible to track smaller companies. An IPO in the American biotechnology market typically brings in \$70–\$125 million for the company, with the proceeds often used for rapid expansion. At that point, public shares may change hands through various trading markets, but the company does not receive additional funding as a result of that trading.

Clusters of Innovation

Biotechnology companies employ more than 174,000 people worldwide—and the vast majority are highly trained scientific researchers, most with advanced degrees in science and/or medicine. Where do these people work?

Most biotechnology companies are based in clusters within the United States and Western and Northern Europe. On a state-by-state basis, California is home to more than 400 companies, followed by Massachusetts with 200. Maryland and North Carolina are tied for third with about 80 companies apiece. On a city-by-city basis, the San Francisco Bay Area and the Cambridge, Massachusetts region lead with the most biotechnology companies—about 180 companies in each area. San Diego is in third place, with around 120 companies operating in the region. In Europe, the majority of biotechnology ventures are located in Germany, Sweden, and England, with relatively few operating in France, Italy, Spain, and Eastern Europe.

The geographic focus of the pharmaceutical industry mirrors that of the biotechnology industry: Of the 15 fastest-growing pharmaceutical products, nine were developed in the United States, four in Europe, and the remaining two in Japan.

Rich Product Pipelines

In 1982, the nascent biotechnology industry produced two new drug approvals. Since that time, the industry has experienced tremendous growth, with an exponential trend developing in the 1990s. This trend is continuing: more than 30 new drugs were approved for human use in 2000.

The growth of products in the research and development pipeline has been equally impressive. In 1990, only 100 drugs were in clinical studies, with 10 drug products on the market, and total revenues from product sales at just \$2.8 billion. In contrast, in 2002, 400 drugs entered development, with more than 125 on the market. Revenues from product sales are just more than \$18 billion.

By 2005, most industry analysts expect to see more than 800 potential products in late-stage clinical trials, with more than 225 drugs on the market, and product sales-based revenues close to \$50 billion, a top-line growth of 21 percent. Indeed, more than 100 additional drug approvals are expected in the next three years alone, and more than 2,200 products are now in the research and development pipeline.

In contrast, the pharmaceutical industry R&D pipeline is relatively bare; a modern pharmaceutical company grows mainly by mergers and acquisitions. This approach is ultimately self-constrained: Of the nearly 70 global pharmaceutical companies, the top 15 accounted for 58 percent of pharmaceutical product sales in 2000.

Nevertheless, the overall size of the pharmaceutical industry is still more than 10 times larger than the biotechnology industry: global product-sales-based pharmaceutical revenues approached \$320 billion in 2000, an 11 percent increase from the prior year, and more than 10 times the total revenues of the biotechnology industry. Pfizer alone had revenues of \$32 billion last year, which is already greater than that of the entire biotechnology industry. Nevertheless, to continue growing at a double-digit rate, the pharmaceutical industry needs the innovations developed by the biotechnology industry.

Explosive growth is also expected in non-drug product markets. From diagnostics to agricultural biotechnology, from bioelectronics to biomaterials, biotechnology products outside of human therapeutics are poised to increase the industry's revenue stream dramatically. These products are likely to enter the market very rapidly relative to human therapeutics, since, on a global basis, non-therapeutic products are far less regulated, and do not need extensive human testing prior to product launch.

Therapeutic Focus on Disease

Of the late-stage (phase III) clinical trials now in progress, more than 28 percent are focused on therapeutics for cancer, with 11 percent focused on neurological disease, 9 percent focused on infectious and viral diseases, 6 percent focused on cardiovascular disease, 6 percent focused on diseases of blood and coagulation, 5 percent for metabolic disorders, and 5 percent for respiratory disorders.

Interestingly, disease distribution rates are somewhat different. According to the World Health Organization, of a total of 52.2 million deaths in 1997, 17.3 million were due to infectious and parasitic diseases; 15.3 million were due to circulatory diseases; 6.2 million were due to cancer; 2.9 million were due to respiratory diseases (mainly chronic obstructive pulmonary disease); and 3.6 million were due to prenatal conditions.

These distributions do not correlate precisely with the drugs now in development by the biotechnology industry for two reasons. First, some diseases are more accessible experimentally than others, and scientists seeking rapid discovery tend to focus on those with the greatest research promise. Second, companies are for-profit entities, and want to develop products that generate revenues substantial enough to justify the enormous research and development costs associated with new drugs. For these reasons, the choice of which products to develop is not determined solely by the demographics of disease; a central driver is the demographics of who can pay for disease therapy. This leads to a disproportionate focus on diseases impacting highly developed countries whose populations can afford expensive drug treatments. While perhaps morally questionable, this focus is nevertheless necessary for the long-term survival of a for-profit company.

BEYOND THE LIVING: MEDICAL DEVICES

The medical device sector of the biotechnology industry spans a wide spectrum from the development of surgical products (used for medical procedures during operations) to diagnostic products (for monitoring blood and breath) to therapeutic products (such as transdermal skin patches used for drug delivery).

Surgical products include catheters, stents, and other mechanical devices designed for intimate contact and interaction with the living body, often to manipulate tissues and organs, and often used during operations. These products are typically designed by mechanical engineers in concert with design guidelines and feedback from surgeons and other medical professionals.

Diagnostic products include blood glucose monitoring devices (e.g., for diabetic patients), breathalyzer units to test alcohol levels, and lung volume measurement systems to routinely assess lung capacity in patients with asthma. In these cases, the products are typically focused on both clinical use by health care professions and on home use by patients who regularly self-monitor their health. Therapeutic products include drug delivery devices such as the nicotine patches used to alleviate withdrawal symptoms as patients attempt to stop smoking as well as inhalers to breathe in drug products ranging from anti-inflammatories (for asthma patients) to insulin (for diabetics).

The product development cycle for medical devices is typically much shorter and far more market- and application-focused than that for drug products, and medical devices usually undergo a more abbreviated form of clinical testing (“510K” approval) than that required for drug products. Consequently, the entry barriers for developing medical products are lower, competition is intense, and many small medical device companies are short-lived. For those that do survive, the financial rewards can be immense: recently a small, relatively young stent-producing company (AVE, Arterial Vascular Engineering) was sold to a global medical device company (“Medtronic”) for several billion dollars.

BEYOND HEALTH CARE: BIOENGINEERING

Bioengineering promotes the design and development of biotechnology products mostly outside of the area of human health care. Since their development involves far less regulation, these products can be rapidly brought to market.

Bioengineering is an emerging discipline, integrating quantitative engineering principles and approaches with the complex yet powerful techniques of molecular and cellular biology. This focus is inherently interdisciplinary and aggregates the skills and knowledge of people working in inorganic chemistry, materials chemistry, biochemistry, molecular biology, and electrical engineering. Examples of bioengineering include tissue engineering, bioelectronics, biomaterials, enzymatic engineering, agricultural engineering, and environmental remediation. Each of these areas is discussed in greater detail below.

Tissue Engineering

Tissue engineering is an interdisciplinary field focused on the construction of new tissues and organs as replacement parts for diseased or aged body parts. Though still within the health care sphere, the development and manipulation of laboratory-grown molecules, cells, tissues, or organs share many characteristics with other fields of bioengineering. Using the skills and knowledge of cell biologists, molecular biologists, biomaterial engineers, and computer-assisted designers, tissue engineers have set out to grow virtually every type of human tissue, including liver, bone, muscle, cartilage, heart muscles, and pancreatic tissues.

Two fundamental approaches are required to design and grow human tissues outside the body for later implantation. First, it is necessary to prepare highly porous, three-dimensional scaffolds to make three-dimensional engineered, functioning organs. The high porosity of the scaffolds enables the coordination of cell-substrate, cell-cell, and cell-signal interactions during tissue growth. Scaffolds also need to be fabricated with sufficient strength to allow the manufacturing of load-bearing, hard tissue replacement.

Second, culturing cells with signal molecules such as naturally derived “growth factors” is necessary to induce the growth of functional human tissues, without the loss of growth factor activity in the differentiating tissues. Although cells have been successfully cultured outside the body for

several years, only in the last decade have scientists and medical engineers been able to grow complex, three-dimensional tissues that mimic the design and function of human tissue. Together, these strategies permit the development of a wide variety of tissues for therapeutic use in the human body.

Many current medical therapies may be improved by tissue engineering, including organ transplantation that avoids lifelong immunosuppression and the potential for tissue rejection, as well as the de novo development of new types of tissues and organs to counter previously debilitating chronic metabolic disorders such as cardiovascular disease, neurological disorders, and diabetes.

Bioelectronics

Several classes of biological molecules exhibit unique features of recognizing other molecules, such as enzymes recognizing substrates, antibodies recognizing antigens, and electronic molecules that move electrons within biological tissues. By integrating chemical and physical devices, such as silicon chips, cantilevers, and carbon-based structures, we can produce bio-electronic materials that control the nanoscale patterning of hybrid electronic devices. This can be done on super-small-length scales that surpass current lithographic capabilities.

How can biological structures be used to precisely pattern inorganic devices like chips? One approach is to leverage the evolutionary diversity of antibody production, screening a wide range of antibodies to see which can bind to potentially useful surfaces such as silicon and gallium arsenide wafers. Antibodies that adhere to metal have already been isolated, and these can be applied together with the patterning techniques used in the fabrication of protein chips to create biological molds for electronic devices.

Bioelectronics, and its sister field of molecular electronics, focus on the use of organic compounds in electronic and optoelectronic devices. Engineering that exploits the unique properties of organic compounds can be used in the creation of organic electroluminescent displays and chemical sensors. Another approach is to leverage the inherent smallness and precise interactions of biological molecules to dramatically reduce the size and increase the self-organizing potential of elements in electronic circuits.

A central focus in bioelectronics is the design of logical and control circuits using small, self-assembling molecules so that the size of today's computers can be dramatically reduced by several orders of magnitude.

Biomaterials

The enormous diversity inherent in naturally evolved biological materials provides a rich source for creating novel materials for engineered, intentional applications. In particular, the re-engineering of molecular and cellular processes will create functions unrelated to the conditions in which they originally arose.

Biotechnology companies are currently developing ultra-strong and light-weight materials based on spider silk. Multiple organisms are often used in the intermediate production steps. For example, the molecular components comprising ultra-strong spider silk can be synthesized in bacterial cells and then purified and polymerized into ultra-strong synthetic textiles.

Enzymatic Engineering

Enzymatic engineering can be used to replace traditional industrial manufacturing processes and thus contribute to a more sustainable environment. Industrial manufacturing processes have traditionally relied upon high temperature and energy, hazardous chemicals such as acids, and often require the production of phosphorus and the generation of hazardous metal wastes. In contrast, the use of enzymatic processing in manufacturing plants provides a relatively inexpensive, controlled, and sustainable manufacturing environment.

Enzymatic reactions serve the same role as high temperature and energy processes: to bring together reactants and promote the intermediate state of a reaction. The molecular structures of enzymes have evolved to catalyze reactions at body temperature, while the typical equivalent industrial reaction might require a temperature of several thousand degrees centigrade. This biocatalytic approach can be learned from the body and applied in a variety of manufacturing processes, in which enzymes such as lipases, proteases, cellulases, and amylases can be substituted in place of both noxious chemicals and high temperature and energy use.

The range of manufacturing processes to which a biocatalytic approach can be applied includes the production of detergents, starches, textiles, and grain processing. For these and many other industry segments, biotechnology can be used to promote environmentally friendly, highly efficient and cost-effective alternative manufacturing processes.

Agricultural Biotechnology

The products of agricultural biotechnology can be used to increase the carrying capacity of the planet, providing food for a rapidly growing population. Traditionally, food crops such as wheat, corn, and rice were bred for hardiness and yield through the slow and laborious crossing of different crop strains, and the ultimate results of these experiments took years to unfold. Today, the highly refined genomic and genetic engineering of agricultural products can be carried out in weeks or months, compressing the breeding cycle from one-hundred to one-thousand fold. IF THE CYCLE WERE COMPRESSED, SHOULDN'T IT GET SMALLER? ISN'T FOLD TO MULTIPLY?

A variety of traits are being targeted for genetic modification. Crops are being reengineered to yield increased environmental resistance (e.g., to temperature and moisture extremes) and improved resistance to insects and pests. These enhancements allow crops to be grown over a greater range of environmental conditions than ever before, ultimately increasing the carrying capacity of our environment. Plants are also being structurally modified to yield alterations in leaf and petal shape and size, and changes in stem, branch, root, and seed structure. These structural modifications can reduce the energy requirements of plants, further increasing crop yields. The nutritional content of crops can be substantially enhanced through molecular tuning and adjustment of the relative percentages and distribution of oils, proteins, fats, and carbohydrates contained within fruits, leaves, flowers, and seeds. Finally, the breeding and growth cycles of plants can be modified to allow for more continuous growth, yielding an independence from or at least less dependence on seasonal growth cycles. Taken together, these advancing fronts in agricultural biotechnology offer the possibilities of rapidly improving our capacity to feed a growing population.

Environmental Remediation

Biotechnology can be used to precisely target and reverse environmental damage ranging from oil spills to contaminated air. Many environmental challenges have arisen from the unregulated use of technology developed from the onset of the Industrial Revolution. Often these technologies resulted in contaminated soil, water, and air, with far-reaching and unanticipated consequences for the global ecology. Some of these industrial era environmental challenges can be resolved by applying biotechnology in the development of sustainable environmental “cleansing” processes. In particular, microbial “cleaner” organisms may be designed to clean up contaminated soil, industrial effluent, groundwater, contaminated air, and petrochemical spills.

For each of these environmental challenges, the cleansing function of biotechnology arises through highly controlled and localized biodegradation processes, in which a genetically engineered microbe consumes the target waste over a discrete time window, after which the microbe expires. This can be designed into a cleaning process by having a microbial cleaner organism depend on a complex combination of extraordinarily scarce nutritional inputs not found in nature, so that when that small supply of artificially-created nutrient is fully consumed, there is none available to sustain the organism's existence beyond the cleaning period. In this way it is possible to both resolve current environmental issues and anticipate potential problems without creating a solution that may have more environmental impact than the original problem.

These are among the major areas in which biotechnology will introduce new opportunities and unexpected consequences for companies across a variety of industries within and outside of the traditional biotech space. And understanding their potential requires both a broader and deeper familiarity with the scientific building blocks.

TOWARDS AN UNDERSTANDING OF BIOFUTURES BUILDING BLOCKS

Why discuss DNA? Proteins? Cells? Tissues? Physiology?

Each of these topics represents increasingly complex levels of biological organization, and at each level, significant industry efforts are underway to develop products that may have a profound effect on health care and other industries. This GBN report provides a concise, foundational summary of modern biology to support a better understanding of the emerging biotechnology industry. It also illustrates current and potential industrial and commercial activity that intersects with each area of biological knowledge and includes representative company snapshots and industry analyses.

The biotechnology industry is dynamic and diverse. Even so, deeper insight into the structure and potential of this field can be achieved by classifying the companies within each market segment into one of three functional categories: Comprehend, Cure, and Create.

Comprehend

The total amount of information accessible to modern biologists is staggering. From a baseline of hundreds of terabytes of data, the pool of available biological knowledge is exponentially increasing. Accordingly, a growing market segment has formed within the biotechnology industry that focuses on the analysis and synthesis of biological data and the mining of patterns within this data. The “Comprehend” category within this framework includes those biotechnology companies engaged in developing, manufacturing, and marketing products and services that focus on data analysis, synthesis, and extracting meaning from biological data.

Cure

Biotechnology companies that are developing, manufacturing, and marketing products and services intended to diagnose and/or treat diseases represent the “Cure” category. This category includes companies developing traditional therapeutic products, such as testing kits to screen for specific diseases, and therapeutic medicines designed to alleviate the symptoms and causes of particular diseases.

Create

Companies that are developing, manufacturing, and marketing biotechnology-based products and services that fabricate new biological structures never before seen in nature represent the “Create” category. Here biology can be used to engineer new molecules and materials whose greatest use may lie far outside the domain of traditional biology.

Whereas most industry analyses of biotechnology classify companies based on products or financial metrics, we find that the Create / Comprehend / Cure framework offers a valuable snapshot for companies that may not presently be engaged in the industry. By analyzing the market at each level of biological complexity (e.g., DNA, proteins, etc.) within this framework, we can quickly grasp the ongoing evolution of the industry and the potential for interdisciplinary and inter-industry interaction.