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Millennium Pharmaceuticals, Inc. (A)

"Great meeting" were the words echoing in the halls of Millennium's new headquarters in Cambridge, Massachusetts as a dozen people in business suits swarmed out of the meeting room, shaking hands and slapping backs. Their dark suits contrasted sharply with the daily informal wear at the fast-moving biotechnology firm where even the CEO often appeared in loud Hawaiian shirts. Six of the meeting participants representing the European agribusiness conglomerate Lundberg had flown in by private plane. Their eagerness to access Millennium's genetic technology for agricultural applications showed throughout the meeting. The proposed alliance enjoyed support from the very highest levels at Lundberg; in fact, C. Marie Lundberg, heiress to the closely held family business and a senior Vice President herself, had attended this August 1999 meeting.

The real question, however, that CEO Mark Levin pondered was the amount of middle-level support from Lundberg for the deal. Although no specific amount of money had been discussed, both sides remained aware that since 1993, Millennium had graduated to multi-hundred million dollar technology and drug discovery deals. The firm was currently involved with a half-dozen technology and pharmaceutical deals worth over a billion dollars. In fact, even without a single drug even close to clinical development, just on the basis of its technology and drug discovery deals alone, Millennium had broken into the ranks of the top biotechnology firms. Just one year ago, it had created history by signing a half-billion dollar alliance with the German multinational company Bayer AG—the largest deal ever between a biotechnology and a pharmaceutical firm.

Over the past year, Millennium's stock had skyrocketed, creating unexpected fortunes for its staff, which received part of its compensation as stock options. But continued performance on Wall Street meant pleasing both investors and analysts who wanted to see the company continue its highly successful alliance stream (see **Exhibit 1** for financials). Already many biotech firms were starving for money and a clear sense of strategic direction.

Although the firm attracted some of the world's leading human genetics experts, it viewed itself as operating in a much larger context; in the words of its CEO and founder Mark Levin, "I never thought of Millennium as just a technology company." Millennium, in fact, sought to break into the ranks of the giant pharmaceutical firms. And it planned to do so by revolutionizing drug development—a process as notoriously lengthy as it was unpredictable. As Chief Technology Officer Michael Pavia, Ph.D. outlined his vision, "Developing drugs ought to be managed like any other complex development process; some day, we will make it as predictable as developing and making automobiles." To accomplish this vision would require time and a lot of cash.

Professor Stefan Thomke and Research Associate Ashok Nimgade prepared this case. HBS cases are developed solely as the basis for class discussion. Cases are not intended to serve as endorsements, sources of primary data, or illustrations of effective or ineffective management.

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The Biotechnology Revolution(s)

In the mid-1970s, stunning biological breakthroughs set the stage for the modern biotechnology industry. Scientists could now cut and paste snippets of deoxyribonucleic acid (DNA), the blueprint of life and the longest known molecule in the universe. In fact, if all the DNA in any given human cell were laid end to end, it would span over a meter across. Since there are trillions of cells in the human body, all of the DNA in a given adult would easily stretch from earth to the sun and back, *several times over*. This provides just one index of the complexity of the human body. Each second in the body, millions of basic compounds are being synthesized and thousands of interrelated biochemical reactions occur. These all rely ultimately on the accuracy with which DNA in each cell is being deciphered to create proteins, vital building blocks of the body. A small misstep virtually anywhere in these processes can potentially result in morbidity and mortality.

By gaining the power to revise DNA and create new protein products, biologists in the laboratory could more precisely manipulate the primary biological molecules of life. In the 1970s and 1980s, commercial possibilities for the new technologies were seen well in advance of the ability to deliver on them. In these decades, Wall Street and individual speculators poured millions of dollars into new biotech firms, often even without the faintest idea of what differentiated a gene from its homonym.

Part of the excitement stemmed from the fact that the traditional way of finding cures for diseases was extremely effort-intensive and expensive. Large pharmaceutical companies spent up to 15-20% of sales in R&D. In the United States, as part of an extensive, highly regulated safety approval process, each drug had to pass three phases of clinical trials under the scrutiny of the U.S. Food and Drug Administration (FDA): Phase I, which tested clinical safety, Phase II, which assessed drug efficacy, and Phase III, which tested adverse effects from long-term use. For each successful product the sponsoring drug firm typically spent more than \$230 million, with the average time to market being 14.8 years—over twice as long as it took the US space program to get a man on the moon. (See **Exhibit 2** for a description of drug development.)

Metaphorically, drugs were molecular-sized “keys” that had to fit “locks” or targets; chemists were the locksmiths. Indeed, they were effectively semi-blind locksmiths, for they had to make up thousands of different keys to find the one that matched. Newly synthesized molecular keys were then tested by biologists, typically using animals that served as models for a disease (for example, a mouse with a neurological problem similar to Parkinsonism). Most compounds would show no activity or be too toxic for further evaluation. A few, however, might show promise, and chemists would modify these “lead compounds” until a good clinical candidate emerged. Typically, for each successful drug that made it to market, a firm began with roughly 10,000 starting compounds. Of these, only 1000 would make it to more extensive *in vitro* trials (i.e. outside living organisms in settings such as a test tube), of which 20 would be tested even more extensively *in vivo* (i.e. in the body of a living organism such as a mouse) before ten compounds made it to human clinical trials. The entire process represented a long and costly commitment, with the human trials closely monitored by the US government.

Biotechnology, by promising a shortcut through the cumbersome and risky drug development process, promised investors wealth. It attracted entrepreneurs and maverick scientists. The hub of biotech activity was near academic centers like San Francisco and Cambridge (some observers even transformed the old Boston-Cambridge moniker “beantown” into “genetown”). In the 1980s the guiding principle behind quicker drug discovery was “rational drug design.” By finding out about the disease causing receptor in the body on which a potential drug compound acts, scientists hoped to make better compounds. The analogy would be to find out about key features of a lock before

designing a properly fitting key rather than a brute force strategy of making keys at random with the hope that one might eventually fit.

But rational drug design often turned out difficult to implement because of the subtle complexities of biological systems and the difficulties of finding the right receptors. In fact, the biotech industry generally disappointed investors in the 1980s partly because of the hype, and partly because biotechnology firms were not large enough to absorb the high rate of failures in drug development. A crushing blow to a biotech firm might be absorbed like a gnat's sting by a pharmaceutical firm. The crushing blows, unfortunately, came usually late in the drug development process during human clinical trials, after considerable investments of time and money had been made. Following announcements of negative human clinical trial outcomes, stock prices for biotech firms dipped by an average of a third—quite often they remained depressed for the following half-year.¹ Thus, even with the newest technologies up their sleeves, small biotech firms often played David to the pharmaceutical Goliaths, with a few exceptions such as the California firm Amgen.

Here, however, Biblical parallels end, for most biotech upstarts wanted nothing more than to become fully integrated pharmaceutical giants themselves. But after more than a decade of inflated promises made by biotech firms, investors became increasingly wary. Biotech firms established primarily for product discovery often disappointed investors. As a result, many biotech firms were forced to form partnerships with pharmaceutical firms or even merged with one another.

In the 1990s, the nascent fields of “combinatorial chemistry” and “high throughput screening” breathed new life into the industry by allowing scientists to create and screen prodigious numbers of novel compounds. Returning to the lock-and-key metaphor, scientists could now churn out keys by the thousands and test them almost equally rapidly. Drug companies, however, would still need to muster as many biochemical tricks as they could to identify worthwhile pharmaceutical “targets” (the industry parlance for the “locks” in the lock-and-key metaphor).

While technologies evolved, so did industry dynamics. Biotech firms in the late 1990s wove more intricate alliances with their pharmaceutical partners, often leveraging these relationships to gain access to Wall Street money and gaining downstream synergies for manufacturing and marketing infrastructures. The giant firms, in return, gained access to emerging technologies that could often be protected; furthermore, they could add to their product pipelines. For a pharmaceutical giant with \$10 billion annual revenues to continue growing at 10% a year would require three to four new products a year (a typical product generating \$300-\$400 million annually). Even more would be needed to cover drugs going off patent. With internal pipelines producing less than one significant product a year, big firms increasingly needed to partner with smaller firms.

Many newer generation biotech firms began emphasizing sales of drug development technologies more than pharmaceutical products. These firms, sometimes termed “tool companies,” hoped to generate revenue faster by providing services to drug discovery companies, thus avoiding the high cash “burn-rates” involved in searching for drugs. Many of these firms developed multiple relationships with different drug firms, thus blurring the line between sales and strategic partnerships. By the late 1990s, two decades into the biotech revolution, about 300 biotech-based drugs were on the market, and nearly 450 were in clinical trials.² These seemingly impressive numbers paled in comparison to the over 1,300 biotech firms actually in existence. The year 1997 saw 228 new biotech-pharmaceutical collaborations, valued at \$4.5 billion³. Those biotech firms unable to

¹ *Biotech 98: Tools, Techniques, and Transition*, G. S. Burrill, San Francisco: Burrill & Co., 1998.

² D. Stipp, “Hatching a DNA giant,” *Fortune*, May 24, 1999.

³ *Biotech 98*: . . . , op. Cit.

create products or merge with other companies often foundered, leaving their investors holding worthless stock. In such an environment, pharmaceutical firms could often “cherry-pick” drug candidates from financially troubled smaller companies. Only a half-dozen U.S. biotech firms had marketed major drugs without selling majority stakes to pharmaceutical firms. Of these, only Amgen, a Californian firm with a market valuation of over \$30 billion, had emerged as a major drug company with very successful drugs. Onto this sea of broken dreams and treacherous regulatory currents Millennium set sail in 1993.

Birth of A New Millennium

When Mark Levin interviewed early in his career at the pharmaceutical giant Eli Lilly without socks, his staid recruiters thought him “a little weird.” Even as CEO, he continued raising eyebrows, taking family outings to the local horse racetrack, and appearing annually at Millennium Halloween parties in drag—in a recent year he appeared, wife and daughter in tow, dressed as a French maid in a low-cut dress. Photographs of Levin in any of his large collection of colorful shoes, including zebra-patterned, adorned investor publications.

A one-time Midwestern shoe salesman and former donut shop owner, Levin leveraged his training in chemical engineering to climb his way out of small-town obscurity. After helping start up a beer-brewing plant and getting exposure to the pharmaceutical world through Lilly (he did get the job), Levin quickly found his niche in the emerging biotech industry of the early 1980s. While working for Genentech, the pioneering California-based biotech firm, Levin’s brilliance in managing complex projects won him a job at Mayfield Fund, a San Francisco venture capital firm. Here Levin founded some 10 biotech firms—serving as interim CEO of five. His crown jewel, however, proved to be Millennium Pharmaceuticals (see **Exhibit 3** for historical milestones).

Levin’s concept for Millennium proved so new and strange that an extensive executive search concluded that only Levin could head up the proposed company. According to Grant Heidrich, general partner at Mayfield, Levin “has tremendous vision for what is looming out there. For most people, there are those elements that are hidden in the fog bank. But Mark finds these disconnected pieces and just pulls them together.”⁴ The plan was to build a drug development company around findings emerging from the Human Genome Project, an ambitious international effort to identify and map every bit of human DNA (which in its entirety is termed the “genome”).

Genes causing disease could prove potential targets for drug development. These targets could then be used to develop families of new drugs the world has never seen before. Mapping the human genome “may be the most important step we’ve taken in science,” according to Nobel laureate James Watson, co-discoverer of the DNA structure.⁵ Since every disease has a genetic component, deciphering the “Book of Life,” as some scientists refer to the genome, promised to revolutionize medical research over decades to come. Even if only 5%-10% of all estimated 30,000 to 100,000 human genes would yield viable drug targets, it could still open up a rich lode of pharmaceutical drug leads. For the past 100 years, after all, the painstaking efforts involved in drug research had limited medicines developed to less than 500 targets. Even several decades after Watson and Crick discovered the structure of DNA, scientists of the 1980s took years to find and sequence just a single gene or a stretch of DNA of particular interest. For drug companies in 1999, the new revolution could

⁴ “Millennium’s chief found his calling starting up new biotechnology firms,” *Boston Business Journal*, December 5-11, 1997.

⁵ A. Zitner, A. and R. Saltus, *The Boston Globe*, Sept 26, 1999, p 1+.

not have been better timed because patents on some 30 major drugs were to expire in the next three years, placing pressure to add to the product pipeline.

With this vision in mind, starting in 1993 with \$8.5 million in venture capital funding, Levin set up the company in Cambridge, Massachusetts in order to court the nation's leading genome scientists. Even without a written business plan or formal organizational charts Levin sold his vision for a new Millennium well. "The reason spectacular scientists want to come to Millennium is that spectacular scientists work at Millennium," according to Professor Eric Lander, a scientific founder of Millennium and himself one of the leading genome experts in the world, "Mark saw that from the beginning."⁶ Levin and his team leveraged off the star scientist reputations to raise large amounts of funding with which to create far better research facilities than even the finest universities.

The firm's roster of brilliant technologists included its Chief Technology Officer, Michael Pavia, a pioneer in the combinatorial chemistry revolution. Pavia wanted to leverage the lessons he learned as former head of research at Sphinx Pharmaceuticals, another Cambridge-based biotech firm that was acquired by Eli Lilly, and also wanted to take part in the next revolution: that of transforming the drug development process itself. Millennium also recruited top business people and legal counsel, some of whom were high-performing mavericks in larger pharmaceutical firms and many of whom had nontraditional backgrounds. The company's Chief Business Officer, Steven Holtzman, for instance, is an Oxford-trained Rhodes Scholar whose philosophy training in making fine distinctions helped craft partnership deals that left Millennium with sizable shares of finely cut pies.

Senior management strategically highlighted technology development from the very start. Levin and Holtzman wanted to avoid the mistakes of other biotech firms, which often found themselves stranded in the vise of big pharmaceutical firms because of not having resources to market drug compounds or not having a broad enough technology platform to avoid becoming research boutiques. If risk diversification for a biotech firm proved difficult on the basis of different products, then at least it should occur on the basis of leading edge technologies.

The initial vision of Millennium was to marry molecular biology with automation and informatics. This would allow for discovering and processing huge amounts of information about genes, making thousands of new targets possible. A dramatic increase in targets would also require quicker screening technologies in order to test many more compounds. Proprietary lab technology included software for analyzing gene function, and machines that decode DNA sequences. Harking on Levin's background as a chemical engineer with work experience in process control, the *Economist* noted:

Whereas biologists tend to see biotech as the search for a compound, Mr Levin thinks of it as a complex production process. While they concentrate on the bio, he also thinks hard about the technology. Mr Levin focuses on trying to make each link in the discovery chain as efficient as possible... He has assembled an impressive array of technologies—including robotics and information systems as well as molecular biology. He then enhances them and links them together in novel ways to create what the engineer in him likes to call "technology platforms," [which] should help drug searchers to travel rapidly on their long and tortuous journey from gene to treatment. And Mr Levin is prepared—keen, even—to use or buy other people's technology to help in the struggle to keep up to date. One observer has called him the "Mao Zedong" of biotech, a believer in continuous revolution in both technology and organization.⁷

⁶ K. Blanton, op. cit.

⁷ Anonymous, "Millennium's bugs," *The Economist*, Sept 26, 1998, p. 70.

By creating a technology platform considered the finest available, the firm generated capital for updating the platform to keep ahead of the competition. Biotechnology promised a shortcut for finding cures for human genetic diseases. It allowed for skirting the traditional time-consuming study of family trees of diseased individuals in order to track down the responsible genes. Since these genes could be anywhere along the vast expanse of human DNA, some firms tried to take advantage of rulings that allowed for filing patents on naturally occurring gene sequences as fast as they could find them. “The important thing is to get California instead of Appalachia” in this pharmaceutical land grab, according to Millennium executive John Maraganore⁸. To find these prime pieces of genetic real estate, researchers analyzed hundreds of gene sequences simultaneously using miniature “DNA probes” that could ferret out promising stretches of DNA. These probes were derived through research on DNA samples from people suffering from diseases of particular interest.

Not only could a gene sequence be patented, but also the specific protein produced by that gene as well as the engineered drug produced by splicing the gene into a microbe for production could be. In addition, patents could be filed for the use of the gene in diagnostics tests as well as in drugs targeted at the gene. By 1999, although every large drug company had incorporated combinatorial chemistry into its R&D arsenal, such was not the case with genomics. In April 1999, several large drug companies including the two giant firms Glaxo Wellcome and Bayer AG started a collaboration to locate tens of thousands of areas on the genome that may be implicated with disease and put these in the public domain.⁹ Skeptics view this as an effort of the Goliaths to thwart growth of the biotech Davids.

Millennium’s genomics-based approach reversed the traditional process by first identifying and understanding the role of genes implicated in causing a disease. This should allow for selecting drug candidates based on their ability to intervene in disease initiation and progression—thus targeting the root genetic basis of illness. The firm’s strategy relied on using many advanced biotech technologies as well as other computer and robotics technology advances based on the Human Genome Project (see **Exhibit 4** for some of the technology).

Some experts warned that the new interest in genomics might turn out to be another disappointment just as rational drug design of the 1980s had. According to genomics entrepreneur Craig Venter, himself involved with co-founding of the leading-edge genomics firm Celera, “genomics has been oversold, although it does mark a ‘new starting point.’”¹⁰

Managing Growth

Millennium’s vision is to focus on activities that allow us to take the highest downstream share of a drug’s profit—wherever these profits may occur. How much you participate in downstream activities and what you have to do has changed and will continue to change in this industry.

— Steven Holtzman, Chief Business Officer

From its genesis in 1993 with only 20 individuals, Millennium grew rapidly, drawing upon its founders’ willingness to experiment and try new strategies, and systematically learn from failures of other firms. Itself a small company, its rapid growth stemmed from research collaborations with

⁸ D. Stipp, op. cit.

⁹ I. Amato, “Industrializing the search for new drugs,” *Fortune*, May 10, 1999.

¹⁰ Ibid.

dozens of other biotech firms and university scientists. Although the company prided itself on avoiding the trappings of hierarchy—no formal organizational charts existed—several divisions and subsidiaries evolved over time. By the late 1990s, Millennium saw itself as a family of the different groups working toward a common end of developing expertise in genomics as well as revolutionizing drug development (see **Exhibit 5**).

Central to its success and growth, however, was its ability to attract good employees based on scientific merit and interpersonal skills. “You get interviewed about twelve times before they hire you,” stated Kenneth Conway, who was recruited to head the predictive medicine subsidiary in 1997. “First they want to know if you have the drive and intelligence to do the job. Then they reinterview you six times to find out if you’ll fit in personally.”¹¹ According to Vincent Miles, Vice President of business and technology management, “In spite of a tight labor market, we have managed to get to 800 excellent employees without major politics. At a small biotech firm I worked at previously, there were always two camps of seven individuals each, and the CEO would have to act as tie-breaker. Here, people will cover for each other.”

Many workers attributed the relative lack of internal politics to top management’s low-key approach in running the company. At meetings, Levin often remained in the background, speaking primarily to keep the discussion from going off-track. His office, a modest affair with wall-mounted shelves underlined the flat structure of the organization. Levin, Holtzman and Pavia also set the pace for the hard-working environment, usually arriving every morning to their spartan offices before five or six a.m. Employees arriving early enough were often treated to the sight of their CEO working with headphones to the beat of rock music. All employees received stock options which had resulted in very significant capital gains after the Millennium’s stock started to skyrocket in mid-1998.

Through its half-dozen years in existence, senior management realized it needed to chart its own destiny despite its need for large partners. According to Miles, “we did not want to be managed by remote control by committees of larger firms.” Indeed, biotech managers often complained of the manner in which large companies dragged their feet. A life-or-death decision for a biotech firm, after all, could represent an hour’s revenues for a pharmaceutical giant. Scientists at biotech companies were often demoralized by these delays, since it frequently meant delaying their valued scientific publications because of patent considerations.

To achieve its goals of independence senior management adopted several strategies. First, it intended to eschew the traditional full-time equivalent (FTE) model of funding favored by many biotech firms. In the FTE system, biotech firms would charge their partners for the time spent on alliance specific activities—similar to the way a consulting firm would bill its client for time spent on a project. Although this FTE system tied funding for individual researchers to specific partnership deals and generated predictable cash flow, it often led to a “clock puncher” attitude, with researchers focused on meeting goals of individual partnership projects rather than on the growth and mission of the company itself. Second, Millennium sought partnerships that would fund the type of R&D that would bring it closer to becoming a major drug development firm. Third, as much as possible, it signed only those partnership deals that would enhance, rather than stymie, its ambitious goals for future growth. (See **Exhibit 6** for its revenue structure.)

Management’s negotiating strategy for strategic alliances reflected the company’s long-term goals by carefully carving out enough choice cuts for the firm itself. Because countless other biotech firms had been frustrated by the slow pace of their larger partners, Millennium crafted agreements that held the feet of its larger partners to the fire, making them answerable for unmet scheduled

¹¹ D. Stipp, op. cit.

milestones. For instance, in a recent Millennium alliance, once it found a potential drug target, the partner would need to screen it within a given time; otherwise the rights to the target would revert back to Millennium.

Millennium also sought to retain rights to unforeseen discoveries in the course of a partnership. “We grant select rights of high value to our partners,” according to Miles, “while retaining new knowledge and the remaining rights to ourselves.” Focusing on such select rights actually worked well with pharmaceutical partners, largely because the big company executives tended to think along divisional lines and focused on rights that fell within their strategic focus. This allowed Millennium to reserve some rights for its own future drug development, such as selected geographic markets or particular therapeutic applications, that were not of immediate interest to its alliance partners. Millennium’s contracts were long and explicit, drawing upon some of the most talented lawyers in biotechnology as well as upon Holtzman’s attention to both big picture issues and small but crucial details. For instance, in the field of cancer, senior management carved out separate arrangements with three different firms in a manner that eventually boosted its revenues by tens of millions of dollars. At the same time, few of its partners complained. In the words of Paul Pospisil, Associate Director of business development and strategy, “Large companies salivate over parts of our state-of-the-art technology platform, and our negotiating team is smart enough not to discuss money prematurely.”

Millennium underwent one merger when, in 1997, it bought neighboring biotech firm ChemGenics for \$90 million. At that time, it had five alliances with drug firms for finding specific gene targets (the “locks”). Through these alliances, Millennium began to realize that it lacked expertise in going from drug targets to actual lead compounds (the “keys”)—a major weakness if the firm itself wanted to develop its own drugs some day or simply validate the feasibility of targets that it supplied to its larger partners. Buying ChemGenics with its expertise in lead discovery was a step towards addressing this weakness and would also allow Millennium to negotiate with big firms from a position of greater strength. There was also a feeling among senior executives that general drug targets were becoming increasingly commoditized. Validated targets, on the other hand, where evidence for downstream drug development potential could be demonstrated early were still rare.

Thus, when Millennium realized that ChemGenics was planning an initial public offering, it essentially bought out ChemGenics. A bonus was ChemGenic’s expertise in the area of infectious disease—an attractive area for drug development with more predictable and shorter clinical trials than newer therapeutic areas such as central nervous diseases. Culturally, too, the companies appeared compatible. Both, having been launched next to the Cambridge Brewery, were imbued with the very same spirit—the hard-working, hard-playing, high-tech ethos.

By drawing on world-class personnel, and through tough negotiating strategies that led to key mergers, acquisitions, and value-adding relationships with universities and other firms, Millennium had vaulted into the front rank of biotech firms. Unlike most other biotech firms, it posted profits early. For three of its first six years—not counting a one-time charge for the ChemGenics acquisition—Millennium had posted profits.

Being a pioneer in a new field, Millennium got surprisingly little heat from direct competition. Somewhere between two and three dozen genomics biotech firms existed, with a market value of the leading 14 firms of \$4.7 billion. Only two of these biotech firms, however, could be considered the firm’s peers: Human Genome Sciences (HGS) in Rockville, Maryland, and Incyte Pharmaceuticals in Palo Alto, California.

In the late 1990s, HGS rode high after finding more disease-related gene targets for its pharmaceutical partner SmithKline Beecham (under their original 1993 \$125 million agreement) than

even one multinational drug company could use. HGS had also negotiated to retain several targets for itself, and by spring 1999 one HGS compound was already undergoing human trials with 25 other candidates to follow suit. HGS also claimed to have applied for patents on 3,000 genes.¹² Incyte, on the other hand, used an entirely different strategy to become a leading genomics firm. It sold drug companies' information in user-friendly databases about the genome. Despite licensing out this information non-exclusively it reaped subscription fees well over \$100 million in 1998 alone.

Part of what shielded Millennium from direct competition with other biotech firms was its own success in attracting large partners to create record-breaking alliances which generally had either a pharmaceutical or technology focus or sometimes a combination of both (see **Exhibit 7** for a list of alliances).

Technology Alliances: The Monsanto Deal

For thousands of years, farmers have crossbred crops and herders have crossbred livestock. Agriculturists, unencumbered by human genetic ethics or the long life span of humans, could experiment with crops in ways not possible with humans. Darwin, in fact, drew upon the accumulated centuries of knowledge gleaned from agriculture in explaining the theory of evolution through natural selection. Thus, agriculture should have drawn upon biotechnology earlier than pharmaceutical companies. Surprisingly, however, agricultural firms were slow to do so despite the fact that in the late 1990s the 1.5% world population growth rate outstripped the rate of growth of agricultural productivity (<1%) in a global setting of decreased availability of fresh water and arable land.¹³ The slowness of agribiotech to bloom, however, stemmed partly from tremendous technical challenges facing agricultural biotechnologists: unlike human researchers, agriculturalists diffused their research efforts across dozens of different species, some of which possessed genomes even larger than human genomes.

One of the first of the giant multinational giants to realize the potential of biotechnology, however, was the Midwestern U.S. firm Monsanto. In 1997, Monsanto approached Millennium to gain access to state-of-the-art genomics technologies. The acquisition of ChemGenics had made it even more attractive to Monsanto. (ChemGenics had already been talking with agricultural firms in a preliminary fashion.) Millennium, in turn, was looking to leverage the integrated platform for agriculture and create near-term value.

The challenge to senior management, however, was to avoid being distracted from its focus on human therapeutics, particularly at a time when the staff was already extended. Millennium contemplated several structures for its partnership including a typical biotech-pharmaceutical partnership, a joint venture, and a technology transfer. To avoid being distracted from its focus on human health, Millennium sought the last option. By agreement with Monsanto, it agreed to replicate or "clone" its technology platform in an agricultural milieu through creating Cereon Genomics, a Monsanto subsidiary. Even the local character was preserved by basing Cereon in Cambridge.

Millennium would receive up to \$218 million (\$118 million in an up-front fee, and the remainder in yearly \$20 million increments based on achieving milestones over the next five years). The milestones were set to be "80% achievable." This was to avoid the game of the biotech firm being conservative and the pharmaceutical firm being aggressive. Examples of milestones included:

¹² Ibid.

¹³ *Biotech 98*: . . . , op. cit.

number of DNA lanes sequenced over a given time period; total sequencing capabilities of Cereon by certain time intervals; and software to be set up.

Millennium involved 100 of its scientific staff to help deliver the technology to Monsanto. Nonetheless, the firm learned quickly that the venture would require hiring new staff largely in order to help Cereon *receive* the technology. Technology transfer, after all, always takes place at both ends of the transfer mechanism. Monsanto, however, had generally underestimated the size, infrastructure and training of its technological staff that were necessary to make full use of genomics technology. The middle-ranking scientists and technologists generally found the technology transfer relationship symbiotic; the transfer process, for instance, forced Millennium to document its protocols and software more formally—steps that would help its own new staff members. In the course of working out glitches, useful new information also flowed back to Millennium. Socially, strong bonds were formed through weekend activities such as a joint softball team that consisted of Millennium and Cereon employees.

Over the course of the Monsanto alliance and other deals, Millennium grew from 400 to 700 employees, with 30 new applicants arriving each Monday for five interviews each, and eventually added over \$20 per share to its stock. It achieved all the milestones agreed with Monsanto, thus obtaining the maximum fees outlined in its contract. According to Miles, “This was our first value-based deal. We thought we could replicate this model over and over again. We were blown away by our success at replicating our technology platform.” But only a string of success stories could keep the stock price continuing upward.

Pharmaceutical Alliances: The Bayer Deal

With the ink still drying on the Monsanto-Cereon deal, Millennium underwent a period of soul-searching. It realized that its staff was increasingly stretched across a variety of medical areas in terms of upstream drug target development. Although the Monsanto-Cereon deal indicated that Millennium could go on creating new technology deals, the company still lacked the capabilities to take drugs all the way to market and a robust pipeline of drug development opportunities to pursue on its own behalf. It would have to look for strategic alliances with drug firms to make up for these weaknesses.

At the same time, across the Atlantic, Bayer AG, a large German research firm with 145,000 employees worldwide—best known for introducing Aspirin—was also undergoing a soul-searching exercise termed internally the “Vision 2000” initiative. In 1997, pharmaceuticals accounted for a third of Bayer’s \$30 billion business but senior management realized that it lagged behind in terms of target discovery and biotechnology. To address this, the company surveyed hundreds of biotech companies for acquisition or partnership deals. With a large war chest it could easily broker deals with a dozen or more biotech firms.

In late October 1997, Bayer invited 55 senior managers from leading biotech companies to what industry insiders termed a “biotech beauty pageant.” Millennium, a leading contender, had a prime place on the roster. This came as no surprise, since as early as June of 1996, a Bayer manager had put out “feelers” (i.e., tentative approaches) to a Millennium executive in Paris. A few days later, Bayer invited the firm to partner with it in several areas. With Millennium, Vision 2000 had recognized a natural partnership—one that extended far beyond the similarity of names—and which would allow for “one-stop-shopping” for both sides.

The two companies signed an agreement under which Millennium would find 225 new drug targets for Bayer—an impressive number considering that over the past century, all of the world’s

drug discoverers combined had found around 500 drug targets. In effect, Millennium would take responsibility for finding half of all targets going into Bayer's drug development pipeline. Areas to be covered included cancer, cardiovascular diseases, pain, osteoporosis, viral infections, and blood disorders. Consistent with its strategy, Millennium would also retain rights to several targets found in the course of the collaboration.

In return for up to \$465 million over five years, Bayer would also obtain a 14% equity stake in Millennium. The Bayer deal ended up becoming the largest alliance ever between a biotech firm and a pharmaceutical firm. Again, Millennium's stock jumped, creating remarkable capital gains for its stockholders inside and outside the firm.

A New Drug Development Paradigm

"When Mark hired me, he told me that I had five years to revolutionize drug development. I have about four and a half years left."

—Michael Pavia, Ph.D., Chief Technology Officer, July 1999

Fundamental to Millennium's strategy was its ability to revolutionize drug development which, in the late 1990s, was still long, costly and very risky. In 1997, CEO Mark Levin hired Michael Pavia as Chief Technology Officer with the charter to help make the drug development process "twice as fast and half as expensive" within five years, with the countdown starting in the beginning of 1999. As Pavia translated his charter for industrializing the drug discovery process, "the only way to achieve such an aggressive goal is to question everything and to hire people that challenge assumptions held by the industry for decades".

Millennium was by no means the only company thinking along these bold lines. Most large pharmaceutical firms had initiatives under way to shorten the development cycle significantly and make drug development more predictable. Current practice seemed unsustainable. Pharmaceutical firms would bring several successful drugs to market each year and bear the cost of failure in the very long and expensive clinical phase where only one out of ten drug candidates would make it to the market. Eli Lilly, for instance, had announced its internal goal of "2000 days by the year 2000," implying an aggressive compression of the traditional 12- to 14-year drug development cycle into less than seven years.

Nonetheless, recruits were often attracted to Millennium because of their frustration with the slow progress of large firms. The revolutionary technology platform they saw mirrored the very different training and mindset of the firm's founders. Millennium, being new and unencumbered by corporate inertia—let alone formalized plans—could learn from the mistakes of prior firms and aggressively challenge conventional wisdom. For instance, could traditional drug makers drive costly drug failures to the early phases of development when failure was relatively inexpensive? After all, drug discovery would always involve trial and error. But errors discovered in late development were very costly and could only be absorbed by large firms.

Many lessons in drug development were brought in through recruits from larger companies. It was an experienced job candidate interviewee, for instance, who pointed out that the Federal Drug Administration (FDA) nowhere mandates that pre-clinical trials must be done in defined sequential phases in lock-step. (Perhaps, therefore, attempts to "frontload" problems—one of Millennium's development strategies—might lead it to reshuffle the order in which drugs would be tested.)

To revolutionize drug development, Pavia's group aggressively approached its task using the following three strategies: (1) speed up individual steps of the development process, including rapid feedback on critical tests such as toxicology; (2) carry out serial steps in parallel wherever possible; and (3) "front-load" drug failure modes through the use of new technologies. More will be said about each of these strategies below:

1. *Speed up individual steps of the process:* For the early research phase of drug discovery, scientists and engineers sought to speed up the various steps involved in isolating, characterizing and understanding DNA. By drawing on automation experts and engineers with manufacturing experience, Millennium sought to automate truly complex process steps and create an industrial "R&D factory" (see **Exhibit 4**), using robots and other equipment often used in advanced production of other products. To achieve this, engineers opportunistically outsourced and modified emerging technologies, often creating machines envied even by leading universities. Like other firms, Millennium also planned to use combinatorial chemistry and high-throughput screening to reduce the time required in the laborious, traditional random search process for drug candidates. Interestingly, no matter how much each step was sped up, however, a crucial bottleneck in the entire R&D process remained: the ability of scientists to assimilate and make sense of the staggering amount of information made available. To address this, Pavia felt that an increased focus on the rapidly growing field of bioinformatics was essential for Millennium.
2. *Carry out serial steps in parallel wherever possible:* In early 1999, Pavia established a group that reviewed the entire drug development process, using basic principles of operations management, for ways to compress the drug development timeline by allowing more steps to be conducted in parallel. This shift in thinking could save considerable time during drug discovery as well as human clinical trials when drug developers evaluated each candidate compound for *target validity*, *organ-specificity* (i.e., was the target specific to the organ of interest), *bioavailability* (i.e., would the compound be absorbed appropriately by the body), and *toxicity*. Rather than addressing each of these issues one by one in the traditional sequential fashion, Millennium decided it would seek to do a series of several "quick and dirty" tests on minute quantities of each candidate compound in a fairly simultaneous fashion to see if a candidate was even in the "right ballpark." This was analogous to prescreening job candidates over the telephone in parallel so that only a smaller batch of higher yield candidates would be invited in for in-depth interviews.
3. *Find new technologies that could "front-load" critical problems, thus eliminating less-promising drug candidates early:* In the 1990s, only 1 out of 10 drug candidates typically made it through clinical development—by far the costliest phase of drug development. Pavia wanted to improve these odds by at least half. His staff sought to diminish this wastage by trying to find the potential failure modes through, for instance, prescreening drug candidates as discussed above. Gaining information about, say, the toxicological profile of a drug early on could significantly improve the predictability of its likely success. Pavia's group also decided that it would systematically seek to use other failed drug candidates to see if new technologies could indeed pick up these "failures" earlier (for an example of such a new technology, see **Exhibit 8**). Pavia charged Paul Pospisil, a chemist trained at Harvard who also had strategic responsibilities, to scour conventions and trade fairs for cutting-edge technologies that would provide earlier feedback on candidate drugs. The point was not necessarily to avoid failure, but to shift failures to earlier phases in the process.

Thus, in terms of reducing the product development cycle, much potential for technological improvement existed alongside the uncertainties inherent in all drug development projects. Like most of the major pharmaceutical firms aiming to shorten the drug development cycle, Millennium

realized it would have to focus on many, if not all, links in the drug development process. Focusing on just early drug development through combinatorial chemistry and high-throughput screening, for instance, could save only an estimated half-year to one year. Thus, downstream phases would also need to be shortened. These downstream changes could be achieved through administrative as well as technological changes. For instance, reviewing toxicology data as it was generated might compress the traditional nine-month cycle for a toxicology review into as little as a month.

Taking Stock

At Millennium we believe that nothing is impossible.

—Millennium Corporate Value Statement

With the Bayer deal, Millennium entered the realm of very large pharmaceutical alliances and now basked in the glow of Wall Street's approval. Unlike other biotech firms, however, it resisted the temptation to sell stock after going public, preferring instead to live off its deals. It did not want to get locked into the traditional pattern of seeking up-front funding in return for royalties—the type of arrangement that pleased investors but did not necessarily build up a biotech firm's long-term capabilities. With Millennium's stock price now at unprecedented heights—having doubled to \$60 per share from spring through the summer of 1999, *Fortune* magazine observed, “No drug company wannabe has mustered as much value with as little red ink.”¹⁴

By 1999, the company had grown to about 800 scientists. Millennium remained aware that the current tight job market did not apply to it. In fact, a recent newspaper ad for jobs for mid-level research personnel led to a line well over a block long just for the privilege of dropping off resumes. Many had come from other local biotech firms. Nonetheless, senior management now planned for its growth, at least for the foreseeable future, to plateau at 1,000 scientists.

But even at that size the company dynamics would have to change, despite the best of efforts to retain its small company roots. CEO Levin exclaimed in a 1999 press interview, “It was a lot easier to walk out the bathroom with my [Halloween] costume on when there were 30 people in the company and I knew them all well. Now I walk out into this crowd of 800 wondering if most of them are thinking, ‘Who is this idiot?’ But it’s fun.”¹⁵

But signs of strain in the organization were showing throughout all levels. According to Pavia, “Growing the organization from 100 to 200 was relatively easy; doubling from there to 400 was a bit harder but manageable; but to think of growing beyond 800 would place all sorts of new strains and would need re-thinking on how we do things.” With growth, high-ranking scientists had to supervise more people while contending with having their skills marketed to more outside partners. Indications of increased stress at lower levels came from the Human Relations department's latest semi-annual survey from March 1999. It showed that despite general high employee satisfaction, the areas that scored the lowest were in terms of workload, expectations, and manageability of stress. These areas scored a hairline lower than a half-year ago.

“I absolutely love what I am doing,” one worker commented on the questionnaire, “but the workload sometimes is unmanageable. . . . Sometimes you don’t know whether you are swimming

¹⁴ I. Amato, op. cit.

¹⁵ D. Stipp, op. cit.

or sinking.” Another worker added, “I think my workload and the expectations are higher than in the other industrial settings where I’ve worked—I’ve worked for three other companies.” Yet another worker quantified this frustration: “I am currently committed to do two scientists’ worth of work. Consequently I feel that I have to make a choice between trying to do it all in a mediocre way, or I can only do part of it well and leave the rest undone—if I take the latter route, there is no good decision mechanism to tell me what is the most important: I’m told ‘Everything is important!’”

To manage stress within the firm, the company’s human relations department under Peter McLaughlin wanted to avoid stopgap measures such as occasional stress-reduction seminars. Instead, in early 1999, it sought to make all managers responsible for having regular one-to-one sessions with subordinates to discuss such issues. How this change in approach would work had yet to be seen. In any case, the company was more aware that money alone could not buy its way out of the stress dilemma. According to Miles, VP of business and technology management:

In the past we were driven by financing. We made commitments without detailed planning. For example, the Bayer deal was so huge that we would do whatever they wanted. Now we are pickier. Our strategy just two years ago was not as clearly defined as now. But we realized that technology alliances could be either financing vehicles or distractions. Every time we thought about a new deal we worried about several tensions: were we biting off more than we could chew? After all, we were already quite extended. Were we in danger of losing our focus? Several other prominent biotech firms have a hard time stating exactly what they do.

Without a formal plan, Millennium had found its path to its present prosperity. Its vision had encompassed becoming a genomics firm and helping revolutionize the drug development process. Already, with these two visions not even fully implemented, its managers and scientists were talking about what could only be whispered at most other biotech firms: the prospect of growing into a fully integrated pharmaceutical firm.

Big Deal

In June 1999, after a presentation at an industry conference, a Millennium senior executive was quietly approached by an executive from Lundberg, a multinational agribusiness concern and one of the largest privately held companies in Europe. Despite not being a household name, Lundberg impacted the daily lives of most Europeans through its dealings in livestock and agricultural produce. It was ironic, therefore, that a company that made fortunes in the futures market from one-cent price swings of commodities sold by the ton now approached a firm that operated on the scale of milligrams.

Through Millennium, Lundberg sought access to genomics technology, much in the manner of the Millennium-Monsanto deal. Lundberg specifically sought access to technology that would help identify plant genes as well as for high throughput screening capabilities. For Lundberg, the applications were limitless. It would, for instance, allow for facile manipulation of the fat content of livestock or the carbohydrate content of grain. For Millennium’s senior management, three issues loomed large in their minds as they thought about a potential deal with Lundberg: strategic fit, impact on its R&D productivity, and potential conflict with its prior relationship with Monsanto.

If the Lundberg deal did not fit strategically with Millennium’s own goals, the company decided it would consider the deal a distraction. Strategic fit would have to be analyzed by considering impact on the entire company. For instance, although at first glance informatics did not appear to be directly

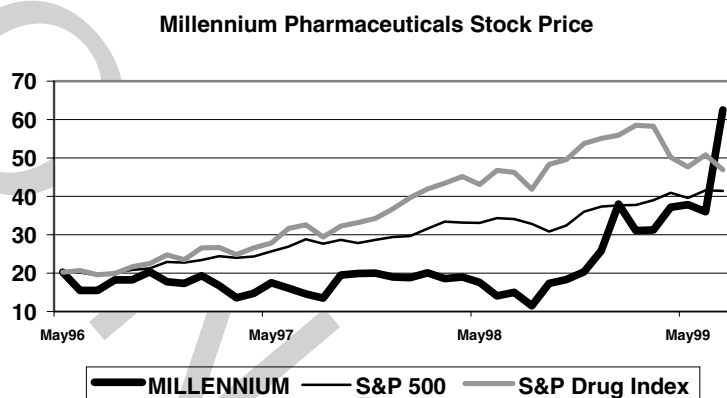
involved, the firm would have to help create software for the new venture. This was no small venture, because the Millennium software platform was orders of magnitude larger than commercial office software and would require frequent upgrades. On the other hand, through a partnership with Lundberg, it could pay for some of the work it needed to do for itself anyway. For instance, software documentation for Lundberg would also help Millennium internally.

In terms of the impact of the Lundberg deal on Millennium's own productivity, many variables remained unclear. If a deal with Lundberg were to hamper productivity, it could stifle growth several years later. For instance, it was clear that Lundberg did not possess an infrastructure for receiving any transferred genomics technology, and therefore Millennium would have to set up a system that would allow Lundberg to receive the technology. This implied using Millennium's senior staff to interview and hire new personnel on Lundberg's behalf. On the other hand, once the interviewing was done, Millennium's top-level staff would be minimally distracted by the Lundberg deal. Furthermore, Millennium's staff generally appeared confident it could repeat its first agribiotechnology technology transfer even quicker the second time, building on experience and expertise that was built as a result of the Monsanto alliance.

Potential conflict with the Monsanto deal turned out not to be an important consideration. The Monsanto agreement allowed for considerable areas of collaboration between Millennium and any other agricultural concern. For instance, while Millennium could not help manipulate the fat content for plant foods because of its relationship with Monsanto, it could do so for livestock.

While Millennium grappled with the issues discussed above, eight senior Lundberg executives created time on their busy calendars to come to Cambridge. No figures were quoted by either party, although Millennium's senior management hinted from the outset that the alliance would have to be at least as large as the Monsanto deal. As these issues were discussed in the meeting, Levin and Holtzman were surprised to learn that Lundberg, for its part, had done little due diligence; it had not even examined the SEC filings for the Monsanto-Millennium collaboration. It was also unclear how the company expected to receive the technology platform as its middle management had not been involved in any of the discussions. On the other hand, Lundberg's senior management, led by a family member that held a majority position in the privately-held firm, showed strong consensus and were ready to make a major financial commitment right away.

The business development team that had prepared the meeting for Levin felt very good—the discussions showed little conflict or disagreement between the two senior executive teams. Announcement of the deal would please Wall Street analysts and probably add a quarter billion dollars or more of cash to Millennium's financial coffer. After the meeting, Levin sat down in his office and reflected on his company's future. In a few minutes, several key executives, including Holtzman and Pavia, would come to his office to discuss the final decision on whether to pursue the Lundberg alliance. Counting the chairs in his modest office, he wondered whether there would be enough room for the small group.

Exhibit 1 Selected Financials for Millennium Pharmaceuticals

Selected Financial Data (dollars in millions, except per-share data)

	1995	1996	1997	1998
Sales	22.9	31.8	89.9	133.7
Cost of goods sold	19.4	38.9	81.6	125.0
Gross profit	3.5	-7.1	8.4	8.7
Operating Income Before Depreciation	3.5	-7.1	8.4	8.7
Depreciation, Depletion & Amortization	1.7	3.9	12.2	16.3
Operating Profit	1.7	-11.0	-3.8	-7.6
Net income	1.2	-8.8	-81.2^a	10.3
Other data:				
EPS (Primary)	0.07	-0.39	-2.87	0.34
Dividends per share	0	0	0	0
ROA (%)	5.1%	-10%	-56%	4%
ROE (%)	9.8%	-13%	-88%	5%
Market value (\$ Mil.)		415.5	554.2	903.6

Source: Financial Reports

^a includes acquisition of ChemGenics

Exhibit 2 Summary of Drug Development in the United States¹⁶

New drug development is a costly affair with high failure rates. For each therapeutic drug entering the market, pharmaceutical firms invests more than \$230 million (estimates go up to \$359 million) and 14.8 years (up from 14.3 years in the 1970s). Estimated costs include out-of-pocket expenses, costs of failed projects, and opportunity costs. A brief outline of the drug development process follows:

Basic Research (About 2 years) This phase typically starts through the initial screening of plants, microorganisms, and other naturally occurring substances to find a “hit” or “lead” compound. In a painstaking iterative process, organic chemists would then make analogues or modifications of existing leads. Although this stage typically cost a firm \$30-50 million, it represented a point of great leverage for speeding up a firm’s drug development process. Only 40 out of an initial 10,000 compounds might make it to the next stage of pre-clinical testing.

Pre-Clinical (Biological) Screening (About 3 years) Pre-clinical trials, which often overlapped the basic research phase, involved animal testing to assess drug safety and to gather data on biological effects (e.g., absorption, metabolism, and excretion). Only one in four drugs typically made it through this phase to enter human clinical testing as “Investigational New Drugs” (INDs).

Human Clinical Trials (About 6 years) Investigational New Drugs faced the FDA’s regulatory hurdles, the most stringent and time-consuming approval process for therapeutic drugs in the world. Total costs for conducting clinical trials topped \$200 million, but with increasing proportions of this cost occurring with each of the three successive phases describe below.

Phase I Safety Trials (1 year): In Phase I trials, researchers determined highest tolerated doses, toxicities, and safe ranges in one or two dozen healthy volunteers. This phase also yielded invaluable information on absorption, metabolism, and excretion of the drug in humans.

Phase II Efficacy Trials (2 years): Phase II tested efficacy of drug candidates in up to several hundred volunteer patients based at test sites composed of participating hospitals. To ensure statistically relevant data, from this point onward, a portion of the volunteers received the drug while the others received placebos. Roughly one-third of all drug candidates survived Phases I and II.

Phase III Long-Term Efficacy Trials (3 years): In the longest and most expensive phase of drug testing, researchers monitored drug use in thousands of volunteer patients for long term safety, optimum dosage levels, and subtler adverse effects. Only about a fourth of all drug candidates survived Phases I, II, and III, and moved on to the FDA review stage.

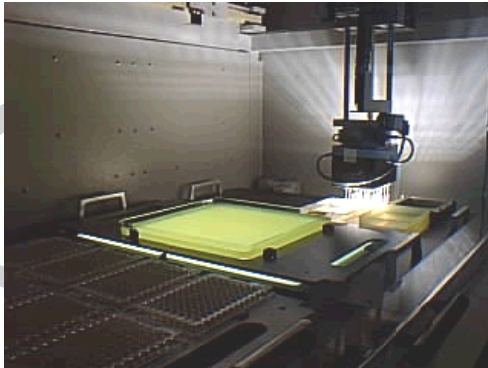
FDA Review (About 2-3 years) Despite a trend toward computer-assisted applications, the hundreds of thousands of pages submitted in the New Drug Application (NDA) to the FDA represented a tribute to the pharmaceutical industry’s data-generating capacity. The NDA included data on each patient, as well as on the company’s plans for producing and stocking the drug. The FDA committee took up to three years to review the NDA. Even after approval, however, post-marketing surveillance by the FDA continued. Only one-tenth of all drug candidates entering clinical trials ultimately reached the market.

¹⁶ Sources: J.A. DiMasi (1995), “New Drug Development: Cost, Risk, and Complexity,” *Drug Information Journal*, May; FDA (1995), “From Test Tube to Patient: New Drug Development in the United States,” *FDA Consumer*, Special Issue, January; Kenneth I. Kaitin, and Hub Houben (1995), “Worthwhile Persistence: The Process of New Drug Development,” *Odyssey, The Glaxo-Wellcome Journal of Innovation in Healthcare*, June.

Exhibit 3 Important Milestones for Millennium

1865	Austrian monk Gregor Mendel's plant breeding experiments find evidence for hereditary transmission of traits. He postulates building-blocks of heredity that later scientists would term "genes." Mendel's findings collect dust for decades.
1869	Swiss scientist Miescher discovers an abundant and seemingly useless material in the cell nucleus that he terms "nuclein." Later known as DNA, nuclein's role in transmitting genetic information would not be appreciated until later.
1953	Structure of deoxyribonucleic acid (DNA) elucidated by Watson and Crick who would later receive a Nobel prize for their work.
Early 1970s	Biotech industry starts, primarily in California and Massachusetts, based on discoveries that allow scientists to excise and recombine bits of DNA.
1990	Human Genome Project launched by U.S. government with the mission of identifying every bit of human DNA including all 100,000 or so human genes. Technological advances accelerate anticipated project completion date (by three years to 2002) in a manner worth emulating by other government initiatives.
1993	Millennium founded with Mark Levin as CEO in Cambridge, Massachusetts and with \$8.5 million in venture capital funding.
March 1994	Millennium signs its first major pharmaceutical deal with Hoffman-LaRoche. The deal centers around finding new drug targets in obesity and diabetes.
October 1995	Millennium signs equity funding and research deal with Eli Lilly & Co.—the first of several deals with Millennium CEO Mark Levin's old employer.
February 1997	Millennium acquires neighboring biotech firm ChemGenics for \$90 million. This expands Millennium's downstream capabilities for developing drug targets into leads and boosts Millennium's bargaining power with big firms.
October 1997	Millennium signs agreement with Monsanto and creates Cambridge-based Cereon to transfer the genome technology platform for agricultural purposes.
September 1998	Millennium announces the biggest biotech-pharma alliance ever: the nearly half-billion-dollar deal with Bayer AG. The agreement covers drug target identification in several medical fields.
August 1999	Case setting: Current offer from Lundberg for a technology deal paralleling the Monsanto alliance.

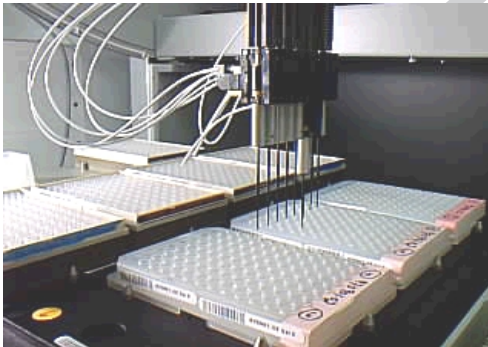
Exhibit 4 Millennium's R&D Factories: Automated DNA Sequencing



Colony Picking: "Libraries" of DNA corresponding to healthy and diseased individuals are grown in bacteria and picked up by robot arm for DNA sequencing.



DNA Preparation: The DNA molecules are isolated from the rest of the bacterial materials



Reaction Assembly: Pure DNA materials are dispensed for automatic sequencing.



DNA Sequencing: The identity of DNA molecules is "read" by an automated sequencing process.

Source: Millennium Pharmaceuticals.

Exhibit 5 Millennium's Corporate Structure

Millennium saw itself as a family of the following groups working toward a common end of developing expertise in genomics as well as gearing toward ultimate drug development:

- *Pharmaceutical Division*: This division worked on providing pharmaceutical companies with high-value drug targets and drug leads. Scientists here generally focused on small therapeutic molecules. Customers included multinationals such as Hoffman-LaRoche, Lilly, Astra, Wyeth-Ayerst, and Pfizer. The 1997 acquisition of ChemGenics (see below) greatly extended the downstream drug development capabilities.
- *Millennium BioTherapeutics, Inc (MBio)*: Millennium's first subsidiary, launched in 1997, used biotech and genomics technologies to discover and develop larger therapeutic molecules such as proteins and gene products for drug companies. From the very beginning, Lilly invested \$20 million in MBio for an 18% ownership interest. Millennium retained rights to half the drug candidates identified by the research collaborations with Lilly.
- *Technology Division*: This division provided to other branches of Millennium as well as third-party clients, high-value R&D technologies pertaining to genomics and related fields such as high-throughput screening, combinatorial chemistry. Despite a preference for technologies based on internal efforts, the division actively scanned the industry for external acquisition of technologies useful for enhancing the company's technology platform. Many of this division's customers overlapped with those of MPharma.
- *Millennium Predictive Medicine, Inc. (MPMx)*: This subsidiary, launched in 1997, focused on genomics-based products and technologies for improving the diagnosis and prediction of disease. By elaborating the relationship between genes and patients' reactions to drugs, this group would hopefully help physicians with deciding with tailoring therapeutics toward individual patients.
- *Cereon Genomics*: This wholly-owned subsidiary of Monsanto marked Millennium's foray into agriculture. This allowed for making the company's technology platform available to a partner in an area far removed from Millennium's general province of human healthcare: plant agriculture.

Exhibit 6 Millennium's Revenue Structure

Consolidated Revenue (dollars in 000s; 12/31/94 through 6/30/99)

	1994	1995	1996	1997	1998	6/30/99
Contract (FTE)	5,963	11,250	23,171	44,569	51,983	25,226
License Fees (One Time)	2,000	11,130	6,250	43,438	20,000	15,000
Milestones	---	500	1,400	1,100	23,350	3,625
Bayer Alliance	---	---	---	---	33,400	42,500
Reimbursed Collaborations/Support	---	---	944	827	4,949	1,913
Total	7,963	22,880	31,764	89,933	133,682	88,264

Source: Millennium Pharmaceuticals

Exhibit 7 Lists of Millennium's Alliances (by company, year, therapeutic area, dollar amount)

Date	Alliances	Terms	Focus
3/94	Hoffmann-LaRoche Inc.	Equity: \$6 M; Full-Time Equivalent (FTE) Funding: \$10 M/yr over 5 yrs.; milestone fees and royalties	Obesity, Type II diabetes
10/95 & 3/96	Eli Lilly and Company	Equity: \$8 M; Up-front Licensing Fee: \$4 M; FTE Funding: \$10 M/yr over 5 years; milestone fees and royalties	Atherosclerosis & oncology
12/95	Astra AB	Up-front Licensing Fee: \$10 M; FTE Funding: \$8 M/year over 5-7 years; milestone fees and royalties	Inflammatory respiratory diseases
6/96	American Home Products (Wyeth-Ayerst)	Up-front Licensing Fee: \$10M; FTE Funding: \$10 M/yr over 5-7 years; milestone fees and royalties	Central Nervous System disorders
2/97	ChemGenics Pharmaceuticals, Inc.	4,783,688 shares CG common stock	Antibacterial small molecule drug targets
5/97	MBio	Joint funding with Eli Lilly; share rights to discoveries (see below)	(see below)
5/97	Eli Lilly	Research Funding: \$8-\$10 M/yr over 3 years (option to renew for 2 years); \$20 M MBio stock; 18% equity interest in MBio; licensing and milestone fees' royalties	Therapeutic proteins
10/97	Monsanto Company	Up-front Licensing Fee: \$38 M; Technology Fees: \$180 M over 5 years; royalties; exclusive rights to plant agritechnology; nonexclusive rights to nonagritechnology	Agritechnology (via Cereon)
9/98	Bayer AG	Up-front Licensing Fee: \$33.4 M; Ongoing Licensing Fee and Research Funding: \$219 M; Performance Target Delivery: up to \$116 M; \$96.6 M (4.96M shares) Millennium common stock	Cardiovascular disease; Oncology (separate. from Eli Lilly targets); Osteoporosis; Liver fibrosis; Hematology; Viral Infections 225 targets over five-year period

Source: S. Matthews and M. Watkins, "Strategic Deal-Making at Millennium Pharmaceuticals," Harvard Business School Case No. 899-242 (1999).

Exhibit 8 Genomics Technology in Drug Discovery: Front-Loading Toxicology Assessment through Transcriptional Profiling

Extreme diseases demand severe cures.

– Hippocrates

Hippocrates notwithstanding, in a world where most drugs have undesired side effects, modern drug makers continually sought kinder, gentler drugs. To achieve this goal, drug makers screened compound candidates for those with a high margin of safety between doses producing the desired, therapeutic effects and doses producing toxic doses. Sometimes, as in the case of anti-cancer chemotherapies, for lack of better alternatives, physicians were forced to use rather toxic drugs.

To understand and assess the potential damage wrought by drug compounds in the body, we must examine the liver, since most of the body's detoxification occurs here. Liver cells, often described as the body's factory, use a variety of mechanisms to rid the body of toxins. All detoxification steps in the specific mechanism are ultimately controlled by specific genes. Toxins that cannot be removed may ultimately damage the liver itself over time, leading, for example, to the liver cirrhosis of excessive alcohol drinkers.

The classic approach to examining the liver's actions against a drug involved studying drug metabolism in lab animals at the pre-clinical stage. This proved a long and expensive process, since weeks or months would pass before the effects on the animal livers could be assessed. Newer methods, however, allow for exposing liver tissue slices to the test chemicals to assess for drastic effects such as cell death on liver tissue. In the late 1990s, this was routinely done. Through increasing biochemical finesse, however, researchers sought to discover which of the many important detoxification mechanisms in the liver were being used in order to create strategies for modifying the chemical compound to less toxic forms.

A powerful genomics technology for assessing toxicology is "transcriptional profiling." Transcriptional profiling is a technology that allows for assessing what genes are active (i.e., being "transcribed" by the cell's genetic machinery into genetic messages that would serve as architectural blueprints for making proteins, the building blocks of the body). The DNA in each human cell contains the same set – or genome – of about 100,000 genes, of which about 15,000 different genes will be active during a cell's life-time. Different combinations of genes would be active in different cell types, with the highly active liver cells likelier to activate a large number of genes.

To identify the set of genes in liver cells associated with detoxifying a specific class of drugs, genomics researchers compare the "transcriptional profile" of a dormant liver cell with liver cells actively metabolizing the drugs in question. Any discrepancies likely reflect the use of genes specifically activated for ridding the body of the specific toxins. (To ferret out these discrepancies, copies of all known genes are placed in a systematic array on a surface. The cellular genetic 'messages' churned out by the activated liver cells would then combine in a "like-seeks-like" fashion with the genes on these arrays most like their parent genes.) By thus identifying the genes most relevant for detoxifying a given compound, drug makers could now quickly understand how difficult a drug might prove to be to detoxify.

Transcriptional profiling, thus, can potentially provide a quick way to "front-load" failure modes early in the drug development process and thus steer a company away from a likely unfruitful avenue of research at a stage when it was still inexpensive and quick to switch course.

Exhibit 9 Glossary

Analog: A structural variation of a parent molecule. Useful analog compounds may exhibit fewer adverse effects or might be therapeutic in smaller doses.

Assay: A test to determine properties of a chemical entity such as strength or purity or activity in a biological system.

Chemical Library: A collection of differing compounds (analogous to a library of books), usually maintained for further study. Drug firms often maintain libraries of all compounds synthesized in the past by their scientists.

Combinatorial Chemistry: A branch of synthetic chemistry developed that allows for systematically generating large numbers of chemically diverse but related compounds. Combinatorial chemistry, thus, potentially allows drug makers to rapidly generate and explore thousands of compounds in just weeks in order to find promising compounds.

Compound: A distinct chemical entity formed by the union of two or more ingredients in a distinctive proportion. Drug compounds are formed from a distinctive proportion of differing chemical elements.

Molecular Diversity: The importance of molecular diversity—analogue to diversity found within the human race—stems from the fact that even minor changes in molecular structure can tremendously alter function. As a result, drug makers seek to adequately explore molecular diversity of a promising drug's analogues in order to field the best possible drug, (just as a good company recruits from an adequate diversity of candidates).

Receptor: A specialized protein located on or within cells in the body capable of detecting specific environmental changes. Receptors in the nervous system, once activated by neurotransmitters, will often trigger specific responses within the body.

Rational Drug Design: An approach that uses very advanced scientific methods such as x-ray crystallography and/or nuclear-magnetic resonance (NMR) spectroscopy to determine the three dimensional shape and structure of a target that they wish to influence with a drug. With the aid of computer simulation, scientists would then be able to design drug molecules that bind to the target receptor.

Screening: A process of systematically examining a collection of compounds to find those with the most promise for a given purpose (such as drug development). "High throughput screening" refers to the ability to screen a large number of compounds in a short time period – a capability needed to successfully apply combinatorial chemistry.

Synthetic Chemistry: The branch of chemistry dealing with the creation of compounds in the laboratory

Target: A receptor, enzyme or molecule associated with a particular disease. The goal of drug discovery is to find or create compounds that will bind to a particular target with a required degree of tenacity (binding affinity) and, at the same time, not bind to other targets that may be structurally similar but have different functions.