



BIG PICTURE

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In its 30 years of life, the biotechnology industry has attracted more than \$300 billion in capital. Much of this investment has been based on the belief that biotech could transform health care. The original promise was that this new science, harnessed to new forms of entrepreneurial businesses that were deeply involved in advancing basic science, would produce a revolution in drug therapy. Unencumbered by the traditional technologies and organizations of the established pharmaceutical giants, these nimble, focused, science-based businesses would break down the wall between basic and applied science and produce a trove of new drugs; the drugs would generate vast profits; and, of course, investors would be handsomely rewarded.

So far, the promise remains largely that. Financially, biotech still looks like an emerging sector. Despite the commercial success of companies such as Amgen and Genentech and the stunning growth in revenues for the industry as a whole, most biotechnology firms earn no profit. Nor is there evidence that they are sig-

nificantly more productive at drug R&D than the much maligned behemoths of the pharmaceutical industry.

This disappointing performance raises a question: Can organizations motivated by the need to make profits and please shareholders successfully conduct basic scientific research as a core activity? For 30 years, debate has been intense about whether business's invasion of basic science—long the domain of universities and other nonprofit research institutions—is limiting access to discoveries, thereby slowing scientific advance. But the question of whether science can be a profitable business has largely been ignored.

As always, the prevailing outlook in the industry itself is that the revolution in drug creation will succeed; it will just take a little longer than anticipated. That may be wishful thinking. Over the past 20 years, I have conducted extensive research on the strategies, structure, performance, and evolution of the biotechnology and pharmaceutical sectors. I learned that the “anatomy” of the biotech

sector—much of it borrowed from models that worked quite well in software, computers, semiconductors, and similar industries—is fundamentally flawed and therefore cannot serve the needs of both basic science and business. Unless that anatomy changes dramatically, biotech won't be able to attract the investments and talent required to realize its potential for transforming health care.

By “anatomy,” I mean the sector's direct participants (start-ups, established companies, not-for-profit laboratories, universities, investors, customers); the institutional arrangements that connect these players (markets for capital, intellectual property, and products); and the rules that govern and influence how these institutional arrangements work (regulations, corporate governance, intellectual property rights). For biotechnology to fully succeed, its anatomy must help the players collectively to excel in three ways: managing risk and rewarding risk taking, integrating the skills and capabilities that reside in a range of disciplines and functions, and advancing critical knowledge at the organizational and industry levels.

The parts of an industry's anatomy should support one another in meeting these challenges. In biotech, they work at cross-purposes. For example, the way the industry manages and rewards risks—how businesses are funded—conflicts with the long R&D timetable needed to create new drugs. The fragmented nature of the industry, with scores of small, specialized players across far-flung disciplines, is a potentially useful model for managing and rewarding risk, but it has created islands of expertise that impede the integration of critical knowledge. And biotech's market for intellectual property, which allows individual firms to lock up the rights to basic scientific knowledge, limits the number of scientists who can advance that knowledge by learning through trial and error.

While all this sounds pretty gloomy, it does not mean that the industry is doomed. It does not mean that science cannot be a business. It does mean that biotech's anatomy needs to change—an undertaking that would have a major impact not only on drug R&D and health care but also on university- and government-funded scientific research, other emerging industries engaged in basic science, and the U.S. economy. The purpose of this article is to provide a framework for such an un-

dertaking and to offer some ideas about the new organizational forms, institutional arrangements, and rules that will be required.

The Biotech Experiment

Science-based business is a relatively recent phenomenon. By “science-based,” I mean that it attempts not only to use existing science but also to advance scientific knowledge and capture the value of the knowledge it creates. A significant portion of the economic value of such an enterprise is ultimately determined by the quality of its science.

Before the emergence of biotech, science and business largely operated in separate spheres. Conducting research to expand basic scientific knowledge was the province of universities, government laboratories, and nonprofit institutes. Commercializing basic science—using it to develop products and services, thus capturing its value—was the domain of for-profit companies. Historically, a handful of companies, including AT&T (the parent of Bell Labs), IBM, Xerox (the parent of the Palo Alto Research Center), and GE, did some remarkable research, but they were the exception. By and large, businesses did not engage in basic science, and scientific institutions did not try to do business.

The biotech sector fused these two domains, creating a science-business model that nanotechnology, advanced materials, and other industries have adopted. For-profit enterprises now often carry out basic scientific research themselves, and universities have become active participants in the business of science. They patent their discoveries; their technology-transfer offices actively seek commercial partners to license the patents; and they partner with venture capitalists in spawning firms to commercialize the science emanating from academic laboratories.

In numerous instances, the boundary between a university and a biotech firm is blurred. The founders of a substantial number of biotech firms include the professors (many of them world-renowned scientists) who invented the technologies that the start-ups licensed from the universities, often in return for an equity stake. These companies frequently maintain their links with the universities, working closely with faculty members and postdoctoral candidates on research projects, and sometimes using the university laborato-

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ries. In many instances, the founding scientists even retain their faculty posts.

The science business was born in 1976, when the first biotech company, Genentech, was created to exploit recombinant DNA technology, a technique for engineering cells to produce human proteins. It was founded by Robert Swanson, a young venture capitalist, and Herbert Boyer, a professor at the University of California at San Francisco who had coined the technology. In addition to demonstrating that biotechnology could be used to develop drugs, Genentech created a model for monetizing intellectual property that has proved remarkably powerful in shaping the way the biotech industry looks and performs. This model consists of three interrelated elements:

- technology transfer from universities to the private sector through creating new firms rather than selling to existing companies;
- venture capital and public equity markets that provide funding at critical stages and reward the founders—investors, scientists, and universities—for the risks they have taken;
- a market for know-how in which young companies provide their intellectual property to established enterprises in exchange for funding.

In 1978, Genentech struck an agreement with Eli Lilly, a major pharmaceutical company. In return for the manufacturing and marketing rights to recombinant insulin, Lilly would fund development of the product and pay Genentech royalties on its sales. This agreement knocked down one of the chief barriers to new firms' entering the pharmaceutical business: the huge cost (\$800 million to \$1 billion in today's dollars) over the long time (ten to 12 years) generally required to develop a drug. This was also the first time a pharmaceutical company had essentially outsourced a proprietary R&D program to a for-profit enterprise. Since then, virtually every new biotech firm has formed at least one contractual relationship with an established pharmaceutical or chemical company, and most have formed several.

This market for know-how has encouraged venture capitalists to provide seed money for start-ups. It has also helped biotech companies tap public equity markets for capital by providing investors with an alternative to profits and revenues as a gauge of value. Genentech's wildly successful initial public offering in 1980 demonstrated that a firm with no product revenues or income could go

public—which made the sector even more attractive to venture capitalists.

The Promise

The rise of this system for monetizing intellectual property was intertwined with high hopes for biotech. Through the 1980s and into the 1990s, the sector seemed to offer a solution to the looming crisis in R&D productivity that threatened established pharmaceutical companies. Facing a shortage of potential blockbuster drugs in their pipelines, these companies had dramatically increased their R&D spending, but to no avail. With new drugs unable to compensate for the major drugs that were losing their patent protection, financial analysts questioned the sustainability of the industry's profits. Biotech's champions in the scientific and investment-banking communities believed that its technologies would create an avalanche of profitable new drugs. They argued that small, specialized biotech companies had a comparative advantage in research over bureaucratic, vertically integrated pharmaceutical giants; Big Pharma should therefore focus on marketing and leave innovative R&D to nimble biotech firms that were closer to the science. Even some executives at major pharmaceutical companies appeared to believe this, as evidenced by their decisions to aggressively pursue alliances with biotech firms.

Because the products of the first wave of biotech companies—including Amgen, Biogen Idec, Cetus, Chiron, Genentech, and Genzyme—were proteins found in the human body, scientists, managers, and investment bankers involved in the sector argued that they would have a much lower failure rate than conventional, chemical-based drugs. The lower technological risks would mean lower business risks. The initial success of a few genetically engineered replacement hormones—insulin, human growth hormone, and clotting factor VIII to treat hemophilia among them—seemed to validate this view.

The sequencing of the human genome and the invention of so-called industrialized R&D techniques further bolstered predictions that biotech would generate breakthrough therapies and tremendous gains in R&D productivity. The reasoning was that the massive amount of biological data produced would help enormously in identifying the precise causes of diseases, and that techniques such as

Despite the commercial success of several companies and the stunning growth in revenues for the industry as a whole, most biotechnology firms earn no profit.

combinatorial chemistry (for creating new compounds), high-throughput screening (for testing the compounds' medicinal potential), and computational chemistry (for "rationally designing" drugs to have specific effects) would greatly increase the quantity and quality of drug candidates. The days of inefficient, trial-and-error, craft-based, one-molecule-at-a-time approaches to drug discovery were deemed to be numbered.

Progress to Date

Excitement about these emerging technologies, the exploding number of biotech startups (some 4,000 over three decades), and the sector's soaring annual revenues (now about \$40 billion) only reinforced this optimism. But if the industry's success is measured by profitability and progress in revolutionizing R&D to generate an avalanche of breakthrough drugs, a troubling picture emerges.

First, only a tiny fraction of biotech companies have ever been profitable or generated positive cash flows, and the sector as a whole has lost money. (See the exhibit "Profitless Growth for Biotech.") Of the firms that have

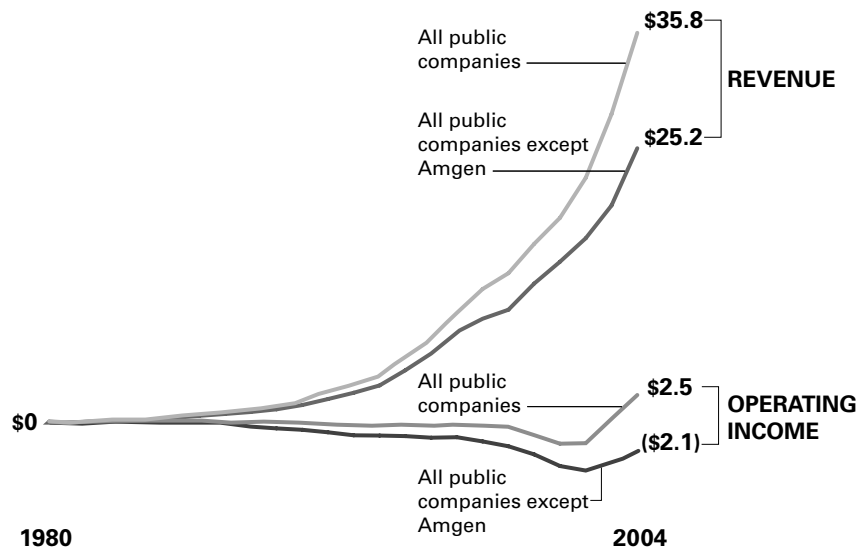
been profitable, only an elite handful of the oldest—including Amgen, Biogen Idec, Genentech, and Genzyme—have generated substantial profits. Only Amgen and Genentech have broken into the league of established pharmaceutical companies. It's especially noteworthy that Genentech, after pioneering the system for monetizing intellectual property, then took a different path: along with Amgen, Genzyme, and a few others, it vertically integrated by investing heavily in manufacturing and marketing even as it continued to build internal scientific capabilities. In addition, Genentech forged a long-term relationship with Roche, the Swiss pharmaceutical giant, which owns 56% of its shares.

Second, there is no sign that biotechnology has revolutionized the productivity of pharmaceutical R&D, despite many claims to the contrary. The average R&D cost per new drug launched by a biotech firm is not significantly different from the average cost per new drug launched by a major pharmaceutical company. (See the exhibit "Biotech Has Produced No Breakthrough in R&D Productivity.") Nor has industrialized R&D dramatically increased the

Profitless Growth for Biotech

The revenues of publicly held biotech companies have grown dramatically but their profits have hovered close to zero. Excluding Amgen, the largest and most profitable firm, the industry has been consistently in the red. Its losses would be even greater if private companies were included in the data pool.

Revenue and operating income before depreciation (\$ billions 2004)



number of compounds that make it to human clinical testing, let alone into the market. (See the exhibit “Industrialized R&D Has Yet to Deliver for Biotech.”) There is no conclusive proof that the unexceptional productivity of biotech firms is due to the complexity and risk of the projects they undertake.

Nor is there reason to believe that biotech’s productivity will improve with time. Optimists point out that biotech firms account for a growing percentage of drugs in clinical development. This suggests that we should expect a great number of drugs to emerge from the biotech pipeline in the future. But while industry spending on R&D continues to increase substantially, the attrition rate of biotech drugs in development has also grown over time. Thus it is doubtful that biotech’s output per dollar invested in R&D will improve significantly.

Finally—and perhaps not surprisingly—the

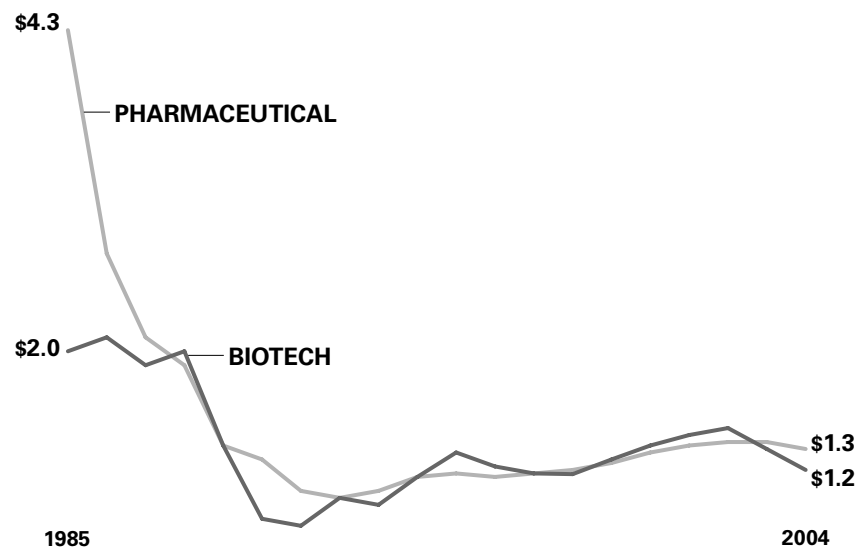
biotech sector appears to be retreating from its distinctive position at the radical and risky end of the R&D spectrum. Since 2001, when the genomics bubble burst, the strategies of startups and the preferences of venture capitalists have undergone a marked change. Rather than forming so-called molecule-to-market companies, whose first product revenues might be more than a decade away, entrepreneurs and investors have begun to look for lower-risk, faster-payback models, such as licensing existing projects and products from other companies and then refining them.

Refinements such as new formulations, including new technologies for delivery, are certainly valuable. They can lead to significant therapeutic improvements and expanded treatment options. That said, the change in strategies raises a major concern: If young biotech firms are not pursuing cutting-edge

Biotech Has Produced No Breakthrough in R&D Productivity

As the graph below indicates, the average R&D cost per new drug launched by biotech firms is not significantly different from the average cost per new drug launched by major pharmaceutical companies.

R&D spending per new drug launched (\$ billions 2004)



The sample of biotech companies includes all publicly held companies that tried to develop new drugs. The sample of pharmaceutical companies includes the top 20 companies in the world according to their R&D spending. The drugs do not include line extensions, reformulations, or approvals for new uses. Every annual data point represents the cumulative R&D expenditures from 1985 through the given year divided by the cumulative number of drugs launched during the same period. The first four and last four years of data were adjusted to account for the lag between R&D spending and the resultant output. Credit for a jointly developed new drug was divided equally between the biotech firm and its partner, the established pharmaceutical company.

science, who will focus on the higher-risk long-term projects that offer potential medical breakthroughs?

People involved in biotechnology have long contended that the sector will flourish eventually. Some still say it's just a matter of time and money. Others insist that technology will save the day. Genomics, proteomics, systems biology, and other advances will make it possible to identify promising drug candidates with a high degree of precision at extremely early stages of the R&D process, which should lead to a dramatic reduction in failure rates, cycle times, and costs.

Such optimism assumes that the underlying structure of the sector is healthy and the strategies of the players make sense. My research suggests otherwise. This structure and these strategies cannot solve the fundamental business and scientific challenges facing the sector.

A Flawed Anatomy

Like living things, industries are not “designed” but they have designs. In living things, these designs are called anatomies. Anatomy helps us understand what a given species is capable of and why certain species can thrive in some environments but not others. Anatomy explains why a cheetah can run 65 mph and a turtle can't. The fit between anatomy and environment matters in economics, too.

The anatomy of the biotechnology industry

looks quite similar to those of other high-tech sectors, such as software and semiconductors. It involves university-spawned start-ups that focus on specific pieces of the R&D value chain; a role for the venture capital and public equity markets; and a market for know-how. What some might call the Silicon Valley anatomy has worked wonderfully well in these other sectors. Biotech's anatomy was based on the premise that it would be a lot like them. But when it comes to R&D, biotech differs radically in three ways:

- Profound and persistent uncertainty, rooted in the limited knowledge of human biological systems and processes, makes drug R&D highly risky.
- The process of drug R&D cannot be broken neatly into pieces, meaning that the disciplines involved must work in an integrated fashion.
- Much of the knowledge in the diverse disciplines that make up the biopharmaceutical sector is intuitive or tacit, rendering the task of harnessing collective learning especially daunting.

Contending with profound uncertainty and risk. The basic feasibility of technologies is not an issue for R&D in most industries, where the effort and resources go primarily into developing concepts already known to be technically feasible. Car designers may grapple with engineering problems concerning a vehi-

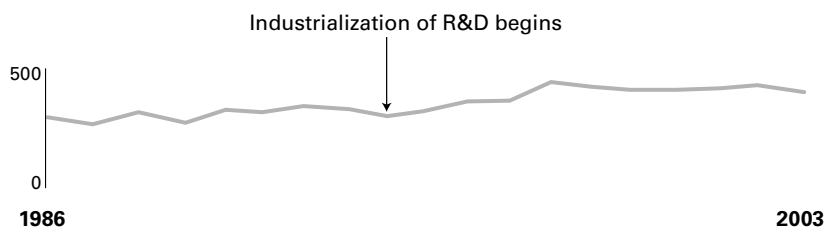
Industrialized R&D Has Yet to Deliver for Biotech

Since the mid-1990s, a combination of genomics, combinatorial chemistry, high-throughput screening, and IT has been used to create new drugs and to identify possible

targets in the body for attacking diseases. Despite this industrialization of R&D, however, the number of compounds developed by commercial organizations that have pro-

gressed at least to human clinical testing has not increased significantly.

Number of compounds in human clinical trials



Source: www.fda.gov/cder/rdmt/Cyindrec.htm

cle's various parts and worry about whether the design can be manufactured and whether customers will buy the vehicle. But they can be virtually certain that at the end of the process the vehicle will work. Even in high-tech industries such as semiconductors, high-performance computers, and aircraft, it is usually fairly clear which commercial R&D projects are scientifically feasible and which are not.

This is not the case with drug R&D. Whether a drug candidate is safe and effective can be determined only through a lengthy process of trial and error. Despite extraordinary progress in genetics and molecular biology over the past few decades, scientists still find it extremely difficult to predict how a particular new molecule will work in humans. Even today, they can assume that the most likely outcome of a project, after years of effort, will be failure. Historically, only one out of about 6,000 synthesized compounds has ever made it to market, and only 10% to 20% of drug candidates beginning clinical trials have ultimately been approved for commercial sale.

Advances in basic science may eventually improve these odds. But so far (and contrary to expectations), biotechnology has actually increased the uncertainties in drug R&D. Although the number of targets (possible causes of diseases), weapons (therapies) with which to attack them, and novel approaches for identifying new potential causes and cures has exploded, knowledge about many of these options remains superficial, forcing scientists to engage in more trial and error, not less. So even though biotechnological advances may eventually reduce the technical risks in R&D, they have to date had the opposite effect.

Profound, persistent uncertainty translates into high, long-term risks. At first glance, biotech's system for monetizing intellectual property seems to have functioned fairly well in managing such risks. The rapid formation of new firms has given rise to a plethora of experiments. The allure of equity ownership has encouraged scientific entrepreneurs to take the risks inherent in starting new firms. And venture capitalists have had the wherewithal to manage early-stage risks and to diversify them by building portfolios of firms. A closer examination, however, suggests that hidden flaws in the system have impeded the overall business performance of the sector.

Venture capitalists have a time horizon of

about three years for a particular investment—nowhere near the ten or 12 years most companies take to get their first drug on the market. In addition, because they need to spread their risks, not even the largest funds can afford to sink a vast sum into any one start-up. According to data from the National Venture Capital Association on fund investment policies, the average investment in a biotech firm is about \$3 million. The average maximum is \$20 million—far less than the \$800 million to \$1 billion typically required to develop a successful drug.

Biotech firms rely on public equity and strategic alliances to close the gap. These solutions, however, create other problems.

Public equity markets are not designed to deal with the challenges of enterprises engaged in R&D only, which compose most of the biotech sector. These companies cannot be valued on the basis of earnings; most of them don't have any. Their value hinges almost exclusively on their ongoing R&D projects. But trying to value them on the basis of projects that face years of great technical and commercial uncertainty is next to impossible. Information is simply inadequate. No clear disclosure and valuation standards exist for intangible assets in general and R&D projects in particular. Generally accepted accounting principles (GAAP) typically don't require companies to disclose their R&D projects, and although biotech and pharmaceutical firms must disclose information on the state of their development pipelines, the requirements are vague. For example, companies have discretion over how much detail to provide about possible therapeutic uses of a given product, clinical trial results and progress, and future development plans. Without adequate information, even the most sophisticated valuation techniques, such as real options and Monte Carlo simulation, are of limited use.

The other challenge for investors is interpreting the publicly announced results of clinical trials. Companies can and do interpret these results in different ways. Even if they interpret them similarly, they may make different decisions about whether to proceed to the next stage, based on their differing appetites for risk.

Public investors have looked to the market for know-how to fill this information gap. With their years of experience and armies of scientists, the big pharmaceutical companies that

The way the industry manages and rewards risks—how businesses are funded—conflicts with the long R&D timetable needed to create new drugs.

have struck deals with biotech firms surely have the knowledge to assess projects' technical and commercial prospects. So the willingness of Merck or Novartis or Eli Lilly to invest in a biotech company's project should signal that its prospects are good, right? Not necessarily. Pharmaceutical companies often make alliances in precisely those areas where they lack expertise. Moreover, in many cases they have spent lavishly on alliances and reaped little in return—or have walked away from licensing early-stage drugs that eventually became blockbusters.

Further evidence that the system for monetizing intellectual property is flawed is that, on the whole, the long-term returns on investments in biotech have not been commensurate with the substantial risks. While venture capital funds have enjoyed some stellar years, and individual biotech stocks have performed spectacularly, average returns overall have been disappointing relative to the risks. From 1986 through 2002, venture capital funds generated an average annual internal rate of return of 16.6%. And an analysis conducted by Burrill, a San Francisco-based merchant bank, found that an investor who bought all 340 biotech IPOs from 1979 through 2000 and held on to those shares until January 2001 (or until a company was acquired) would have realized an average annual return of 15%.

All this may explain why biotech start-ups appear to be retreating from the riskiest projects. Although it is hard to know conclusively, indications are that investors are becoming more cautious.

Integrating diverse disciplines. Thanks largely to the emergence of the biotech industry, the tool kit of drug R&D has become much bigger and much more diverse. In the mid-1970s, it was dominated by a single discipline: medicinal chemistry. Today it includes molecular biology, cell biology, genetics, bioinformatics, computational chemistry, protein chemistry, combinatorial chemistry, genetic engineering, high-throughput screening, and many others. These new tools are opening up new opportunities, but each sheds light on only one piece of a very complex puzzle. Discovering and developing drugs effectively requires that all the pieces come together. Therefore, integration across diverse scientific, technical, and functional domains is more important than ever if the scientific promise of

biotech is to be realized.

The challenge of integration is not unique to drugs. Virtually all R&D involves solving multiple types of problems. Not only must the many problems be solved, but the solutions must ultimately work together as a whole.

In some cases—including highly complex systems such as electronics equipment, automobiles, software, and airplanes—a big R&D problem can be broken down into a set of relatively independent subproblems, to be solved independently and then put together. Modularity makes possible the division of labor among different organizations specializing in different parts of the system, but it generally requires well-defined interfaces and standards that specify how different components of the system are supposed to fit and function together. In addition, modularity requires that intellectual property be codified and the rights to it be clearly defined and protected. Drug R&D lacks these requirements.

Most of the numerous functional and technical activities involved in drug R&D tend to be highly interdependent. A case in point is identifying a target for drug discovery. The big questions to be resolved are what the underlying mechanism of the disease is and where drug therapy might intervene in it. Because human biology is extraordinarily complex, target identification is extraordinarily multifaceted. What is the pathway? What genes might be at work? How do they interact? What are the proteins those genes express, and what do they do? What is their structure? How likely is one or more of them to be a “druggable” target? Answering these questions requires insights from different disciplines—including structural genomics, functional genomics, cell biology, molecular biology, and protein chemistry—and also a broad range of approaches, including computational methods, high-throughput experimentation, and traditional “wet” biology.

The same kind of integration must also occur further downstream in development but with still other disciplines, such as toxicology, process development, formulation design, clinical research, biostatistics, regulatory affairs, and marketing. It is difficult, if not downright impossible, to successfully develop a drug by solving problems individually in isolation, because each technical choice (the target you pursue, the molecule you develop, the formulation, the design of the clinical trial, the

choice of the target patient population, and the choice of manufacturing process) has implications for the others. Arriving at a solution requires that different kinds of scientists repeatedly exchange huge amounts of information. In other words, they must work together in a highly integrated fashion.

There are two basic ways of achieving integration. One is by having individual firms own all the requisite pieces of the puzzle (vertical integration). The other is with market-reliant networks, in which independent specialists integrate their work through alliances, licensing arrangements, and collaboration. The traditional pharmaceutical business employs the former, and the biotech industry the latter.

Most biotech firms were formed to allow small teams of highly dedicated scientists to focus on exploiting a specific finding or body of work initiated at a university. The result was hundreds of islands of specialized expertise. The biotech sector has relied heavily on the market for know-how to link these islands. There are indications, however, that this market can't facilitate the flow of information and the collective problem solving needed to develop new drugs.

To function in a highly efficient fashion, a market for any property—whether real estate or intellectual property—requires well-defined, well-protected rights. Strong IP protection generally exists in software and semiconductors. A piece of software code, for instance, is a fairly distinct entity that can be protected by legal mechanisms, and its theft can be detected quite easily. In biotechnology, the IP regime is more complex and murkier. It is often not clear what is patentable and what is not. Moreover, the most valuable IP is often not a specific molecule but data, understanding, and insights relating to how that molecule behaves, what it can do, what its potential problems are, and how it might be developed. Such knowledge can be much more difficult to patent.

Murky IP creates two problems: It makes its owners think twice about sharing it in the first place, and it provides fertile ground for contract disputes over what will be shared. Biotech has suffered both. Suits between former partners and collaborators have been fairly common. Indeed, Genentech and Lilly, whose recombinant-insulin deal became a template for the industry in many ways, wound up in a legal contest over rights to use genetic-

engineering technology to produce human growth hormone. After codeveloping recombinant human erythropoietin, a synthetic protein that stimulates the body's production of red blood cells, Amgen and Johnson & Johnson fought a bitter legal battle over the division of marketing rights. Years after that, they had another dispute about whether a later version of the drug was a completely new product or an improved form of the original.

Another formidable barrier to sharing information is the tacit nature of much of the knowledge critical to drug R&D. Such knowledge cannot be fully described in writing, because the cause-and-effect principles behind the techniques or know-how have not been completely identified. This is common in emerging fields, but the magnitude of tacit knowledge in biotech impedes the pace of learning in the sector, as we shall see.

Promoting cumulative learning. It would be hard to overstate the importance of learning to the long-term health of science-based sectors. The profound and persistent uncertainty enveloping biotech in particular and drug R&D in general means that what is known pales in comparison to what remains to be discovered. New hypotheses and findings must constantly be evaluated, and decisions must be made about which options to pursue and which to discard. These decisions must occur in the fog of limited knowledge and experience. Mistakes are common, not because people or firms are incompetent but because they are constantly dancing on the edge of knowledge.

When, as in the case of drug R&D, failure is far more common than success, the ability to learn from failure is critical to making progress. Learning can occur at multiple levels in a system or an industry. A scientist who has spent decades doing research on cell growth factors, for instance, will have accumulated quite a lot of knowledge, and the lab in which he worked will have learned many new things from his research as well as from that of others in the lab. This learning will be not only the aggregate of what individuals know but also the insights shared by the community. Some of this knowledge will be formalized in organizational procedures and methods, but much of it will probably be tacit.

Despite scientific advances, there is still an art to drug discovery that relies on judgment,

Far from being dead, vertical integration has an important role to play in the future drug industry.

instinct, and experience. For example, what individual scientists know about a molecule, or a biological target for attacking a disease, or the behavior of a drug inside the body cannot be codified or reduced to precise rules—if X, then Y. Data from experiments are subject to a wide range of interpretation and opinion. What constitutes a strong signal of potential efficacy for one researcher may give pause to another.

As a result, sharing experiences over an extended period matters enormously in such endeavors, and the breadth of the sharing is extremely important. For the science to advance, each of the disciplines with expertise needed to solve a problem must be able to leverage the collective wisdom.

Unfortunately, the biotech industry is not organized to learn from experience over time. Once again, its system for monetizing intellectual property is to blame. By fueling the proliferation of start-ups, the system has helped create a sector of relatively inexperienced firms. The typical young firm in biotech simply lacks the capabilities that Genentech, for example, accumulated in the course of conducting R&D for 30 years. Nor can newer ventures afford to learn through experience. They have limited financial resources, and investors aren't willing to give them the time to perfect their craft.

Finally, the market for know-how hinders companies from forming long-term learning relationships. The lack of well-delineated intellectual property rights is one problem; the short-term focus of alliances is another. All too often, priority is given to the deal, not to building joint long-term capabilities. As a result, most alliances are at arm's length and fairly brief. According to research by Harvard Business School's Josh Lerner and Stanford Business School's Ulrike Malmendier, the length of a typical contract is just short of four years—much less than the amount of time needed to develop a drug. In addition, the relationship is often centered on reaching specific, short-term milestones; if one is missed, the alliance may be terminated.

All in all, the obstacles to integration and learning in the industry are enormous. Given these impediments, it's hardly surprising that biotech suffers from productivity problems.

A More Suitable Anatomy

To deal with profound uncertainty and high risks, allow closely interdependent problem

solving, and harness the collective experience of disciplines throughout the sector, biotech needs a new anatomy—one that involves a variety of business models, organizational forms, and institutional arrangements. The approaches needed to develop more innovative drugs differ enormously from those required to develop less innovative drugs. One size does not fit all. A more suitable anatomy might include the following elements.

More vertical integration. Far from being dead, vertical integration has an important role to play in the pharmaceutical industry's future. It will be most useful in the pursuit of the most scientifically innovative drugs. Vertical integration requires a degree of scale, which means that established pharmaceutical companies are well positioned to be integrators. But that will require change. Most major pharmaceutical companies have created their own islands of expertise inside their own corporate boundaries, a deeply problematic practice that probably explains their poor R&D productivity. To realize their potential as integrators, they will need new internal structures, systems, and processes to connect technical and functional domains of expertise.

Fewer, closer, longer-term collaborations. Alliances will continue to be a critical complement to internal R&D. Given the breadth and rate of technological change, not even the largest companies can explore all facets of the R&D landscape without help from outside parties—universities and smaller, specialized biotech firms. Their collaborative relationships, however, will differ substantially in form and number from those that currently dominate the sector.

For projects that are scientifically or technologically novel, forging fewer, deeper relationships makes sense. Instead of signing 40 deals in one year, a pharmaceutical company might be better off involving itself at any one time in only five or six that last five to ten years and are broad in scope. Instead of concentrating on a given molecule, for example, a collaboration might focus on specific therapeutic areas or target families. Such relationships would potentially result in much more sharing of proprietary information, greater joint learning, and larger, more productive investments. We simply cannot expect independent enterprises to share knowledge and engage in true collaboration within a business-

development framework that focuses on short-term goals and emphasizes the law of large numbers over commitment.

Fewer independent biotech firms. Small entrepreneurial biotech firms will continue to be an important element of the landscape. But there will be far fewer independent public companies. The publicly held model will work only for companies that have earnings, allowing investors to judge their prospects; under existing disclosure practices, pure R&D enterprises do not belong in the public equity space.

Quasi-public corporations. A possible alternative to the public company is the quasi-public corporation. Its shares are publicly traded, but a large company with a long-term strategic interest in the biotech firm's success owns a majority stake. Such a relationship would provide a firm with much more intensive oversight than is possible with a normal public corporation, as well as a longer-term perspective and assured funding—all of which are crucial for drug R&D. It would also allow the firm to operate with a significant degree of independence and to offer stock options and other incentives to attract and retain entrepreneurs. Genentech, which is majority-owned by Roche, is one of the few existing examples. Genentech has been highly profitable; its R&D programs have been among the most productive in the industry; and despite its growth it has maintained an entrepreneurial and science-based culture.

A new priority for universities. A shift in the mentality and policies of universities is needed. They should focus primarily on maximizing their contributions to the scientific community, not maximizing their licensing revenues and equity returns.

Much of the debate about university activity in the business of science has focused on the impact of patents and has asked the wrong question: Should universities patent their discoveries? The central issue is the extent to which universities make available the knowledge embedded in their patents. They should be much more cautious about granting exclusive licenses to basic scientific discoveries and supporting the creation of new firms. Putting the science into the hands of more explorers is likely to accelerate the pace of advance.

“Open” licensing that makes an upstream discovery widely available on reasonable economic terms works best when the technologies

in question are broadly applicable tools, techniques, or concepts with many potential (but uncertain) paths for development. The advance of biotechnology would have been slowed considerably had recombinant DNA, monoclonal antibodies, and other basic genetic-engineering techniques been exclusively licensed to a single firm. Granting an exclusive license to an existing firm is necessary when the technology in question is specific and further downstream in its development, its value declines as access to it grows, and certain complementary assets and capabilities are needed to fully exploit it. For example, a novel cancer therapy might be more fully exploited if licensed to an organization with experience in both developing cancer drugs and designing and managing clinical trials. But that firm would be less inclined to invest in development if the therapy were also licensed to competitors. Granting an exclusive license to a start-up makes sense only when the technology is so radically different that existing firms lack the capabilities essential to developing it. For instance, it would probably make sense to incubate a highly novel technique such as tissue engineering inside a new firm that could build the essential capabilities from scratch.

More cross-disciplinary academic research. In commercial drug R&D, the fragmentation of the knowledge base into highly specialized niches is a major barrier to integration. There is deep knowledge within, say, chemistry and genomics, but much less knowledge about the connections between them. This is partly because each academic discipline has its own focal problems, language, intellectual goals, theories, accepted methods, publication outlets, and criteria for evaluating research.

Some of the difficulty may be in the peer-review process that universities use to award research grants. The process does an excellent job of ensuring that decisions are based on scientific merit, but reviewers tend to award grants to projects within their own disciplines.

To address this problem, some universities have in the past decade launched interdisciplinary institutes to bring together scientists from biology, chemistry, mathematics, computer science, physics, engineering, and medicine. The Broad Institute, a research collaboration involving faculty, professional staff, and students from the academic and medical communities of Harvard and the Massachusetts Institute of

Technology, is one example. Such collaborations are a step in the right direction.

More translational research. As the name implies, this kind of research translates basic scientific findings and concepts into specific product opportunities. It connects early basic research with clinical testing, encompassing activities such as target identification and validation, *in vitro* and *in vivo* screening, and perhaps some early-stage human clinical trials. Working to understand how stem cells divide and specialize is an example of basic scientific research. Developing hypotheses and insights about using stem cells to treat diabetes is an example of translational research. Historically, the problem with translational research has been that the National Institutes of Health and other government agencies that fund basic research view it as applied science, and private venture capitalists view it as too risky and too long-term. Moreover, to undertake translational research requires investments in intellectual assets, such as novel animal models, that may be difficult to commercialize or even protect.

Translational research may be funded in two ways. The first is by extending the reach of government funding further downstream. This is already starting to happen with the NIH Roadmap for Medical Research, an initiative launched by the agency's director to identify and address major opportunities and gaps in biomedical research. The second is through more private funding. The largest pharmaceutical companies could increase their support for the translational research they conduct on their own or in collaboration with universities. Novartis, for one, has been pursuing both strategies. Venture philanthropies, too, hold promise. These organizations tend to be privately funded, not-for-profit entities that focus on advancing treatments for specific diseases. Some examples are the Bill & Melinda Gates Foundation (for research on AIDS and infectious diseases in developing countries), the Michael J. Fox Foundation for Parkinson's Research, the Multiple Myeloma Research Foundation, and the Prostate Cancer Foundation. These organizations approach

funding and management much the way traditional for-profit venture capitalists do, with a couple of big differences: They have long time horizons, and their goal is to make a therapeutic difference, not to return a profit to limited partners within three to five years.

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With such organizational forms and institutional arrangements, science can be a business. Is it realistic to think that the anatomy of biotech could change so radically? Yes, for two reasons. One is that many of the elements I have listed already exist, even if they are still the exception, and their success will undoubtedly attract a following. The other is that evolution is the norm in business. Epochs of major technological innovation have been accompanied by transformational innovations in industry design. For example, the development of the rail and telegraph systems, which required enormous investments and the management of vast operational complexity, gave rise to the modern corporation, which separated ownership (shareholders) from management (salaried professionals). Throughout the past century, the modern corporation has continued to evolve. Venture capital's emergence in the United States in the latter half of the twentieth century, for instance, helped produce entrepreneurial organizations that played a crucial role in semiconductors, software, computers, and communications.

We can hope that biotech will similarly evolve and create a model for emerging science-based businesses like nanotechnology. After 30 years of experimentation, it is clear that biotech is not just another high-tech industry. It needs a distinctive anatomy—one that will serve the demands of both science and business. Only then can it deliver on its promise to revolutionize drug R&D, conquer the most intractable diseases, and create vast economic wealth.

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