

# **Wheel of Fortune: The Evolution of a Drug Discovery Platform Through Strategic Alliances and Acquisitions**

by

**Seth Taylor**

Ph.D., Biology  
The Johns Hopkins University (1996)  
B.S., Biological Sciences  
Cornell University (1986)

Submitted to the Alfred P. Sloan School of Management and the  
School of Engineering in Partial Fulfillment of the Requirements for the Degree of

**Master of Science in the Management of Technology**

at the

**Massachusetts Institute of Technology  
June 1997**

© 1997 Seth Taylor  
All Rights Reserved

The author hereby grants to MIT permission to reproduce and to distribute publicly paper  
and electronic copies of this thesis document in whole or in part.

Signature of Author: \_\_\_\_\_  
MIT/Alfred P. Sloan School of Management  
May 19, 1997

Certified by: \_\_\_\_\_  
Charles H. Fine  
Associate Professor of Management  
Thesis Supervisor

Accepted by: \_\_\_\_\_  
Rochelle Weichman  
Director, Management of Technology Program

MASSACHUSETTS INSTITUTE  
OF TECHNOLOGY

JUL 01 1997

ARCHIVES

# **Wheel of Fortune: The Evolution of a Drug Discovery Platform Through Strategic Alliances and Acquisitions**

by

Seth Taylor

Submitted to the Alfred P. Sloan School of Management and the School of Engineering  
on May 19, 1997 in partial fulfillment of the requirements of the Degree of  
Master of Science in the Management of Technology

## **ABSTRACT**

This thesis analyzes the role of strategic alliances and acquisitions in the development of a new drug discovery platform in the biotechnology and pharmaceutical industries which the author terms the 'Drug Discovery Triad'. The components of this new drug discovery platform are examined for their benefits to the pharmaceutical industry. Established pharmaceutical companies are using strategic alliances to gain access to the technologies that comprise the Drug Discovery Triad. Alliance strategies are examined for their impact on research productivity at these pharmaceutical companies.

Biotechnology companies are adopting a new Service Model in response to the Drug Discovery Triad. An analysis of the strengths and weaknesses of this business model includes a case study of Millennium Pharmaceuticals. Finally, biotechnology companies are using acquisitions to boost the value of their technology platforms. A case study of the three-way merger that lead to the formation of Aronex Pharmaceuticals is used to examine how mergers and acquisitions shape the development of a technology platform.

Thesis Supervisor: Charles H. Fine

Title: Associate Professor of Management

## **Acknowledgements**

I am dedicating this thesis to my parents and Catherine A. Shea, they each provided invaluable good cheer and guidance to me throughout the MOT program. In addition, Dan Rodriguez was a crucial source of a support and advice in developing this thesis. Finally, I am indebted to guidance I received from Charles H. Fine, my thesis advisor.

# Table of Contents

<b>ABSTRACT.....</b>	<b>2</b>
<b>ACKNOWLEDGEMENTS.....</b>	<b>3</b>
<b>I. INTRODUCTION.....</b>	<b>6</b>
AN OVERVIEW OF THE PHARMACEUTICAL INDUSTRY .....	6
THE EMERGENCE OF BIOTECHNOLOGY IN THE PHARMACEUTICAL INDUSTRY .....	9
STRATEGIC ALLIANCES IN THE PHARMACEUTICAL INDUSTRY .....	10
A LITERATURE REVIEW .....	10
ANALYSIS.....	14
METHODOLOGY.....	15
<b>II. TECHNOLOGY ALIGNMENTS IN THE BIOTECHNOLOGY INDUSTRY.....</b>	<b>16</b>
INTRODUCTION.....	16
THE GENOMICS PLATFORM.....	18
<i>Background.....</i>	<i>18</i>
<i>Technology and Methodology.....</i>	<i>19</i>
<i>Patenting Genes.....</i>	<i>21</i>
<i>Industrial Genomics.....</i>	<i>21</i>
THE SCREENING PLATFORM .....	24
<i>Background.....</i>	<i>24</i>
<i>Technology and Methodology.....</i>	<i>25</i>
COMBINATORIAL CHEMISTRY.....	28
<i>Background.....</i>	<i>28</i>
<i>Technology and Methodology.....</i>	<i>29</i>
BIOINFORMATICS.....	30
<i>Background.....</i>	<i>30</i>
<i>Technology and Methodology.....</i>	<i>31</i>
MICROFABRICATION AND ROBOTICS .....	33
THE DRUG DISCOVERY PLATFORM.....	33
INCORPORATION OF THE DRUG DISCOVERY TRIAD INTO THE PHARMACEUTICAL VALUE CHAIN.....	37
<b>III. OUTSOURCING OF R&amp;D BY PHARMACEUTICAL COMPANIES.....</b>	<b>40</b>
ALLIANCE STRATEGIES IN THE PHARMACEUTICAL INDUSTRY .....	41
<i>State of Pharmaceutical Drug Development Pipeline.....</i>	<i>41</i>
<i>Response of Pharmaceutical Companies to the Shortfall of NCEs.....</i>	<i>43</i>
<i>The Influence of Managed Care Organizations on Drug Discovery.....</i>	<i>44</i>
<i>Alliances between Pharmaceutical and Biotechnology Companies.....</i>	<i>44</i>
<i>R&amp;D Alliances based on the Drug Discovery Triad.....</i>	<i>46</i>
<i>Structuring an Alliance.....</i>	<i>48</i>
<i>Stacking Royalties.....</i>	<i>51</i>
<b>IV. THE RISKS OF BUILDING A COMPANY AROUND R&amp;D.....</b>	<b>53</b>
BIOTECHNOLOGY COMPANIES AND THE DRUG DISCOVERY TRIAD .....	53
<i>Cor Therapeutics- The Old School.....</i>	<i>54</i>
<i>Incyte Pharmaceuticals and Human Genome Sciences-The New School.....</i>	<i>55</i>
<i>The Service Model.....</i>	<i>58</i>
CASE STUDY: MILLENNIUM PHARMACEUTICALS .....	62

<i>Business Strategy</i> .....	62
<i>Technology Strategy</i> .....	64
<i>Alliance Strategy</i> .....	68
<i>Alliance Agreements</i> .....	71
<i>Goals 2000</i> .....	73
<i>In the Balance</i> .....	75
<b>V. MERGERS AND ACQUISITIONS IN THE BIOTECHNOLOGY INDUSTRY</b> .....	<b>77</b>
INTRODUCTION.....	77
<i>Building Value Through Mergers and Acquisitions</i> .....	77
CASE STUDY: THE FORMATION OF ARONEX PHARMACEUTICALS .....	81
<i>A Tale of Three Companies</i> .....	81
<i>Reasons for the Merger of Argus, Oncologix and Triplex</i> .....	85
<i>Aronex Pharmaceuticals, Inc.: Strategies Going Forward</i> .....	87
<i>Conclusion</i> .....	89
<b>VI. CONCLUSION</b> .....	<b>90</b>
<b>VII. REFERENCES</b> .....	<b>94</b>

## **I. Introduction**

The last several years have seen a substantial change in the pharmaceutical and biotechnology industries. The emergence of health maintenance organizations (HMOs) has significantly altered the marketplace dynamics for pharmaceuticals. At the same time, biotechnology companies are capitalizing on rapid advances in molecular biology to challenge the technological prowess of established pharmaceutical companies. One result of these changes has been a wave of strategic alliances in the pharmaceutical industry, with two trends emerging during the 1990's. First, established pharmaceutical companies have begun to outsource R&D to biotechnology companies. Second, biotechnology companies are shunning the integrated approach to drug development, opting instead to service the research needs of established pharmaceutical companies. This thesis will examine what role strategic alliances have in reshaping the pharmaceutical and biotechnology industries, and how these changes are leading to a new business model for biotechnology companies.

### ***An Overview of the Pharmaceutical Industry***

Until recently, the pharmaceutical industry has consisted primarily of separate entities that create pharmaceuticals, provide health care, and insure patients. This decentralized administration of health care lead each entity in the health care delivery chain to pass their costs down the line to the patient, who in turn passed the costs on to a health insurer that was typically funded by either a corporation or a government agency. Physicians and patients had little incentive to restrain rising health care costs because medical expenses were paid for by insurance companies, and no single health insurer had enough buyer power to influence pharmaceutical pricing (Pisano 1997, p. 60). This environment allowed pharmaceutical companies to reap large profits from new drugs. From the period between 1950 and 1978, the accounting rate of return on new drug introductions averaged 20.9 percent (Pisano 1997, p.55). These high rates of return were also defended by drug

patents, and a regulatory environment that discouraged new entrants to the pharmaceutical industry.

The development of buyer power through HMOs in the 1990's brought about a decline in the profitability of new drugs. This loss in earnings is apparent in the trend towards an elastic pricing model in the pharmaceutical industry. The growth in the average list price of drugs has declined from 8.32 percent in 1989 to 5.19 percent by 1992, a decline that has been compounded by discounts off the list price of these drugs (Pisano 1997, p.57), (Kolassa 1993). Buyer power has further eroded profit margins for pharmaceuticals by whittling away at the premium that companies can charge for new drugs. The average price premium for drugs introduced between 1979 and 1988 was 57 percent relative to the market leader (Pisano 1997, p.58). By 1992, this premium had turned into a 14% percent discount relative to the market leader (Pisano 1997, p.59). These two studies point to a shift in the drug development strategies pursued by pharmaceutical companies. For these companies, the importance of being first to market has dramatically increased during the 1990's.

Another recent industry trend is that pharmaceutical companies are vying for similar disease markets at a level of competition unseen in previous decades. This last observation is borne out by a study that shows that the Herfindahl Index across five major therapeutic categories has dropped in most of these segments from 1989 and 1993, a trend that is indicative of an increase in competition across the industry (Pisano 1997, p.67) (Kolassa 1995). This trend towards competition is likely to increase in the future because many companies in the pharmaceutical industry are targeting their current research programs at the same disease markets. The intense competition means that multiple drugs will compete in the marketplace for the nearly the same disease indications. This places a premium on

innovative new technologies that can boost the efficacy of a drug relative to that of other competing drugs.

The pharmaceutical industry is characterized by long product development cycles. This is the result of risky R&D investments that take a long time to progress to an effective therapeutic, and substantial federal regulations of the clinical trials and manufacturing facilities needed to bring these therapeutics to market. Recent data suggests that it takes an established pharmaceutical company an average of seven to eleven years to complete the drug development cycle (Powell, Koput et al. 1996). In addition, the drug development cycle is expensive. The average pharmaceutical compound costs between \$100-300 million to bring to market (Persidis 1996) (Powell, Koput et al. 1996). The combination of high development costs and heightened competition from existing industry players has forced pharmaceutical companies to emphasize rapid product development cycles, with a focus on being first-to-market.

Long product development cycles lead the pharmaceutical industry to rely on patents, federal regulations and economies of scale to protect the investment of time and capital required to bring a drug to market. Patents are used by pharmaceutical companies to protect themselves from generic drug makers and competing pharmaceutical firms. The impact of competition from generic drugs is evident in a slow decline of effective patent life, or the remaining portion of the patent life following the introduction of a new drug to the market, from 1967 to 1984 (Pisano 1997, p. 62). The Waxman-Hatch Act attempted to rectify the decay of patent life by lengthening the life of the patent by the time it takes a company to receive regulatory approval for a drug (Pisano 1997, p. 62). However, this act also made it easier for the generic companies to enter the drug market upon expiration of a patent.

In addition to patents, the pharmaceutical industry also relies on federal regulation of the drug development process to create a barrier to entry for new pharmaceutical companies. The expertise and costs required to navigate the drug approval process are stacked against new entrants to the industry.

Finally, established pharmaceutical companies rely on their enormous investments in proprietary R&D and manufacturing facilities to provide them with an advantage against new entrants to the industry through economies of scale. In spite of these barriers to entry, the pharmaceutical industry has been awash with new companies that are attempting to exploit advances in molecular biology and the life sciences for drug development.

### ***The Emergence of Biotechnology in the Pharmaceutical Industry***

The biotechnology industry is an outgrowth of major advances in the field of molecular biology. Prior to the advent of biotechnology, most pharmaceutical compounds were made using synthetic chemistry. This approach to drug design required an R&D facility to have a large number of chemists in order to synthesize a vast array of distinct, small chemicals used in the drug screening process. The key benefit of molecular biology is the capacity of this technology to make complex protein molecules and DNA available as therapeutic agents, or as therapeutic targets for more traditional approaches to drug development. This advance has allowed biotechnology companies to effectively address a wide range of human diseases. The first pharmaceuticals to emerge from biotechnology were naturally-occurring proteins from the human body, such as recombinant erythropoietin (Epogen®) from Amgen Corporation that is used to treat anemia [Amgen, 1995 #532]. By 1994, there were more than 220 biotechnology products under development, and sales of these compounds on the market exceeded \$60 billion (Powell, Koput et al. 1996).

Biotechnology provides innovative new drugs with unique characteristics, and a scope of potential applications that dwarfs those available using synthetic chemistry.

In addition to increasing the number of diseases that can be addressed by pharmaceuticals, biotechnology has led to a shortening of the product development cycle for pharmaceuticals from 7-11 years, down to 4-8 years (Powell, Koput et al. 1996). Because biotechnology requires skill-sets not present in synthetic chemistry scientists, biotechnology can be viewed as a competence destroying technological discontinuity in the pharmaceutical industry (Tushman 1997, p. 45-52). However, biotechnology-based compounds face the same regulatory and distribution constraints as traditional pharmaceutical compounds, allowing pharmaceutical industry leaders to maintain their competitive edge against the competence-destroying biotechnology firms. Previous studies have shown that as long as industry veterans can maintain strengths upstream and downstream of a process discontinuity, they should eventually be able to exploit the benefits of the new technology (Tushman 1997). Therefore, many veteran pharmaceutical companies are turning to strategic alliances with biotechnology companies in their efforts to internalize biotechnology.

## ***Strategic Alliances in the Pharmaceutical Industry***

### ***A Literature Review***

A number of theoretical frameworks concerning the role of strategic alliances can be applied to the pharmaceutical industry. This portion of the report examines how models for strategic alliances can be applied to the pharmaceutical industry.

One trend in thinking about alliances posits that the decision to enter an alliance is based largely on strategic issues (Parkhe 1993). These issues include environmental uncertainty,

lack of trust, asset specificity, and differing capacities for organizational learning and complexity of the project (Pisano 1989). The partnering decisions are based on the respective positions of the firms in their industry and technological competencies. In this regard, the decision to collaborate is based on transaction costs and an evaluation of risk versus return (Williamson 1991). The desire to obtain new assets must be weighed against the risks of collaborating with another firm.

A different theory suggests that the capacity for organizations to learn from each other is dependent on the learning environment (Brown 1991) (Powell, Koput et al. 1996). Organizations require a dynamic community in which to learn and share information. A static or bureaucratic organization thwarts the creation of knowledge. The sources of innovation are found both inside the firm as well as in the interactions of the firm with universities, research laboratories, suppliers and customers (Powell, Koput et al. 1996). When knowledge is broadly distributed, and it constitutes a technological discontinuity, then innovation is fostered by a network of inter-organizational relationships, or networks of learning (Powell, Koput et al. 1996).

A theory was proposed recently that brings together these two approaches to analyzing strategic alliances (Doz 1996) (Tushman 1997, p.561). This theory examines the motives of organizations that plan to participate in an alliance, and the degree to which the technologies involved with the alliance are embedded in each firm.

First, firms that intend to create value through the alliance itself will behave differently from firms that seek to exchange skills through organizational learning and internalization (Tushman 1997, p.561). The behavior of the firms towards this decision will be driven by the scope of the knowledge to be shared between the firms, the perception by the partners

of their relative strengths, and the uniqueness of the knowledge assets in each firm relative to the other.

Second, firms that see an alliance as a discrete relationship will act differently to an alliance than firms that approach an alliance as part of a dynamic network over time (Tushman 1997, p. 561). To a certain degree, this decision is dictated by the nature of the industry in which the partnering firms reside. However, the perspective of management is also of great importance because the discreet treatment of each alliance may result in a missed opportunity to leverage knowledge and skills across alliances. If a firm approaches an alliance as one node in a network of alliances, then it becomes critical for that firm to carefully manage its network of alliances. This entails using the knowledge from one alliance to leverage the firms position in subsequent alliances.

Finally, the more embedded a technology is within an organization, the more tightly the partnering firm will need to cooperate with this firm in order to share or transfer the technology (Tushman 1997, p. 559). This last point is especially salient. After a certain point, embeddedness can deter internalization of a skill or technology by a partner.

This theory by can be comfortably applied to the strategic alliances between biotechnology firms and veteran pharmaceutical companies (Doz 1996). Biotechnology is not a single technology platform, but rather a compendium of technology platforms that share some knowledge and skill-sets. While the manipulation of DNA is often seen as a common thread between technology platforms, other critical technologies are necessary on a platform by platform basis. This affects the formation of strategic alliances in two ways. First, the knowledge necessary to exploit a technology platform in biotechnology requires skills that are widely distributed between universities, research institutes and commercial firms. This encourages the formation of a network of alliances over individual alliances for

internalizing biotechnology within a firm (Mullin 1996). These sorts of partnerships have been critical in the development of the biotechnology industry. Second, because a wide distribution of skills and knowledge are required to develop a technology platform in biotechnology, the platforms that do develop are highly embedded within the firm. The core technologies of a biotechnology firm depend on a network of interactions in order to stay current. Simply viewing the technology by itself does not take into account these critical interactions. A culture develops in biotechnology firms that is highly efficient at utilizing the knowledge networks necessary to advance the state-of-the-art for each technology platform. This culture represents both the scientific talent of the scientists and the connections these scientists have with other researchers in labs across academia and industry. These alliances or partnerships are often of a non-contractual nature, so they are not apparent to people outside of the biotechnology firm (Shrader 1991). The CEO of Centocor recently stated that number of formal alliances was "...the tip of the iceberg--it excludes dozens of handshake deals and informal collaborations, as well as hundreds of collaborations by our company's scientists with colleagues elsewhere" (Powell, Koput et al. 1996).

The embedded nature of technology platforms in biotechnology plays an important role in the decision by a partnering firm of how the alliance fits into the corporate strategy. The critical issue in these situations is whether or not the partnership is being used to create value through the partnership, or as a vehicle to internalize a technology into one of the partnering firms. This is of great concern for resource constrained biotechnology firms whose core competencies are the technology platforms under development. Efforts by veteran pharmaceutical firms to internalize the core technology platform of a biotechnology firm may meet with strong resistance from the biotechnology firm. A recent study of a strategic alliance between Alza Pharmaceuticals, a biotechnology firm, and Ciba-Geigy, a veteran pharmaceutical firm, shows how the perception that Ciba-Geigy was attempting to

internalize Alza's technology eventually led to the cessation of the alliance, with little benefit to either firm (Doz 1996). In this situation, the stark differences in the cultures of the two firms greatly contributed to the inability of the partnering firms to achieve their initial goals.

A study of the pharmaceutical industry found that firms tend to internalize R&D and avoid technical alliances in technologies where R&D capabilities are concentrated in a small number of potential partners, and when the firm has high sales or R&D competencies in a technology (Pisano 1990). The most likely scenario for a technical alliance between two firms is when the technology involved is new or unproved. Under these circumstances, the likely goal of the partnering firms is to derive value from the alliance rather than to internalize the technology.

## ***Analysis***

The initial sections of the thesis will examine the technology platforms of genomics, combinatorial chemistry, functional bioassays, bioarrays and bioinformatics. Each technology platform will be described, with a focus on the top players in each category. Next, the thesis will examine a trend in the pharmaceutical industry to combine these diverse technology platforms into a robust, over-arching, platform for drug discovery. This trend towards a new platform for drug discovery is catalyzing a major shift in the business models for both biotechnology and pharmaceutical companies. Finally, Millennium Pharmaceuticals and Aronex Pharmaceuticals will be analyzed in order to better understand the role of strategic alliances and acquisitions in building competitive technology platforms.

## ***Methodology***

The data to support the analysis will be drawn from industry literature, interviews with industry participants and an on-line database of strategic alliance data maintained by Recombinant Capital (San Francisco, CA).

## **II. Technology Alignments in the Biotechnology Industry**

### ***Introduction***

Platform or enabling technologies are usually defined as key skills or technologies that one or more companies possess that generate novel products or process improvements (Persidas 1995). Platform technologies are usually protected by a patent position, but a patent position is not a prerequisite for developing a platform technology. The commercialization of molecular biology has generated a large number of technology platforms over the past twenty years. However, no single technology platform has become a leading source of therapeutic leads, leading some to argue against investments in biotechnology. The Utterback & Abernathy model for technology innovation predicts that following a period of tremendous innovation around a new technology, a single, dominant product platform will emerge that tends to wipe out other competing product platforms (Utterback 1996). This model has been readily applied to product cycles, such as the advent of the automobile, but it is not as easily applied to technology platforms. The biotechnology industry has evolved on a great number of platform technologies, some of which have found only limited therapeutic applications. There are several examples of biotechnology companies with a strong platform technologies that were able to bounce back from disappointing product news better than companies without technology platforms (Ghodsian 1995). Established pharmaceutical companies view investments in platform technologies as a key to maintaining the long-term competitive positioning of their product pipelines. For this reason, both pharmaceutical companies and biotechnology companies rely heavily on publicly sponsored research as a source of new technology platforms.

Academic institutions are of great importance in the development of technology platforms in the biotechnology industry. Biomedical research in academia is funded by 59% of the companies involved in life sciences, with these companies contributing \$1.5 billion, or

12%, of the academic research budget in 1994 (Blumenthal, Causino et al. 1996).

However, a large majority these grants (71%) are for less than \$100,000 per year. This indicates that for the most part, pharmaceutical and biotechnology companies are using academic institutions to perform exploratory research. One of the primary motives for industry to partner with academia is to secure intellectual property rights in emerging technologies (Haber 1996). The commercialization of the nascent technology is usually performed in-house by the sponsoring company. Apart from direct sponsorship of university research, biotechnology companies and pharmaceutical companies often license technology from academic institutions.

The evolution of technology platforms in the biotechnology industry is slower than in other industries such as microelectronics because of the time frames necessary to test new technology platforms. Multiple technology platforms need to interact with each other to create new pharmaceuticals, with the complexity of the problem dictating an equally complex array of solutions. Different technologies are being used to target multiple points in the progression of a disease related gene from its DNA code to its functional form- DNA (Genome) ->mRNA->Protein (Proteome)->Function. A number of these technologies, when integrated together, may create a compelling drug discovery platform. The resulting platform would be validated by the number of products that succeed in human clinical trials. It is difficult for a single company to control all of the technologies necessary to create a drug discovery platform. For established pharmaceutical companies, the question is whether or not to develop platform technologies in-house. Biotechnology companies possessing platform technologies must decide whether or not to market the platform technology itself, the products generated by the technology platform, or both.

**Hypothesis:** The biotechnology industry is entering a new era of progress based on simultaneous advances in molecular biology, information technology and nanotechnology.

The union of these technologies is creating a potent new drug discovery platform that links genomics, assay technology, combinatorial chemistry, and bioinformatics. This platform has the potential to generate a very large stream of effective pharmaceuticals. The pharmaceutical industry is rapidly converging on this platform as a standard for drug development.

## ***The Genomics Platform***

### **Background**

Genomics is the application of molecular biology to the study of the information contained within the human genome. A genome is the complete linear array of deoxyribonucleic acid (DNA) sequence contained in an organism. This linear array of DNA is grouped into many discrete entities, called genes, that are the starting point for the process of differentiation that leads to the diverse panoply of cells necessary to create a Human body. Briefly, an intermediate called messenger ribonucleic acid (mRNA), created from genes through the process of transcription, becomes a template for the creation of functional units, called proteins, through the process of translation. It is the intricate interaction between these proteins and other chemical entities in the cell that drive the formation of unique cell types, and the maintenance of normal cell function. In short, cells in a multi-cellular organism are different because only a subset of genes in the entire genome are expressed in each cell type.

The goal of sequencing the human genome is to create a reservoir of genetic information that can be used to develop therapeutics against previously intractable diseases. These diseases are thought to be the result of the aberrant expression of multiple genes through mutations in their DNA sequences, implying a complex interaction of cellular molecules that is not easily attacked by current pharmaceutical R&D. In addition, the genomes of

other organisms such as the mouse, yeast and the fruit fly are also being sequenced in order to compare gene sequences and gene expression patterns across a wide range of species. These organisms can then be genetically modified by scientists in order to create models of human diseases.

## **Technology and Methodology**

The process of deriving genetic sequence information relevant to a particular disease state, called functional genomics, can be broken down into several discrete steps: DNA sample collection; genetic mapping; physical mapping; DNA sequencing and mutation analysis . The first step of the process is purifying DNA from a patient population or an animal model for a particular disease. This DNA is then analyzed with molecular markers that indicate the location of the regions of DNA polymorphisms in a process called genotyping. The pattern of genetic polymorphisms often varies between normal and diseased individuals. Linkage mapping is used to statistically correlate a specific set of polymorphisms with the disease of interest, allowing scientists to focus their search on a small section of the human genome. The subsection of the genome correlated with a specific disease is then physically mapped using positional cloning and DNA sequence analysis. Genes identified in the sequenced DNA are analyzed in normal and diseased patients for abnormal gene expression using differential display, or for mutations in the DNA sequence.

The key technologies that support the genomics platform are high-throughput DNA sequencing, positional cloning, Polymerase Chain Reaction (PCR) and differential display of RNA transcripts. These procedures are used to analyze the DNA from a collection of tissue samples from various human disease patients. Alternatively, the tissue is derived from an animal model. The following section gives a brief analysis of the different kinds of technology used in the genomics platform.

**DNA sequencing** is the process used to determine the linear sequence of the four chemical bases that comprise DNA- Adenine (A), Guanine (G), Cytosine (C) and Thymidine (T). The process for DNA sequencing relies on enzymatic reactions and purification of DNA fragments of differing lengths over a semi-solid plastic gel, which functions like a molecular sieve. This sequencing process is now automated with advanced robotics and software, allowing for high-throughput, or industrial-scale, sequencing of the genomes of all species.

**PCR** is an enzymatic reaction that allows a very small amount of DNA to be amplified 1000-10,000 fold for use in procedures such as positional cloning or DNA sequencing.

**Positional cloning** is the process scientists use to create a 'roadmap' of the human genome, and reduce it down to a manageable level for analysis. In essence, small sections of the human genome are placed into the genome of a bacteria, allowing scientists to easily catalogue and PCR amplify sections of the human genome for DNA sequence analysis. The position of these pieces of the genome are determined relative to regions of DNA polymorphisms, where the DNA sequence varies from person to person. The linkage of DNA polymorphisms to a specific disease indicates that a nearby genetic mutation may be pre-disposing an individual the disease.

**Differential display** of RNA transcripts allows scientists to determine what genes are expressed in a given cell type, and the relative level of expression of a specific gene across many cell types. This technology is essential in ascertaining which genes are differentially expressed in disease tissues. The partial sequence of a gene expressed in a particular cell type is known as an "expressed sequence tag" (EST).

## **Patenting Genes**

Underlying the commercial aspirations of a multitude of genomics companies is the expectation that the sequenced DNA can be patented in some manner. Patents for genes have been issued across the world for the past 15 years, but it is not clear what criteria are used to determine the patentability of a gene (Marshall 1997). The sequence of a gene may allow the inventor to file a composition of matter patent. Given the function of a gene, an inventor can file a methods of use patent. Finally, a drug molecule that can interact with a gene can be protected using a composition of matter patent. In general, just knowing the sequence of a gene is not enough. The inventor must also know either the function of a gene or how the gene can be used in a commercial product. Many patents have been filed for fragments of genes called ESTs. These sequences can be patented only if they meet criteria under existing patent law of utility, enablement, novelty and obviousness (Usdin 1997). Furthermore, allegation of an EST's utility in a diagnostic procedure without further disclosure does not meet the criteria for enablement and utility. In a recent decision, the PTO has ruled that patenting an EST does not preclude future patents of the full-length gene. This removes the fears of many executives in biotechnology that "submarine patents" for ESTs will unexpectedly emerge that undermine a patent for the full-length gene based on the earlier priority date for the EST patent (Marshall 1997).

## **Industrial Genomics**

The genomics technology platform evolved out of a commitment by the Federal government to sequence the human genome in 1990 (Friedrich 1996). Currently, about \$160 million of public funds is spent each year on genome research by the United States (Friedrich 1996). The expenditures on this project have reached \$251 million worldwide. In addition, the pharmaceutical giant Merck & Co. has set up a not-for-profit organization to create a public database of gene sequences called the Merck Gene Index Project that supports the entire research community (Marshall 1997). Merck is also

funding a not-for-profit institute that researches links between genes and associated diseases. These public research expenditures are critical in allowing scientists around the world to incorporate genomics into their existing research programs. Since 1990, there has been a near exponential growth in the number of DNA sequences in publicly available databases (Friedrich 1996). For example, the complete genome of yeast was determined in 1996 (Goffeau and al. 1996). This genome was sequenced by the combination of 92 Internet-linked laboratories (55% of the work), and five large, publicly funded, genome sequencing centers (45% of the work). Both approaches produced sequences of nearly equal quality and at approximately the same rate. The International Human Genome Project plans to complete the entire, three billion base, human genome by 2003 (Cohen 1997).

A number of entrepreneurs realized that pharmaceutical companies might be willing to pay substantial sums of money to gain proprietary access to gene sequences in advance of the rest of the scientific community (Cohen 1997) (1997). Currently, at least eight biotechnology are focused primarily on genomics (see Figure 1) (Friedrich 1996).

**Figure 1**

**Genomics Companies**

<u>Company</u>	<u>Company</u>
Human Genome Sciences	Genset
Incyte Pharmaceuticals	Myriad Genetics
Genome Therapeutics	Millennium Pharmaceuticals
Sequanna Therapeutics	
Mercator Genetics	

The first of these companies, Human Genome Sciences, commenced operations in mid-1992, and was quickly followed by Incyte Pharmaceuticals. These biotechnology companies convinced established pharmaceutical companies that the first company to have access to an important disease gene would gain critical patents and a head start on the drug development process and clinical diagnostics. They were rewarded by large research and development deals with sizable upfront and milestone payments. These companies have generated \$535 million from investors, a tiny amount when compared to the \$15.8 billion of yearly R&D expenditures by the pharmaceutical industry (1996). However, genomics companies are pioneering new techniques for DNA sequencing and gene mapping, leading them to generate genomic information at a rate that was presumed to be unattainable only five years ago (Cohen 1997). Francis Collins, the head of the US National Center for Human Genome Research, remarked,

“It’s impossible to ignore the way things have changed in the last three years [because of industry]” (Cohen 1997).

The genomics company Sequana Therapeutics predicts that in five years people will carry their genetic blueprint on a CD (Cohen 1997). Leroy Hood, a founder of the genomics company Darwin Molecular, suggests that,

“All of the [biotech’s] are going to be forced to broaden into genomics” (Cohen 1997).

Genome companies are taking different strategies to sequence genomes, the human genome as well as those of other organisms. Incyte Pharmaceuticals, Human Genome Sciences, Genome therapeutics and Microcide are examples of companies that perform large-scale sequencing efforts. Other companies such as Millennium Pharmaceuticals, Sequana

Therapeutics, Myriad Genetics, Genset, Chiroscience/Darwin Molecular, and Progenitor/Mercator Genetics are all pursuing positional cloning with DNA from select disease populations.

Pharmaceutical companies are willing to pay substantial sums of money to lock-up access to a complete genome sequence. Genome Therapeutics sold the complete genome sequence of *Helicobacter pylori*, the pathogen responsible for ulcers, to Astra AB for \$22 million in 1995 (Marshall 1997). The genome DNA sequences of pathogens such as *Staphylococcus Aureus* (food poisoning), *Streptococcus pneumonia* (Pneumonia), *Mycobacterium tuberculosis* (Tuberculosis) and *Haemophilus influenzae* (Flu) are complete or nearing completion by a number of genomic or companies. Very little of these genomic DNA sequences have made it into the public domain. This creates a redundancy of genomic sequencing efforts because of the desire, on the part of genomics and pharmaceutical companies, to keep the sequences proprietary. At least \$75 million in upfront cash payments and future milestone payments has been generated by genomic companies for access to these bacterial genomic sequences (Marshall 1997). The payoff for the pharmaceutical companies can be quite large, a new antibiotic can generate between \$200 million -1 billion in sales per year (Fisher 1996). The total value of all of the upfront cash and milestone payments to the genomics companies exceeds \$1.33 billion (Friedrich 1996).

## ***The Screening Platform***

### **Background**

The rapid generation of new genes by genomics companies is driving the demand for new screening technologies that elucidate gene function (Cohen 1997). The function of a new gene must be described in order to obtain effective patents for the gene sequence. In addition, information about gene function enables scientists to devise better disease models

for use in screening libraries of chemical molecules for new drugs. Therefore, a screening platform is being built around two specialties, highly specialized assays for determining gene function, and high-throughput genetic and biochemical assays for screening drug libraries. The emergence of this platform technology will allow pharmaceutical and biotechnology companies to focus their limited resources on those genes that are most likely to result in a breakthrough drug.

Traditional drug development is based on medicinal chemistry and pharmacology. The interaction of a chemical with a protein is examined outside of the cell using a solid matrix or in solution. The benefit of this approach is that the resulting assay is easily adapted to screening large numbers of chemicals in the search for drug candidates. However, the proteins do not usually behave the same way in these assays as they do in an intact cells. The new paradigm is that the intact living cell is the best biological reaction chamber (Simon 1996). Assays based on this paradigm quantify changes in the spatial and temporal relationships of proteins, RNA and chemical ions in the intact cell.

### **Technology and Methodology**

There are several key technologies that are driving the development of the screening platform: Gene expression mapping, proteomics, cellular probes, model organisms, and tissue libraries.

**Gene Expression Mapping:** The genome project is identifying all of the genes present in a multitude of organisms. However, this information says nothing about the dynamic expression of these genes in specific tissues in an organism. Recently developed technologies can now quantify the level of expression of any gene by directly measuring the amount of mRNA from each gene in the cell. The two most popular approaches are the

Serial Analysis of Gene Expression (SAGE) and expression profiling using “GeneChips”. SAGE is a process whereby a fragment from all mRNA’s present in a cell are strung together in proportion to their concentrations and quantified through sequence analysis (Velculescu 1995). A GeneChip contains thousands of discrete DNA sequences on a small silicon wafers that can be used to directly quantify thousands of different mRNA molecules in cellular extracts (Stipp 1997). Both approaches provide a level of detail about gene expression in cells that was unattainable five years ago. It is now possible to directly compare normal tissue to disease tissue and rapidly determine which genes are being aberrantly expressed in the diseased tissue. This information is invaluable in selecting cellular targets for drug development. Digital Gene Technologies, Gene Logic, CuraGen Corp., Perkin-Elmer/GenScope, Novalon Pharmaceutical Corp., Sequana Therapeutics, Incyte Therapeutics and Genzyme/Pharmgenics are examples of companies that are developing capabilities in gene expression mapping.

**Proteomics:** The next logical step following the analysis of gene expression via the concentration of mRNA is to directly measure to concentration of discrete cellular proteins generated from the mRNA. This brand new field has yet to be tackled by genomics companies. The key is to find rapid, high-throughput assays for cellular proteins. Again, robotics and micro-arrays of biological molecules may play a role in identifying and quantifying cellular proteins. Other technologies that might aid in this effort include time-of-flight mass spectrometry and cellular probes. Millennium Pharmaceuticals is a leader in Proteomics.

**Cellular Probes:** These are small molecules, proteins or nucleic acid molecules that are either attached to dyes or chemical markers (Simon 1996). The probes can be visualized with fluorescence confocal microscopy and photo-multiplier tubes. The newest versions of these microscopes will digitally quantify the fluorescent signal from cells in trays as they

automatically pass through the microscope using **robotics systems**. Companies developing platforms in the area of high-throughput screening with cellular probes are: Aurora Biosciences, Evotec, Caliper Technologies and Zymark.

**Model Organisms:** The key to performing effective functional genomics is to develop accurate models of human diseases. The best models of human disease are other organisms such the yeast (*Sacchromyces cerevisiae*), round worm (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), and mouse (*Mus musculus/domesticus*). Each of these organisms has been extensively studied by scientists. Many of the genes in organisms as simple as yeast are very similar to genes in humans (Brown 1996) (Friedrich 1996). This allows scientists to move beyond sequence information by examining the role of new genes in the context of a living organism. According to Sean Carroll, Professor of Molecular and Genetics at the University of Wisconsin,

“As models for human disease are discovered, we can establish animal models through transgenic techniques. If these biological models improve the ability to predict the performance of various compounds in treatment scenarios, then this will be a niche for companies to fill. The person who figures out a good biological model for a particular disease or who synthesizes the right number of observations into a strong medical hypothesis is going to make a big impact” (Lee and Burrill 1996).

It is now possible to add human genes to the genome of an organism such as yeast, or to selectively knock-out genes in an organism such as a mouse (Friedrich 1996). The development of transgenic mice, where human genes are added to the mouse genome, has allowed scientists to recreate human diseases in mice. The effects of missing a specific gene in mice is of great value in determining role of the gene’s counterpart in humans.

These two approaches for modeling gene function and human disease are powerful technologies for unlocking the secrets of the human genome. The following companies are all developing screening platforms around certain organisms: Cadus (yeast), Exelixis (fruit fly and round worm), Sequana Therapeutics/Nemapharm (round worm), Hexagen (mouse), Ontogeny (mouse and fruit fly) and Lexicon Genetics (mouse).

**Tissue Libraries:** Human tissue from autopsies, or removed during surgery as biopsies, are now being collected to aid in the drug discovery effort. The goal is to perform gene expression mapping of these tissues in order to generate clues as to what genes are active in various disease states (Friedrich 1996). This information will be used to help guide the creation of mouse models of human diseases. Pharmagene, Aeiveos and Lifespan are examples of companies focused on developing a proprietary tissue bank.

## ***Combinatorial Chemistry***

### **Background**

The traditional approach to medicinal chemistry is to individually create new chemical entities with synthetic chemistry that can then be sequentially tested against a molecular target (Brown 1996). The average medicinal chemist turns out 50 new compounds per year, which is sufficient to support random drug screening in animal models (Hogan 1997). Rational drug design takes this process to a higher level by using three-dimensional, graphical representations of the physical forces that dictate the recognition of biological molecules to guide the selection of chemical entities (Hogan 1997).

Combinatorial chemistry eschews these approaches by relying on natural selection from a huge library of distinct chemicals to arrive at a new pharmaceutical. It is based on the premise that the probability of finding an effective compound is proportional to the number of available choices (Hogan 1997). Therefore, combinatorial chemistry relies on the

generation of libraries that contain tens to hundreds of thousands of molecules. These libraries can be comprised of either small organic molecules, DNA, or peptides that cover a broad range of chemical characteristics. Small organic molecules are popular because they have excellent pharmacological profiles, and diverse libraries of these molecules can be easily generated using solid-phase split-and-recombine chemistry or parallel unit synthesis (Hogan 1997). The libraries can be used to screen against molecular targets, cells in culture and intact tissue such as tumors (Gold and Alper 1997). The primary benefit of combinatorial chemistry lies in the efficiencies this process brings to the drug development process. By increasing rate that scientists locate effective therapeutics from 1 in 10,000 to 1 in 10 or 1 in 100, combinatorial chemistry has the potential to shave two years off the drug development process (Hogan 1997). Companies that are active in combinatorial chemistry include: Houghton Pharmaceuticals, Pharmacopeia, Arqule, Millennium/ChemGenics, Cambridge Combinatorial, NexStar Pharmaceuticals, Isis Pharmaceuticals, Hybridon, 3-Dimensional Pharmaceuticals, CombiChem, Molecumetics, Cytomed, Ixsys, Panlabs, Peptide Therapeutics, Gilead Sciences and Genta.

### **Technology and Methodology**

- **Solid Phase Split-and-Recombine:** A method of mechanically generating large numbers of molecules. First applied to peptides, this approach results in a complex mixture of molecules that can be screened for binding to a target. The identity of the peptide bound to the target can be determined using a process called deconvolution. The main drawback to this approach is that the process of deconvolution can consume a lot of time.
- **Parallel Unit Synthesis:** A new approach to library generation based on parallel unit synthesis. Here combinatorial synthesis is driven by building blocks, or modules,

that make progressively more complex molecules in relation to both the number of modules and the diversity of their arrangements (Hogan 1997). By maximizing the number of combinations used to generate new chemicals, it is possible to obtain libraries containing 15,000 different molecules with only one hundred building blocks. One benefit of this approach is the ability to bias a library of molecules by restricting the choice of building blocks and combinations during the synthesis stage (Hogan 1997). The results of screening assays will dictate what bias is built into the library. These focused libraries can also be generated in response to information provided from programs of rational drug design and medicinal chemistry. The need for deconvolution is eliminated by preparing the combinatorial library in an array format.

## ***Bioinformatics***

### **Background**

The advent of the Human Genome Project has accelerated the trend towards software support of research and development. DNA sequence data must be carefully catalogued in rapidly accessible databases in order for scientists to use genomic information in target selection and drug design. In addition, new software tools must be developed that allow scientists to analyze DNA sequence information in ways that dramatically reduce the time and financial resources spent performing bench research. By moving the research process from the work bench to the computer, huge efficiencies may be realized that dramatically speed new drugs to market at much lower costs. The basic strategy for developing the software is to focus first on identifying genes in the DNA sequence, then determining how the genes and their encoded proteins function based on homology to similar genes and proteins in different organisms (Taubes 1996). By analyzing the expression of many genes and proteins, it becomes possible to sketch out the “genetic circuits” of the cell. These circuits include complex signal transduction pathways of proteins that ferry information

from receptor proteins on the surface of the cell to cascades of regulatory proteins that control gene expression in the nucleus (Palsson 1997). There are also complex protein pathways that control the division rate of a cell, the process of differentiation that a cell passes through as it becomes part of an organ, or the process of cell death called apoptosis. The sheer complexity of the problem necessitates a very organized, graphical framework that scientists can easily use to track and share information about these genetic circuits. There are few existing software platforms that fulfill this level of functionality. George Post, President of R&D at SmithKline Beecham, believes that,

“Biology in silico will take its place alongside of in vitro and in vivo observations in the experimental trinity” (Poste 1997).

The companies devoted to providing a bioinformatics platform include Tripos, CuraGen, Incyte Pharmaceuticals, Pangea Corp., Cambridge Molecular, MDL Information Systems, and GCG.

### **Technology and Methodology**

There are a myriad of public and commercial tools available to analyze DNA and protein sequence information. The key in developing an effective software framework is linking these tools together so that the output of one tool becomes the input for another tool. This allows a pharmaceutical research scientist to easily integrate software tools into the process of elucidating gene function and cellular pathways. One can better understand the importance of these bioinformatics tools by examining the discrete steps that a pharmaceutical research scientist follows in analyzing the function of a new gene starting with the DNA sequence through the following example:

- A scientist must first isolate the complete DNA sequence for the gene. Starting with a database of Expressed Sequence Tags (EST's), portions of the complete DNA sequence for a gene, a scientist will search for the complete sequence by searching for overlapping sequence information using programs such as the **TIGR Assembler** or **GeneParser**. Public or private genome databases can be search for the complete gene sequence using the **GRAIL** and **GENQUEST** on-line servers, **BLAST** or **GeneFinder**.
- With a complete gene sequence, the scientist will be interested in obtaining a prediction of the amino acid sequence of the new gene. Tools such as **BLASTX** can be used to predict an amino acid sequence from the DNA sequence through homology to the amino acid sequence of a genes in a database. The result of these searches is a string of amino acids that is referred to as a protein.
- With the amino acid sequence of the new protein in hand, the scientist will be interested in obtaining a prediction of the three dimensional structure of the protein. Programs such as **FASTA** search through databases of amino acids in search of homologous proteins. The three dimensional structure of these homologues may be known. Alternatively, programs such as **Hidden Markov Models** or **Threading Algorithms** can be used to determine the three dimensional shape of a protein by searching a database of known protein structures.

The scientist may choose to perform rational drug design with small molecules using the **UNITY** and **SYBYL** commercial software packages from Tripos, Inc.

## ***Microfabrication and Robotics***

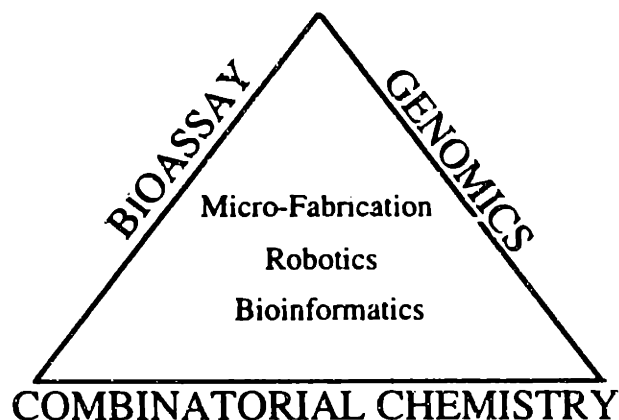
Micro-arrays and robotics are rapidly being incorporated into drug discovery research. Silicon chips (1 cm.<sup>2</sup>) are currently available that can sequence DNA and perform DNA expression analysis. There is a big push now underway to reduce much of what is considered bench research down to the level of a 'biochip' not much larger than a dime using micro-fabrication and robotics (Stipp 1997). The scale of these biochips, however, is still many times larger than the molecules and cells that will be studied using these new biochips. The goal is to have a single biochip process and analyze a tissue sample from a patient in a single procedure with no human intervention. The analysis will entail miniaturizing genomic and bioassay technologies. These biochips will allow millions of chemicals from large combinatorial libraries to be rapidly assayed against multiple drug targets derived from genomics. In addition, FDA approved drugs may be better matched with specific patient populations using these biochips, in a process called pharmacogenetics. The machines that perform biochip analysis incorporate the latest advances in robotics technology in an effort to maximize the assay throughput rate and drive down assay costs. The cost savings possible with biochip-based assays will be a major factor driving the adoption of this technology by pharmaceutical companies. Leaders in micro-fabrication and robotics include Affymetrix, Synteni, Hyseq, Nanogen, Aurora Biosciences, Caliper Technologies, Zymark and Perkin-Elmer.

## ***The Drug Discovery Platform***

The integration of the three enabling technologies of genomics, bioassay, and combinatorial chemistry synergize into a new platform for the discovery of novel pharmaceuticals. These interdependent technologies can be thought of as three sides of the 'Drug Discovery Triad' (see Figure 2).

## **Figure 2**

# The New Drug Development Triad



Bioinformatics, robotics and micro-fabrication technology are critical enabling technologies that are supporting the rapid advance of this new drug discovery paradigm. The Drug Discovery Triad has evolved out of the synergistic union of simultaneous, but independent, advances in a large number of technologies residing in industries unrelated to pharmaceuticals.

“Rich veins of technological convergence wait to be tapped linking healthcare with optoelectronics to fulfill new research needs in automation, miniaturization engineering, robotics and the design of directed molecular arrays such as the “GeneChip” and microsensor technology; to link healthcare with materials science to create novel biocompatibles, tissue engineering, encapsulated cell therapy and in vivo sensors; and between

optics and biology to use femtosecond laser technology to induce selective chemical bond excitation to engineer hitherto precluded chemical reactions and thus make directed quantum chemistry a reality,” says George Poste, President of Research and Development at SmithKline Beecham (Poste 1997).

Advances in robotics and micro-fabrication technology derive from advances in the semiconductor, defense and medical device industries. Similarly, software algorithms propelling the bioinformatics applications are spinning out of the rapid evolution of Internet browsing technology. Stanley Letovsky of the Genome Database at Johns Hopkins University indicates just how important this synergism is when he said.

“Java has come on the scene like gangbusters, and it blew away everything else” (Fischman 1996).

The diffuse nature of the underlying technologies of the Drug Discovery Triad makes it difficult for any one company to be pre-eminent in every aspect of the platform. The rate of technological change of the underlying platforms of the Drug Discovery Triad is too fast for any individual company to easily incorporate all aspects of the Triad into their drug discovery process and maintain a competitive position within the industry.

Pharmaceutical companies are adopting the Drug Discovery Triad as a replacement to the medicinal chemistry and traditional assays used in the previous model for drug discovery.

“Instead of spending \$100 million per target to find through traditional means whether the product works, genomics can give us a much better early

indication of success for a lot less money,” says the head of the genomics effort at Glaxo Wellcome PLC (Delinassios 1996).

Perhaps George Poste, the President of Research and Development at SmithKline Beecham, best describes the benefits of the Drug Discovery Triad when he recently said,

“The rise of the genomics, combinatorial chemistry, automated screening and bioinformatics have completely re-engineered the drug discovery process in less than five years, bestowing vital competitive advantage on those companies who captured these skills ahead of others” (Poste 1997).

The benefit of the Drug Discovery Triad is the rapid and seemingly inexhaustible number of therapeutic targets and drug leads that can be generated by this platform. The full impact of this new platform is just now being realized by both biotechnology and pharmaceutical companies. According to John Richard of Genome Therapeutics Corp. of Waltham Massachusetts,

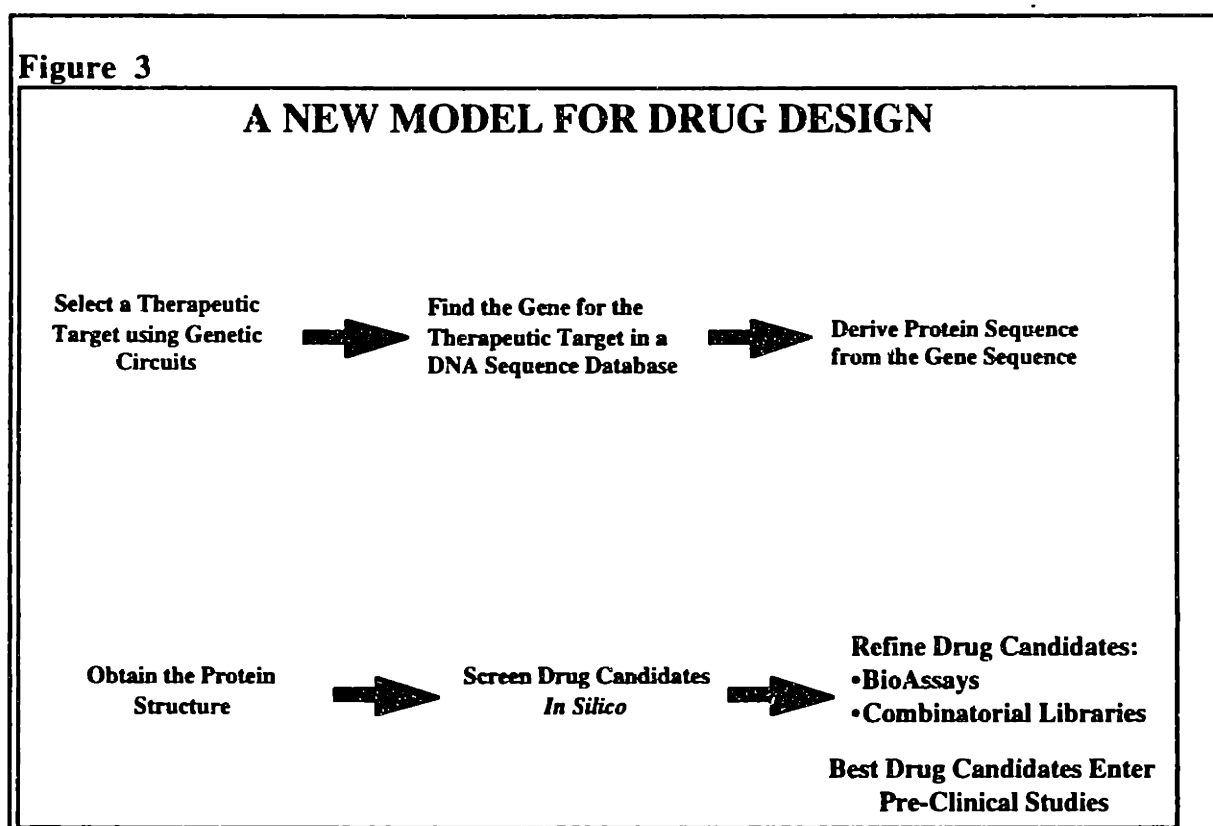
“The difference between genomics and other early stage platform technologies, like antisense, is that genomics is really a production science. It works. Genomics companies are already delivering what they say they can deliver” (Delinassios 1996).

The genomics industry is still very young, but it is very productive in the short term. According to William Haseltine, CEO of Human Genome Sciences (Gaithersburg, MD), his company has discovered over 200 novel proteins, 100 of which have been purified and tested in cell culture (1996). Of these 100 proteins, 60 have proven to be active in modifying cellular function. As for skeptics of this new technology, Haseltine suggests,

“They won’t be skeptical very long” (Cohen 1997).

### ***Incorporation of the Drug Discovery Triad into the Pharmaceutical Value Chain***

The Drug Discovery Triad fits into the research phase of the value chain for drug discovery. The Drug Discovery Triad first produces therapeutic targets, and following the use of bioassays to screen combinatorial libraries, therapeutic leads. This process is shown below (see Figure 3).



Therapeutic leads are the main product of the research portion of pharmaceutical R&D. This process represents about 30% of the funds committed to R&D, with the remaining funds used to support clinical trials, the most expensive aspect of drug development

(Davidson 1996). Clinical trials follow a path that starts with pre-clinical trials performed in order to determine efficacy and safety in animals, Phase I clinical trials performed in order to determine drug toxicity, Phase II clinical trials perform in order to define dosing and obtain initial efficacy analysis, and Phase III and IV trials that are performed in order to determine the efficacy of the drug in large patient sample populations (see Figure 4).

**Figure 4**

<b>The New Drug Development Process</b>				
	<b><u>Pre-Clinical Testing, R&amp;D</u></b>	<b><u>Clinical R&amp;D</u></b>	<b><u>NDA Review</u></b>	<b><u>Post-Marketing Surveillance</u></b>
<b>Timing</b>	1-3 years	3-6 years	2 months - 7 years	As long as the drug is on the market
<b>Description</b>	Identify new molecular entity via animal and chemical testing	Phase I, II, & III clinical trials (safety, efficacy, and then safety & efficacy combined)		Continued Inspections
<b>End Result</b>	Patent & Investigational New Drug (IND) = FDA approval for testing in humans	Results in NDA Submission	NDA Approval	
<b>Drug Discovery Phase</b>		<b>Drug Development Phase</b>		

With the successful clinical trial data in hand, a pharmaceutical company files for approval to market a new drug with the appropriate regulatory agency, such as the Food and Drug Administration in the United States. The Drug Discovery Triad generates value for the pharmaceutical companies because this platform promises to improve the quality and

quantity of therapeutic leads, thereby reducing the risk of product failures in costly clinical trials.

### **III. Outsourcing of R&D by Pharmaceutical Companies**

The history of strategic alliances in the pharmaceutical industry indicates that the veteran pharmaceutical companies and the biotechnology companies are driven into strategic alliances by complementary needs (Powell, Koput et al. 1996) (Woiceshyn and Hartel 1996). A typical alliance is created out of the mutual desire of pharmaceutical and biotechnology firms to develop an emerging technology. Veteran pharmaceutical companies use an alliance to access new technologies that are deeply embedded in biotechnology companies. Biotechnology companies benefit from an alliance because it provides them with access to cash, product development and marketing resources that are often constrained in these companies. Typically, biotechnology companies are more effective than veteran pharmaceutical companies in capturing the value of a new technology for drug development (Arora 1994). However, once a technology has proven itself in the product development process, the veteran pharmaceutical companies are in a better position than the biotechnology companies in widely targeting the technology over other drug development programs (Powell, Koput et al. 1996). These observations have been magnified by a recent trend in certain industries towards outsourcing some components of the corporate R&D effort (Jonash 1996) (Harris, Insinga et al. 1996) (Chatterji 1996).

**Hypothesis:** (A) high competition in the pharmaceutical industry, (b) reductions in the product development and regulatory approval processes, (c) fast changes in the technology platforms in the biotechnology industry, and (d) weakness in product development pipelines, encourage veteran pharmaceutical companies to enter technical strategic alliances with biotechnology firms in-lieu of establishing new technologies in-house.

## ***Alliance Strategies in the Pharmaceutical Industry***

### **State of Pharmaceutical Drug Development Pipeline**

The pharmaceutical industry is facing a crisis in the development of new therapeutic compounds. The drug pipelines of major pharmaceutical companies shows weakness in early stages of the drug development cycle (see Figure 5).

**Figure 5**

#### **The Drug Pipeline**

<b><u>Pharmaceutical Company</u></b>	<b><u>Pre-Clinical</u></b>	<b><u>Phase I</u></b>	<b><u>Phase II</u></b>	<b><u>Phase III</u></b>	<b><u>NDA</u></b>	<b><u>R&amp;D % of Sales</u></b>
Abbott	1	2	4	8	5	10.8%
Alza	3	2	3	8	1	-
American Home Products		1	7	15	7	10.1
Astra	2	10	6	10	7	-
Bayer		2	9	4	3	-
Bristol-Meyers Squibb	7	8	10	7	2	8.9
Chugai		1	5	2	6	-
Daiichi Pharmaceutical		3	10	3	8	-
Dainippon			4	1	1	-
Elan	2	3	7	4	5	19.9
Eli Lilly	6	10	9	7	2	16
Forest Labs	1			2	2	13.9
Fujisawa		1	8	3	4	-
Glaxo Wellcome	11	6	17	17	6	14.4
Hoechst Marion Roussel		7	5	9	11	-
Johnson & Johnson			6	20	14	8.8

Merck	9	2	5	11	3	7.6
Mylan			7	3		9.6
Novartis	3	10	12	14	6	-
Novo Nordisk	4	4	3	2	1	-
Pfizer	8	1	2	12	4	16.0
Pharmacia & Upjohn		2	7	11	7	16.9
Rhone-Poulenc Rorer	3	8	6	7	4	-
Roche	1		7	16	5	-
Sankyo		1	5	6		-
Schering Plough	6	6	3	7	7	13.2
Searle	3	2	7	3	3	-
SmithKline Beecham	2	1	10	18	4	9.8
Takeda			11	5	9	-
Tanabe Seiyaku			3	3	4	-
Warner Lambert	1	1	5	5	4	7.9
Yamanouchi		1	12	5	8	-
Zeneca	9	3	3	1	2	-
<b>Total</b>	<b>82</b>	<b>98</b>	<b>218</b>	<b>249</b>	<b>155</b>	<b>-</b>
<b>Average</b>	<b>4</b>	<b>4</b>	<b>7</b>	<b>7</b>	<b>5</b>	<b>12.2</b>

Source: Cowen & Co.

With a high historical rate of failure for new chemical entities (NCEs) in clinical trials, one would expect to see the largest number of NCEs in pre-clinical or Phase I clinical trials and the smallest number of NCEs in late stage clinical trials. The data reveals there are fewer NCEs in early stages than in late stages of the drug development process. The problem may be the result of inefficiencies in the traditional approaches to drug research that rely on

random screening of chemical compounds on unknown targets in animal disease models. This approach has been proven to work in the past, but it can not provide a flow of new drugs sufficient to support the anticipated growth rate of many of these pharmaceutical companies. Industry experts using reasonable assumptions have calculated that there will be a gap in new chemical entities (NCE), or drugs, within five to ten years (Drews 1996). The analysis suggests that the top 50 pharmaceutical companies must generate at least 42 NCEs per year in order to maintain a 10% growth rate. However, these same companies are only producing about 12 NCEs per year from their existing drug development pipelines. When the same calculations are performed with traditional biotechnology companies such as Amgen, the rate of NCEs generation increases to a range of 13 to 24 NCEs per year. Clearly, the pharmaceutical industry is facing a crisis as their existing drugs come off patent. Their earnings may fall off a cliff following the year 2000, with the biotechnology industry only cushioning the fall.

### **Response of Pharmaceutical Companies to the Shortfall of NCEs**

Pharmaceutical companies have attempted to solve the NCE shortfall through different mergers and acquisitions strategies. First, many large pharmaceutical companies are executing an acquisitions strategy that focuses on obtaining downstream pharmaceutical distribution channels as a way to increase sales of existing drugs. An example of this strategy is Merck's acquisition of Medco in 1995. The Merck/Medco merger will allow Merck to manage the delivery of medical services to about 50 million Americans (Merck 1995). Alternatively, pharmaceutical companies are merging with each other in an effort to consolidate market share in specific disease segments and to reduce costs by increasing the efficiency of their R&D and sales efforts. Frank Spiegel, a former executive vice-president at Merck, describes the rationale for mergers and acquisitions in the following way,

“The economics for traditional pharmaceutical companies will continue to be poor if not poorer. That will drive more horizontal mergers to get the efficiencies. You can see some of that activity recently, and you will see more” (Koberstein 1995).

The recent examples of this strategy include the \$36.3 billion merger of Ciba Geigy AG and Sandoz AG to form Novartis in 1996, and the \$14.7 billion merger of Glaxo Holdings Plc and Wellcome Plc in 1995. Pharmaceutical companies are also merging with health care providers. Unfortunately, this M&A activity does not get at the root of the dearth of NCEs—a lack of innovative pharmaceutical research by these companies.

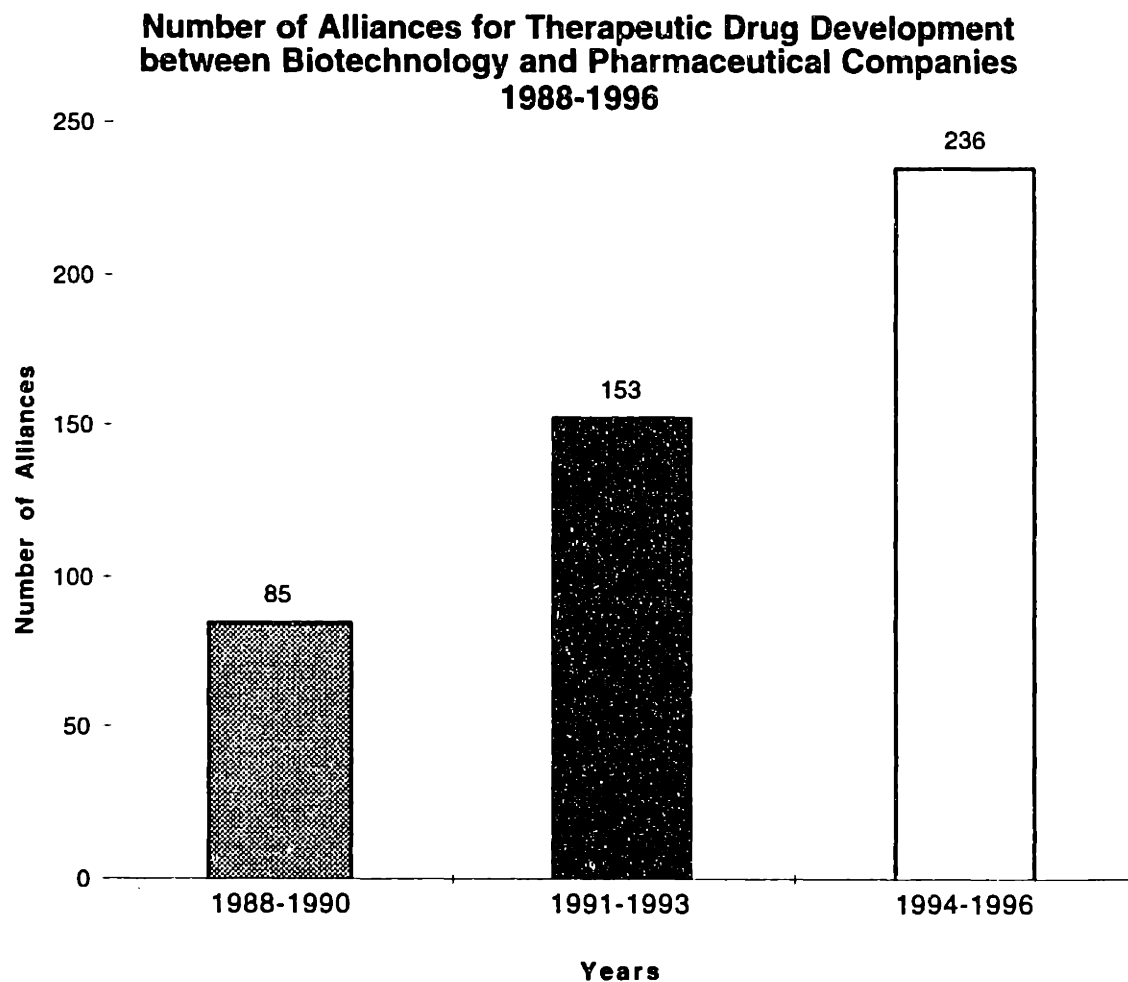
### **The Influence of Managed Care Organizations on Drug Discovery**

In a strange paradox, the managed care organizations (MCOs) are propelling the move towards more innovative research (Lee and Burrill 1996). These companies were unable to close formularies and reduce the reliance on expensive branded drugs because of concerns voiced by both patients and physicians. However, MCOs will not pay substantial premiums for drugs that only incrementally improve patient outcomes. This rewards companies that develop innovative drugs.

### **Alliances between Pharmaceutical and Biotechnology Companies**

Producing innovative drugs requires pharmaceutical companies to either adopt new research strategies or to acquire late-stage drugs from companies with innovative research platforms. This has led many pharmaceutical companies to form alliances with innovative biotechnology companies. There has been a dramatic increase over the past decade in the number of strategic alliances that focus on therapeutic development between biotechnology companies and the top 20 pharmaceutical companies (see Figure 6).

**Figure 6**



Source: Recombinant Capital

According to George Post, President of R&D at SmithKline Beecham,

“The escalating cost and complexity of technical specialization has rendered self sufficiency unattainable. Companies must establish increasingly diverse networks of technical alliances to ensure access to the full range of resources and skills needed for competitive survival. The evolution of the extended enterprise, and building the managerial skills required to sustain a

fluctuating network of alliances, will be increasingly influential in corporate success” (Poste 1997).

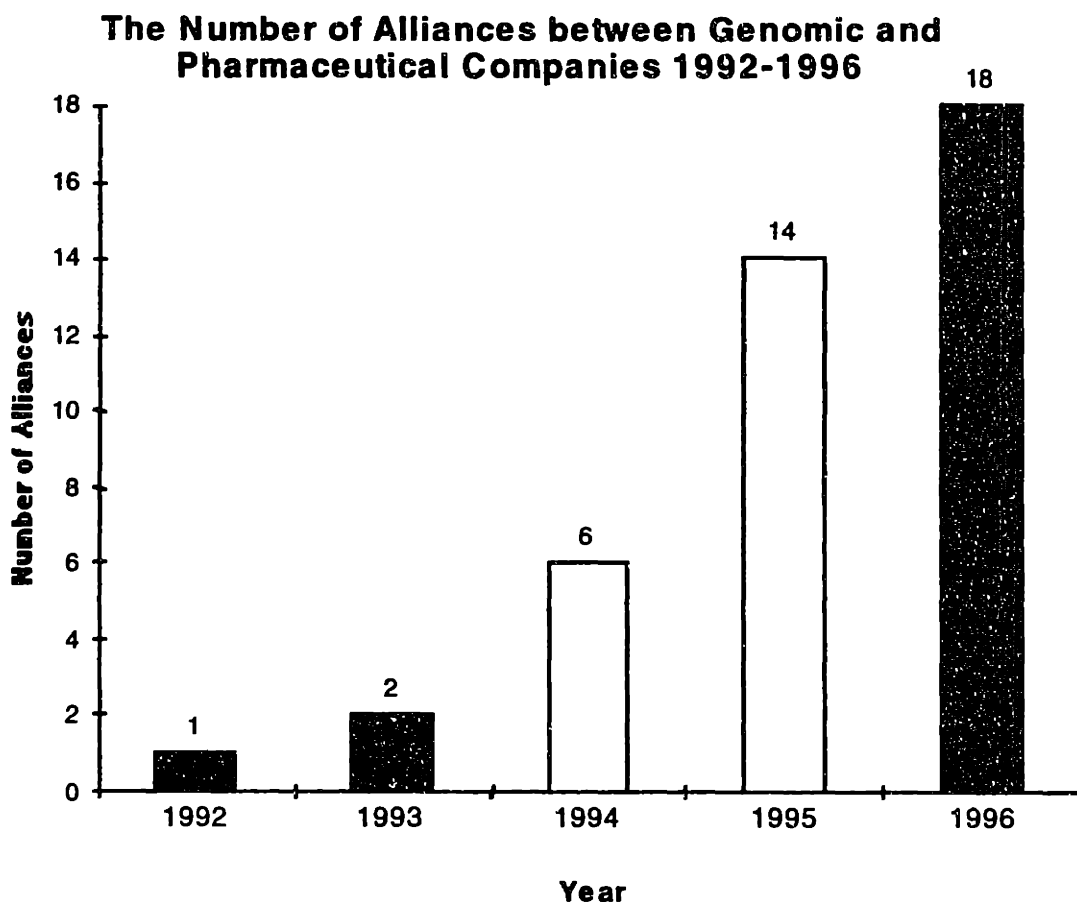
Many large pharmaceutical companies are attempting to leverage their internal research capabilities through external strategic alliances. The goal is usually to increase the number of MCEs produced per year. Hoechst Marion Rousell (HMR) intends to produce at least two NCEs/year by the year 1999 (Hofstaetter 1997). Thomas Hofstaetter, Head of Business Development at HMR, believes that for HMR,

“External alliances will be used to improve our ability to access novel targets. These alliances will help us exploit genomics, new enabling technologies, and pathophysiology expertise in selected diseases” (Hofstaetter 1997).

### **R&D Alliances based on the Drug Discovery Triad**

Many alliances between pharmaceutical and biotechnology companies are currently focused on gaining access to technologies that comprise the Drug Discovery Triad. There has been a near exponential growth in the number of pharmaceutical alliances with genomics companies (see Figure 7).

### **Figure 7**

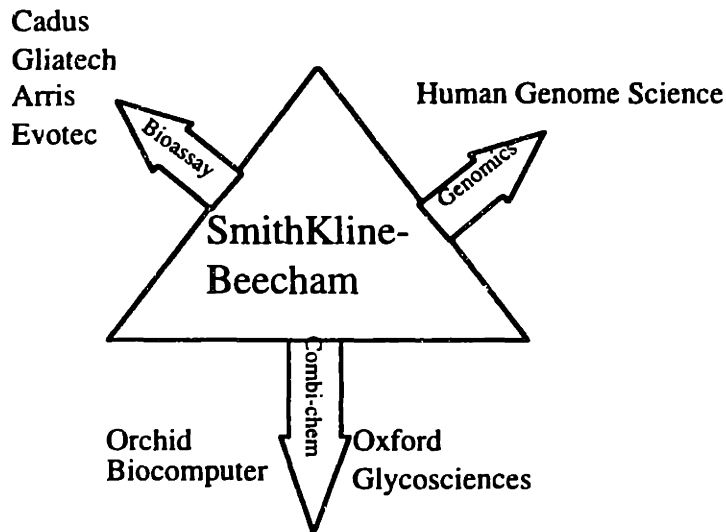


Source: Recombinant Capital

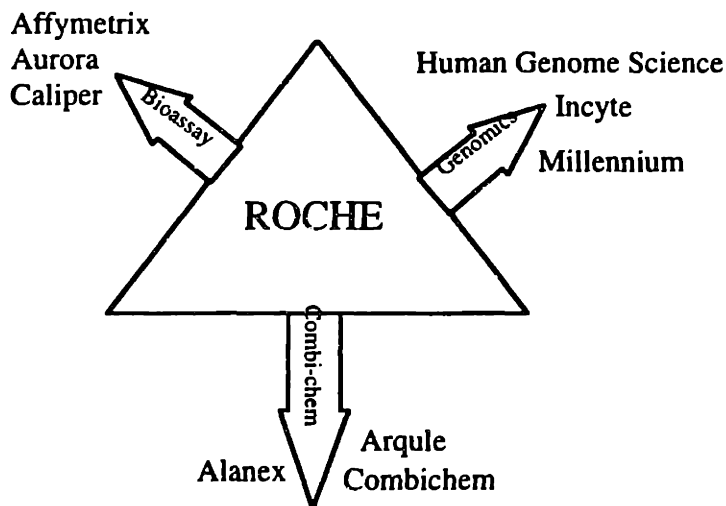
Most of the top 20 pharmaceutical companies have followed an alliance strategy that strings together genomics, bioassay and combinatorial chemistry companies into a “virtual network” devoted to their drug discovery needs (see Figure 8). The European pharmaceutical companies have been especially aggressive in developing alliances in the Drug Discovery Triad because they have traditionally focused on innovation-driven research, whereas their American counterparts tend to be more market-driven companies (Ward 1996). The pharmaceutical companies are now conductors of an orchestra of competing biotechnology companies.

**Figure 8 (Source: Recombinant Capital)**

## SKB's Triad Strategy



## Roche's Triad Strategy



## Structuring an Alliance

The major pharmaceutical companies use five variables in structuring an R&D alliance; an equity position in the partner, an upfront cash payment or licensing fee to the partner, R&D payments, milestone payments tied to research success, and royalty payments on the products that result from the alliance. In addition, there is a great deal of flexibility with regards to the specific terms of an alliance agreement. Important issues include the timeline of the progress expected by each partner of the alliance, the terms of the termination agreement should either partner seek

to end the alliance, and the exact details of the projects or technology covered by the alliance. These details are often redacted on publicly available documents from the alliance

partners. In general, alliances are structured in a way that provides accounting benefits to the large pharmaceutical company and much needed financial resources for the biotechnology company. Biotechnology companies usually announce the NPV of a strategic alliance that is calculated based on the assumption that all of the future milestones are met and the drug successfully makes it to market. A biotechnology company does not typically obtain the full value of an alliance in one lump payment.

#### Equity Payment

An equity position in a biotechnology company is usually taken by the pharmaceutical partner of an alliance between a pharmaceutical company and a biotechnology company. The equity position is often acquired at a premium to the price of publicly traded shares of the biotechnology company. This is beneficial to the biotechnology company because it indicative of a strong commitment by the pharmaceutical company to the alliance. In addition, the equity position is beneficial to the pharmaceutical partner because this type of investment is carried on the accounting books as an investment rather than taken out of earnings as an R&D expense.

#### Upfront or Licensing Payment

The upfront payments to the biotechnology company from the pharmaceutical partner are designed to defray some of the research expenses borne by the biotechnology company prior to the alliance. These upfront payments give some indication of the value that the biotechnology company has created through its technology platform or pharmaceutical program. Because the license grants a pharmaceutical company access to a technology, these types of payments can be capitalized on the balance sheet and amortized over the useful life of the technology, which is the patent life of the drug. However, the conservatism principle of accounting suggests that a company can only amortize a license for a drug that has shown efficacy in Phase III clinical trials. There has been a trend to

more cash payments and less equity payments in both pre-clinical and clinical stage alliances between pharmaceutical and biotechnology companies (1996).

### R&D Payment

The pharmaceutical company uses these payments to defray a portion of the R&D expenses borne by the biotechnology company partner. The lower of cost or maximum payment for full time equivalent is typically used in determining these types of payments. These types of payments are expensed in the same manner as internal R&D budgets.

### Milestone Payments

These payments are used by pharmaceutical companies to build-in incentives for the biotechnology partner to meet the timeline obligations of the alliance. They also allow the pharmaceutical partner to reassess the merits of their investment periodically over the course of the alliance. Typical events that trigger a milestone include the issue of a patent, successful clinical trial results, and FDA submissions or approvals. Data collected by Recombinant Capital shows a trend towards increasing average milestone payments from 1988 to 1996 (Edwards 1997).

### Royalty Payments

The biotechnology companies are usually granted a royalty payment on sales of the drug under development once the drug enters the market. These royalty payments significantly influence the NPV of the alliance for both parties to an alliance. For this reason, the details of the royalty payment are often redacted from public documents. In general, a biotechnology partner can expect to obtain 5-15% royalties for drugs in early stages or development. Most pharmaceutical companies expense the royalty payments in the cost of goods sold on their income statements.

## **Stacking Royalties**

The use of a network of external alliances to perform product development creates a problem for the contracting agent, the pharmaceutical companies, of stacking royalties.

Stacking royalties, as the term implies, is a situation where a number of independent entities are making royalty claims off of the future revenue streams of a drug under development. This can create a problem for the pharmaceutical company that is developing a drug because these royalties substantially reduce the NPV of a project. According to John Walker, CEO of Arris Corporation,

“Asking the pharmaceutical companies for a royalty here, a royalty there- they won’t do it. Pharma companies can’t afford to pay for combinatorial chemistry from one company against a target from another against a knock-out from someone else. It’s also why royalties to these companies are in the low single-digit range” (Bernstein 1997).

The presence of multiple royalties also creates a problem of asymmetric information that favors the biotechnology company. A biotechnology company can independently negotiate an alliance agreement with a pharmaceutical company, with little knowledge about the competing royalty claims that other biotechnology companies may have established with the pharmaceutical partner for the same drug candidates. The pharmaceutical company loses the benefit of negotiating all of the royalty claims with a single entity. In analyzing royalty claims, it is important to understand how the royalties fit into the sale of a drug (Rodriguez ). Pharmaceutical companies usually seek operating margins of 30%, on average, for each drug. The break-out of expenses is shown below (see Figure 9):

**Figure 9**

**Operating Margins for  
Pharmaceuticals**

Sales Revenue	100
<u>Cost of Goods Sold</u>	<u>10%</u>
Gross Margin	90%
Marketing & Sales Exp.	30-40%
R&D	15%
<u>General &amp; Administrative</u>	<u>5%</u>
Operating Margin	30%

Pharmaceutical companies typically obtain margins of 70-90% over the manufacturing costs for branded drugs.

However, about 35-40% of this margin is spent on sales and marketing costs. The sales and marketing expenses are high because of the cost to field a pharmaceutical sales force. A typical pharmaceutical representative makes 1200

visits to doctors/year, can sell only three

products per visit, and costs the pharmaceutical company between \$160,000 to \$180,000 “fully loaded” (Rodriguez ). Therefore, if a pharmaceutical company agrees to give its biotechnology partner a 15% royalty, the pharmaceutical company may be giving up about 50% of its operating margin. This 15% royalty is taken out of the cost of goods sold for the drug.

#### **IV. The Risks of Building a Company Around R&D**

The decision to out source the processes of obtaining regulatory approval, manufacturing and marketing of a drug leaves a biotechnology firm with a single core competency, that of R&D. This is consistent with observations that the culture of biotechnology firms are best suited for the transfer of cutting-edge academic research into useful products (Arora 1994) (Powell, Koput et al. 1996). In addition, a recent study of entrepreneurial biotechnology firms indicates that the rate of new product development is positively correlated with the number of strategic alliances utilized by a firm (Deeds and Hill 1996). However, this study also shows that this relationship drops off with the number of strategic alliances, with the possibility that high numbers of alliances negatively correlate with the rate of product development.

**Hypothesis:** The lifetime of biotechnology companies, which depends on a strong R&D focus and a network of strategic alliances, will be much shorter than the average for a fully integrated pharmaceutical company because: (a) Low barriers-to-entry for competing biotechnology firms will erode the value of firm-specific technology. (b) Technology obsolescence will be tightly correlated with firm obsolescence. This will encourage biotechnology firms to adopt a service model in exploiting their technology rents through strategic alliances with other pharmaceutical companies.

#### ***Biotechnology Companies and the Drug Discovery Triad***

The advent of the Drug Discovery Triad has caused a sea change in the business models of many biotechnology companies. A combination of rapid technological change, limited financial resources and interconnecting technology platforms have led biotechnology companies to pioneer a new business model. This model relies not on developing a stream

of target-driven pharmaceuticals, but rather on providing the tools that create these drugs as a service to established pharmaceutical companies (Persidis 1995).

### **Cor Therapeutics- The Old School**

Until recently, most biotechnology companies viewed themselves as budding integrated pharmaceutical companies, albeit with a thin stream of products. These companies viewed strategic alliances as a necessary step on the road to a self-supporting biopharmaceutical company that would eventually include sales and marketing functions. Cor Therapeutics (Cor) is an example of a traditional biotechnology company with this type of strategy. From the start, Cor expected to build its organization from the proceeds that the company derived from licensing Integrelin, its lead therapeutic (1995). In deals for its three previous drug candidates, the company obtained minimal funding in order to maintain key marketing and development rights. According to Lee Douglas, Cor's vice president of Business Development,

“If you've given away the major geographies on your lead compound- Integrelin-then you can not be there to take advantage of the opportunity. We made tradeoffs in those other deals so that we could build an organization. But that meant that we needed a deal on Integrelin that didn't, like other deals, require us to have an organization in place ahead of time but would allow us to build it as part of the deal” (1995).

Cor looked for a pharmaceutical partner whose marketing skills could help Cor get their lead compound onto the market. The pharmaceutical company would be expected to contribute financial and marketing resources, while Cor Therapeutics would provide the pharmaceutical company with an exclusive license a lead product based from its technology

platform, namely Integrelin. Cor found an corporate partner in Schering-Plough, and the companies entered a strategic alliance before the completion of a pivotal Phase III trial. Lee Douglas mentioned that,

“Time to market was clearly an important factor. We thought about the value doing a deal before the data as opposed to after the data, but the ability of a partner to help us stay on the best possible timelines for getting approvals on a worldwide basis was more important than some extra cash” (1995).

In addition to obtaining financing from Schering-Plough, Cor also retained rights to co-promote some of Schering-Plough’s products in order to develop a sales and marketing force (1995). Unfortunately for Cor, Integrelin has performed poorly in clinical trials, but the strength of the alliance with Schering-Plough has allowed the company to persevere in spite of this setback.

### **Incyte Pharmaceuticals and Human Genome Sciences-The New School**

Incyte Pharmaceuticals is a pioneer in developing a new business model to exploit the rents inherent in the innovative technology platforms at many biotechnology companies. Incyte began its existence in 1991 with the traditional business model for biotechnology companies-a protein therapeutic in early stages of clinical development that addresses an enormous market (Erickson 1996). However, the lead compound, BPI, failed to demonstrate efficacy against sepsis and trauma in early clinical tests. This left the company struggling to redefine its business around a new product. Lacking a traditional technology platform in protein therapeutics, the company decided to enter a new technology niche of high throughput DNA sequencing and gene identification, a technology platform pioneered

by Human Genome Sciences. The company sold access to this core technology capability as a service to established pharmaceutical companies, while simultaneously searching the platform for new therapeutic candidates. By 1994, Incyte decided to break with a strong tradition of granting exclusive licenses to technology platforms, opting instead to provide non-exclusive licenses to its database for moderate upfront fees. This break from tradition was driven by a combination of the huge number of genes that were filling up its genomic database, and by the realization that limiting the number of partners with high-priced exclusive licenses only encouraged new companies to enter Incyte's business (Erickson 1996). The company presumed that there is room enough in the biotechnology industry for only one generally accessible genomic database. For a relatively small subscription fee of \$15-20 million, a pharmaceutical partner obtains non-exclusive access to Incyte's *Lifeseq* genomics database and the option to obtain access to specialized genomics databases available for additional subscription fees (Erickson 1996). This strategy allows Incyte to rapidly sign up many of the world's largest pharmaceutical companies as they transition their R&D programs over to the Drug Discovery Triad (see Figure 10).

**Figure 10**

**Pharmaceutical Alliance Partners with Incyte Pharmaceuticals**

<b><u>Companies</u></b>	<b><u>Date</u></b>	<b><u>Alliance Description</u></b>
Bristol-Myers Squibb	Mar-97	Genomics database subscription
Ariad & Hoechst Marion Roussel	Mar-97	Genomics DB Subscription
Genentech	Jan-97	Gene sequencing
Lilly	Dec-96	Gene sequence and pathogen databases
Monsanto	Sep-96	Genomics for plants
Schering AG	Jul-96	Lifeseq DNA sequences
Zeneca	Jun-96	Genomics database subscription
BASF	Jun-96	Genomics database subscription
Hoffmann-La Roche	Apr-96	Gene sequencing
Johnson & Johnson	Jan-96	LIFESEQ subscription
Abbott	Dec-95	LIFESEQ & PathoSeq databases
Hoechst Marion Roussel	Oct-95	Gene sequencing
Novo Nordisk	Aug-95	Access to LIFESEQ
Upjohn	Nov-94	Non-exclusive license to LIFESEQ
Pfizer	Jul-94	Gene sequencing

Source: Recombinant Capital

Incyte derives revenues from these subscription fees, plus a small 1% royalty from products commercialized using the *Lifeseq* database (Erickson 1996). Unlike many biotechnology companies, Incyte is focused on increasing market penetration and revenues per customer, not on generating innovative new pharmaceuticals. Incyte focuses on the tools not the products. According to Randall W. Scott, Executive Vice President and Chief Technical Officer of Incyte,

“Information is non-exclusive. Everybody wants it and other people can generate it. So the route to competitive advantage is not patents, it’s market share. We just have a normal business, like the rest of the economy. It’s biotech that’s out of synch” (Erickson 1996).

Human Genome Sciences (HGS), the pioneer of genomic databases, took a more traditional approach towards licensing its database by providing SmithKline Beecham (SB)

exclusive access to the entire genomic database for a \$125 million (Erickson 1996). In addition, HGS retains co-promotion rights and 6-10% royalties of profits from sales of pharmaceuticals developed by SB from information derived from the HGS genomics database. The CEO of HGS asserts that,

“Our business is developing therapeutic proteins, not the sale of information. We are not a services company, we are a pharmaceutical company; that is where we believe we have a contribution to make” (Erickson 1996).

The flow of new therapeutic targets from the HGS database has been so large that the alliance between HGS and SB was recently amended to allow Merck KGaA (Germany), Synthelabo (France), Tekeda (Japan) and Schering-Plough (US) to gain access to the database (1997). The licensing fees, milestone payments and royalties from the new consortium of pharmaceutical partners will be shared by SB and HGS.

### **The Service Model**

Both Incyte and Human Genome Sciences sell access to a research tool that can help its partners generate large numbers of innovative therapeutics. Unlike Cor Therapeutics, these two companies are not attempting to commercialize a lead product, rather the clinical development is left to the pharmaceutical partner. The focus of Incyte and HGS on the *process* of generating novel pharmaceuticals versus the pharmaceuticals themselves represents a new business paradigm that is closely associated with the evolution of the Drug Discovery Triad. These “virtual” biotechnology companies develop pharmaceuticals and medical technology with the expectation that they will eventually be clinically tested and marketed by large pharmaceutical companies. Profits are generated for shareholders

through research revenues, licensing agreements and royalties from the sales of products by large pharmaceutical companies. The service-based biotechnology company benefits from this approach by sharing the risks of commercialization with a strategic ally. The large pharmaceutical companies benefit from this approach by exploiting the entrepreneurial culture of these small biotechnology companies.

There are two components to the implementation of this new business paradigm (Longman 1997). First, a biotechnology company will use acquisitions or alliances to obtain access to critical technologies or skills necessary to develop an enabling platform technology. These technologies are usually found in either a university lab or another biotechnology company. For example, Incyte Pharmaceuticals uses a large number of collaborations with both universities and other biotechnology companies to support its technology platform (see Figure 10).

**Figure 11**

**Incyte Pharmaceutical's Biotechnology and University Partners**

<b><u>Compan'</u></b>	<b><u>Date</u></b>	<b><u>Description of Alliance</u></b>
Molecular Dynamics	Feb-97	Use of MDYN's tech. for sequencing
OncorMed	Feb-97	Clinical genomics
PerSeptive Biosystems	Dec-96	GeneSpectrometry technology
Centre National de Recherche Scientifique	Oct-96	Bioinformatics
Scriptgen	Oct-96	Bacterial functional genomics
Oceania	Aug-96	Software for genomics linkages
Combion	Aug-96	Acq. of microarray co. for shares
Vysis	Jul-96	Genomic map using FISH technology
Affymetrix	Apr-96	GeneChip tech. for gene expression
GeneTrace Systems	Mar-96	GeneTrace's spectrometry technology
Science Applications International	Feb-96	Robotic system for DNA sequencing
Oncogenetics	Dec-94	Genes for breast cancer
Boston University	Nov-94	Applications of LIFESEQ database
Layton Bioscience	Apr-94	Non-PCR-based RNA amplification technology
Mayo Foundation	Jan-92	Eosinophil, basophil & mast proteins

Source: Recombinant Capital

Second, when a platform technology creates rents for the biotechnology company, multiple strategic alliances are established with pharmaceutical companies in order to maximize the value of these rents for investors. In order for this model work, both the biotechnology and pharmaceutical companies must be expert managers of strategic alliances. A historical reliance on strategic alliances during the evolution of the biotechnology industry has established an embedded management expertise in this area with most, if not all, of the biotechnology and pharmaceutical companies. This embedded industry intelligence for managing strategic alliances is transferred between organizations through a fluid movement of executives from pharmaceutical companies to biotechnology companies, and between biotechnology companies.

This model has a number of pitfalls (Longman 1997). First, established pharmaceutical companies may acquire the technologies that comprise the Drug Discovery Triad through acquisitions, thereby removing incentives to work with many of the service-oriented biotechnology companies. This would force many small biotechnology companies out of business unless they can quickly innovate along a new technology platform. Second, the technology rents that a biotechnology firm successfully develops can usually be quickly copied by new biotech start-ups via the enormous infrastructure of publicly-funded research. The rapid growth in the number of genomics companies is a case in point. The field has grown from just two companies, Incyte and Human Genome Sciences, five years ago, to over ten companies now. One would expect the value of alliances with genomics to drop with the addition of each new competitor, prompting some to disparage the service-oriented biotechnology companies as being part of a “no-margin rat race” (Longman 1997). John Walker, CEO of Arris Corp., believes that,

“ If the technology is worthwhile, the pharma company will bring it in-house to apply to all their targets, so early success in signing deals in this area isn’t a predictor of long-term success. It should only be seen as a way of enabling you to become a drug discovery company in your own right” (Bernstein 1997).

One way for biotechnology companies to avoid the pitfalls of the ‘Service Model’ is to strike a balance between a service-orientation and integrated drug development. Companies following this model service the research needs of pharmaceutical companies while simultaneously leveraging off this sponsored research to develop pharmaceuticals in-house. There are substantial benefits in the long term for pursuing this ‘Integrated Service Model.’ Chief among these is capturing a greater percentage of the value generated by a new drug. Instead of stopping at a therapeutic target, companies following the Integrative Service Model develop therapeutic leads and take these leads into clinical trials.

“You get a high single-digit to low teens royalty for a technology play, says Mark Levin, CEO of Millennium Pharmaceuticals. “If you take a compound to a partner you get teens, if you take it through Phase I you get teens to early 20s, through Phase II 25-30 percent, and through Phase III you can get 50 percent or higher” (Bernstein 1997).

In order to succeed at this strategy, the biotechnology must obtain access to a suite of drug discovery tools. Biotechnology companies can use either alliances or acquisitions to obtain necessary research capabilities. John Walker suggests that,

“If you have one piece of technology, you’re by definition a tool company. That doesn’t mean you can’t be successful, but your success is dependent on what your partner brings

to the table-i.e. the skills to take your tool and integrate it into a drug discovery program. Most tool companies as they are successful look to bring in new technologies” (Bernstein 1997).

The goal of the Integrated Service Model is to balance the extraction of rents from a technology platform between short-term revenues from research alliances and longer-term revenues from drugs developed in-house. Acquisitions play a big role in establishing the Integrated Service Model. Millennium Pharmaceuticals provides one of the best examples of the application of this business model to biotechnology.

### ***Case Study: Millennium Pharmaceuticals***

Millennium Pharmaceuticals, co-founded by Eric Landers of the Whitehead Institute, was established to commercialize advances in genomics research. The focus on functional genomics platform places the company within the Drug Discovery Triad. Millennium makes a trade-off in both its corporate and technology strategies in order to reach profitability in the shortest period of time. This trade-off enables the company to maximize the scale and scope of its operations. The combination of these strategies allows Millennium Pharmaceuticals to successfully forward-integrate off of the Service Model.

### **Business Strategy**

Millennium Pharmaceuticals uses a two-staged corporate strategy as a biotechnology company. The Company focuses on the following business strategy (1996):

- “Establish strategic alliances with leading pharmaceutical companies to accelerate product development, regulatory approvals and commercialization and to leverage the Company’s technological resources.”

- “Diversify business risk by securing multiple strategic alliance partners, thereby minimizing the Company’s reliance on any single player or disease research program while creating several potential royalty and profit-sharing revenue streams.”
- “Minimize operating losses and equity requirements by obtaining from strategic partners substantial payments that are not contingent on the achievement of research and product development milestones.”
- “Create additional business opportunities by retaining significant rights to develop and market certain therapeutic and diagnostic applications of the discoveries the Company makes in its funded strategic alliance programs.”

This strategy minimizes research risks by securing substantial research revenues from the strategic allies that are not contingent on research or product development milestones.

Millennium depends on its strategic allies for initial drug identification, clinical development, regulatory approval, manufacturing and marketing of products developed from the partnerships. The company reduces the business risks of strategic partnerships by securing multiple strategic allies that each have the potential to generate royalties and profit-sharing revenues. The company gives up a large percentage of future sales revenues to its strategic allies in pursuing this strategy.

The final stage of Millennium’s corporate strategy is to “...retain substantial rights to develop and market certain diagnostic and therapeutic applications of the discoveries it makes in its funded strategic alliance research programs” (1996). However, the company intends to pursue collaborations with biotechnology and pharmaceutical companies for the later stages of development and commercialization of these applications. Nowhere in the business strategy does the company mention any intention of marketing a product. Implicit in the corporate strategy is the assumption that all products generated by Millennium will co-developed and marketed by a partnering company.

“To do our own development and marketing would mean we’d have to raise additional hundreds of millions of dollars”, says Mark Levin. “And if a Phase III trial fails, we’ll have jeopardized our whole approach. The bottom line: value creation is what you own once the product gets to market, not how many people you’ve hired to bring that product to market” (Longman 1995).

Millennium has a core competency in industrial R&D, the high-throughput generation of novel therapeutics and diagnostics. However, there is no emphasis placed on bringing a drug to market. Millennium Pharmaceuticals can best be viewed as a virtual, or networked, company; a company that uses alliances with other pharmaceutical companies to both develop and market products.

In addition, Millennium leases nearly all of its equipment and research space. This strategy is costly in the long term, but it allows the company to avoid investing in scientific equipment that can rapidly become obsolescent. It also allows for a rapid reduction in costs in the event that the company loses a strategic ally.

### **Technology Strategy**

Genomics research is one of the fastest growing fields in molecular biology.

It attempts to sequence and map human genes involved in chronic and inherited human diseases. The linkage of specific genes, and their mutations, to the onset of diseases, such as cancer and heart disease, will revolutionize the delivery of health care. Physicians will practice preventative medicine by using genetic diagnosis of a disease to initiate treatment strategies before the manifestation of deleterious symptoms. Finally, pharmacogenetics

will allow a patient's own genetic information to be used to determine what drugs would work best in the patient's disease.

Millennium lists the following technology strategies in the Prospectus for the initial public offering (1996):

- "Focus on major common diseases that affect millions of individuals and that are underserved by current therapeutic alternatives.
- "Employ multiple synergistic gene identification approaches-including gene mapping, gene sequencing and additional approaches-to optimize the number and relevance of the Company's gene discoveries."
- "Employ a comprehensive set of bench and computational biology technologies to elucidate the function of the genes discovered by the Company and convert them to useful targets for drug discovery and diagnostic development."

The technology platform at Millennium allows the company to perform gene identification, target validation and lead ID/validation. Gene identification requires automated, high through-put DNA sequencing, gene mapping procedures to locate genes, and RNA profiling to analyze tissue dependent gene expression (Levin 1996). A comprehensive set of bench and bioinformatics techniques are then used to elucidate the function of the new genes. When these two processes are successfully completed, the company generates a validated gene target and patents are filed with the Patent and Trademark Office. These validated gene targets can then be adapted into assays and screened against small molecule libraries (combinatorial chemistry) by Millennium Pharmaceuticals or a pharmaceutical partner. Genomics research generates genetic information that augments the discovery of specific drugs or therapies. The focus on the generation of information makes genomics

companies, such as Millennium Pharmaceuticals, similar to companies in the software industry.

Millennium relies on proprietary technology in its genomics platform. Both its computational biology software and the bench technology used to determine the function of genes, called RADE (*Rapid Analysis of Differential Expression*), are protected as trade secrets. In addition, many of the gene sequences in the company's database are proprietary. The company relies on proprietary information as a strategy to reduce legal expenses, and as a way to prevent the required disclosure of key technologies necessary when obtaining a patent. The company risks losing its competitive advantage if these trade secrets are revealed to other genomic companies.

The recent acquisition of ChemGenics provides Millennium with a natural products library (50,000 different fungal molecules) and bioassay capabilities. The addition of these capabilities will allow Millennium to generate of therapeutic leads, thereby retaining more value from the drug development process. According to Lawrence Reid, Director of Business Development at Millennium, a therapeutic target provides the company with high single digit royalties (about 8-9%), whereas a therapeutic lead can be expected to generate double digit royalties (about 12-15%) (Reid 1997).

The critical element of this process is the time it takes to generate a validated gene target. Millennium competes with a host of other genomics companies, and a well-funded government initiative to sequence the human genome. These competitors can foil Millennium in two ways. First, competing genomics companies can patent genes that are being analyzed by Millennium. This would prevent Millennium, and its partners, from exploiting these genes for drug development. Alternatively, the federally funded genome initiative may place the sequence of genes that are being analyzed by Millennium onto

public databases. This prevents Millennium from obtaining patent protection for these genes, but a strategic partner can still use the genes for drug development. In order to address the time dependence of its technology rents, Millennium has embarked on a rapid increase in corporate headcount, growing from 166 employees on April 1, 1996 to over 400 employees by the of that year (over 500 if when the acquisition of ChemGenics is taken into account) (Reid 1997). The large number of employees allows the company to reach the critical mass necessary to efficiently harvest the short-lived technology rents. The genomics research initiative at Millennium is similar in scale to the internal research efforts at many of the major pharmaceutical companies (Davidson 1996).

Millennium retains its strategic partners only if they perceive the technology strategy employed by the company as more likely to succeed at isolating validated targets than competing approaches to genomics. The company must consider issues such as scale, scope and technology synergism's when formulating a technology strategy that maximizes the generation of validated gene targets and therapeutic leads. Millennium focuses its DNA sequencing effort on portions of the human genome containing genes involved with obesity, type II diabetes, atherosclerosis, inflammatory respiratory diseases, bacterial and fungal diseases, oncology and diseases of the central nervous system. The focused nature of this approach to DNA sequencing is likely to result in an increased cost/base for Millennium when compared to the large scale DNA sequencing operations run by competitors such as Human Genome Sciences and Incyte Pharmaceuticals. The additional expense is accrued from the process of target validation. The focus of this effort is on the determination of gene function rather than on the production of copious amounts of DNA sequence information. This provides value to pharmaceutical firms that partner with Millennium. According to Frank Lee, the chief scientific officer at Millennium,

“[Incyte] may want breadth of information that they can sell to a variety of partners, while we want depth-what’s happening in one cell or during one physiological state” (Longman 1997).

The different diseases that Millennium is working on allows it to benefit from economies of scope because the same technology platform can be used to search for multiple gene targets. At the end of 1994, research on genes involved in obesity and type II diabetes and generated \$14,229,797 in costs and expenses (1996). By the end of 1995, research on genes involved in obesity, type II diabetes, atherosclerosis, inflammatory respiratory diseases, oncology and diseases of the central nervous system generated \$21,129,894 in costs and expenses. Millennium saved roughly \$14,000,000 in R&D, and general and administrative expenses through economies of scope. In March of 1996, Millennium added programs in oncology with Eli Lilly, and central nervous system disorders and bacterial diseases with American Home Products. The addition of these programs caused research and development expenses to double to \$31,803,256. However, revenues from strategic alliances increased by only 39% to \$31,763,625. These financial results indicate that Millennium is spending more in research than it receives in revenues, suggesting that the company is funding internal pharmaceutical development off of the proceeds derived from alliances with its pharmaceutical partners.

### **Alliance Strategy**

Fundamental to the business strategy of Millennium is a reliance on strategic alliances within the pharmaceutical industry. The company has successfully negotiated multiple alliances with pharmaceutical companies to harvest the technology rents from its genomics platform. In a recent meeting between investment analysts and Mark Levin, the CEO of Millennium Pharmaceuticals, Levin defined the corporate alliance strategy as,

“To give as little away as possible to our corporate partners. We seek to retain rights to as many therapeutic categories as possible from our partners. If we could retain rights to all therapeutic classes we would, but of course this is not possible” (Levin 1997).

This strategy is evident in the alliances that Millennium has established with pharmaceutical companies over the last two years. Millennium seeks exclusive drug development rights (exclusives), the option to co-promote drugs in the U.S. (co-promote), co-exclusive drug development rights (co-exclusive), or a royalty payment (royalty). There are five categories that the company negotiates rights for; small molecule drugs, therapeutic proteins, gene therapy, antisense drugs and diagnostics. Small molecules drugs are currently the most desirable therapeutic class from the perspective of the pharmaceutical partners. These drugs are popular because they are easy to manufacture, have a successful track record in the clinics, and are based on technologies that currently reside in pharmaceutical companies. Gene therapy and antisense drugs have yet to prove themselves in the clinic, and therapeutic proteins have received mixed success in clinical trials. Millennium grants the greatest number of rights to pharmaceutical partners in the small molecule drugs category. The company then attempts to retain rights in the other therapeutic categories, with a focus on retaining exclusive rights in the areas of diagnostics and antisense therapeutics. Millennium structures these agreements in way that maximizes the amount of milestone, equity and upfront payments that are not dependent on research outcomes. Mark Levin explains how these rights work in the following example,

“If we identify a gene related to atherosclerosis, Lilly has exclusive rights. But the same gene, expressed in another tissue, could be part of the

mechanism for inflammation-and that we can take forward ourselves, on a co-exclusive basis" (Longman 1997).

The benefit of this strategy is that it enables Millennium to use drug discovery research in an alliance with a pharmaceutical company in one disease category to drive the formation of information that can be used to establish a new alliance with a different pharmaceutical partner in a new disease category. In addition, Millennium seeks to maximize the royalties on drugs developed with its partners. Mark Levin recently announced that the royalties were in the "high single-digit" range for most of the alliances (Levin 1997).

Millennium also seeks to maximize the technological value of the alliances with pharmaceutical companies. The company does this by carefully negotiating access to critical complementary technologies of the Drug Discovery Triad that the company does not control. The benefits of this strategy are obvious, it allows Millennium to maximize the value of the rights the company retains for drug development. For example, Millennium retained rights for limited access to the combinatorial chemistry libraries of its pharmaceutical partners Eli Lilly and Wyeth-Ayerst Laboratories (Longman 1997). The company also retained limited access to high-throughput screening technology in the Eli Lilly deal. Both of these technologies will be necessary for Millennium to achieve its goal of generating therapeutic leads from therapeutic targets that spill out of the research sponsored by its partners. However, the technology flows in two directions. Millennium pharmaceuticals transfers technology, such as bioinformatics and the RADE technology, to its pharmaceutical partners. This outward flow of technology has the potential to obsolete the technology platform that Millennium relies on to generate deals. More likely, this technology flow will cement the relationship between Millennium and its pharmaceutical partners. It will also drive Millennium to innovate along new technology platforms that complement those that it already offers to its partners.

Millennium has yet to use strategic alliances as a way to access synergistic technology platforms offered by other biotechnology companies. This is mainly do to the desire of the company to maximize the value of its internal technology platform (Longman 1997). Deals with other biotechnology companies could involve profit sharing and stacking royalties arrangements that might reduce the ability of Millennium to follow its current growth strategy. Millennium is content to use its strong cash position to acquire complementary technologies from biotechnology companies, or to develop these technologies internally. The recent acquisition of ChemGenics is an example of this strategy. According to Mark Levin,

“Moving a project between a 50-50 joint partner is just too slow” (Longman 1997).

### **Alliance Agreements**

Millennium has negotiated eight alliances in the last three years, providing the company with over \$300 million in committed research funding (Levin 1996). These alliances have a number of variables that the company uses in extracting value for the shareholders (see Figures 12 and 13). Many of the alliances were established before Millennium began trading on the stock exchanges. The company was very aggressive in setting up these early alliances, boosting both investor confidence in the firm’s technology platform and the price of the company’s shares at the IPO.

**Figure 12**

#### **Alliance Table**

<u>Partner</u>	<u>Date Signed</u>	<u>Deal Valuation</u>	<u>Disease Focus</u>
----------------	--------------------	-----------------------	----------------------

<u>Partner</u>	<u>Date Signed</u>	<u>Deal Valuation</u>	<u>Disease Focus</u>
Hoffman La Roche	3/94	\$50 million	Obesity and Type II Diabetes
Pfizer Inc.	1/95	\$24 million	Fungal Disease
Eli Lilly & Co.	10/95	\$41 million	Atherosclerosis
Astra AB	12/95	\$53 million	Respiratory Inflammation
Eli Lilly & Co.	4/96	\$28 million	Oncology
American Home Products/Wyeth-Ayerst	7/96	\$90 million	Central Nervous System
American Home Products/Wyeth-Ayerst	12/96	\$20 million	Bacterial Disease

Source: (Levin 1996) (Note: Valuations do not include milestone payments.)

**Figure 13**

**Millennium's Retained Rights in Alliances**

<u>Partner &amp; Date</u>	<u>Small Therapeutic</u>			<u>Antisense</u>	
	<u>Molecules</u>	<u>Proteins</u>	<u>Gene Therapy</u>	<u>Drugs</u>	<u>Diagnostics</u>
Roche 3/94	Royalty	Co-promote	Co-promote	Co-promote	Royalty
Pfizer 1/95	Royalty	Royalty	Royalty	Royalty	Royalty
Lilly 10/95	Royalty	Royalty	Co-Exclusive	Exclusive	Exclusive
Astra 12/95	Royalty	Royalty	Exclusive	Royalty	Exclusive
Lilly 4/96	Royalty	Royalty	Co-Exclusive	Exclusive	Exclusive
AHP 7/96	Royalty	Royalty	Royalty	Exclusive	Exclusive
AHP 12/96	Royalty	Royalty	Royalty	Royalty	Royalty

Source: (Longman 1997)

The most notable of the deals that Millennium has constructed is the alliance with AHP/Wyeth-Ayerst in the area of central nervous system disorders. The deal provides Millennium with an enormous amount of committed research funding, access to a small

molecule combinatorial library, and exclusive rights to antisense and diagnostic products. This deal is so notable that it won an award for the best negotiated alliance in 1996 at the 1997 Allicense Conference based on an industry-wide survey of biotechnology executives (Edwards 1997).

Millennium recently became a member of a consortium of companies searching for ways to apply the information generated by the genome project to drug development, and to develop new functional genomics technologies (Roush 1997). The consortium is made up of Millennium Pharmaceuticals, Affymetrix, Bristol-Myers Squibb and Whitehead/MIT Center for Genomic Research. Each of the corporate members of the consortium will contribute evenly to an \$8 million yearly grant to the Whitehead Institute over the next five years. The corporate members of the consortium will each receive commercial rights to technologies generated by Whitehead. High on the wish list of the corporate sponsors are automated systems for analyzing the changes over time of thousands of genes in a cell.

### **Goals 2000**

Mark Levin has identified six goals that he expects Millennium to achieve in the next three years (Levin 1997).

- Four to five of millennium's own products in the clinics.
- Four to five out-licensed products in the clinics.
- Greater than five of Millennium's own therapeutic leads in pre-clinical trials.
- Greater than five out-licensed therapeutic leads in pre-clinical trials.
- Three to four new alliances with pharmaceutical companies.
- A market valuation that exceeds \$500 million (about \$325 million as of Q1, 1997).

To fulfill these goals, Millennium is embarking on a new business model. Following the example set by Thermo Electron, the company plans to 'spin-out' companies in the fields of predictive medicine and biologics discovery and development (Levin 1997). These new companies would be majority owned by Millennium, but they would trade as separate companies on the stock exchange.

This strategy will allow Millennium to extend its technology platform into areas that were retained by the company in its alliances with the pharmaceutical companies. The management at Millennium expects that the spin-outs will allow the company to establish strategic alliances with new partners that don't conflict with existing alliance relationships. In addition, the spin-out model will allow Millennium to retain key personnel by providing them with the opportunity to work in a smaller, more entrepreneurial spin-out company. The model calls for the creation of two spin-outs that will be linked to Millennium by a bioinformatics backbone. The three companies will have synergistic technology platforms that support the successful operation of each individual company.

#### Millennium Pharmaceuticals

Millennium Pharmaceuticals will focus on developing retained rights in small molecules and natural products. It will continue to expand the genomics platform as outlined above. In addition to these activities, Millennium Pharmaceuticals will support the spin-outs with funding, corporate and administrative support, core production services and technology.

#### Millennium Predictive Medicine

This spin-out will focus on developing the retained rights in diagnostics. The company will focus on expanding market opportunities in pharmacogenetics, diagnostics/prognostics, and health information.

### Millennium Biologics Discovery and Development

This spin-out will exploit retained rights in biologics based therapeutics. Research and development will follow the same platform approach as Millennium Pharmaceuticals, but the focus will be on developing therapeutic proteins, therapeutic antibodies, gene therapy and antisense.

This strategy of separating the risky biologics based therapeutics from the main company will provide a financial benefit to Millennium. The risk of each spin-out and the mother company can be better evaluated by the financial markets, leading to a cost of equity that is in line with each company. In addition, the risk for developing new technologies will be spread to private investors, thereby reducing the financial risks to Millennium. In short, this strategy will allow Millennium to receive the financing and entrepreneurial employees necessary to rapidly commercialize rights retained from its existing alliances.

### **In the Balance**

The corporate strategy chosen by Millennium diverges from that usually used by biotechnology startups. A mix of venture capital, long term debt and shareholders equity is often used by these startups to fund initial operations. The biotechnology startups, and their shareholders, assume all of the risks of developing a pharmaceutical in order to benefit from the large profits expected from the eventual sale of these drugs. However, the long periods of mounting losses necessary to bring these pharmaceuticals to market often makes it difficult for these startups to secure infusions of equity financing at later stages of product development. Many of these companies are eventually forced into strategic alliances with large pharmaceutical companies in order to complete commercialization of their initial products.

Millennium has found a way to maximize research revenues with the Integrated Service Model by functioning as a biotechnology tool company. Currently, Millennium Pharmaceuticals has research commitments (licensing, R&D and milestone payments) in excess of \$306 million (1996). This rapid rate of revenue growth has allowed the company to fund a rapid headcount expansion during 1996. While genomics research is unique in that it is an information-based product, the corporate strategy pursued by Millennium can be applied to other biotechnology companies. As the pharmaceutical industry continues to consolidate around the Drug Discovery Triad, the Integrated Service Model may become the dominant model for new ventures in biotechnology.

## **V. Mergers and Acquisitions in the Biotechnology Industry**

### ***Introduction***

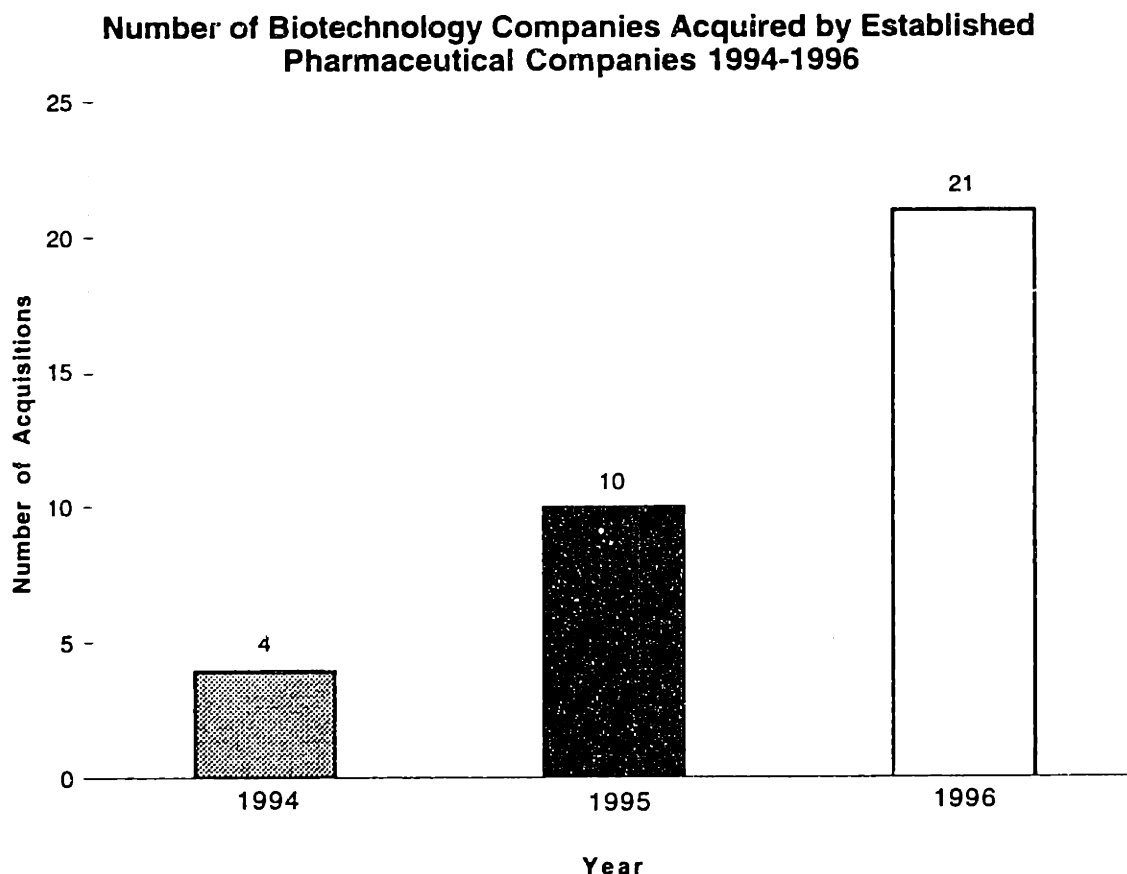
Many firms are better off acquiring new technology competencies than relying on strategic alliances or building technologies from within the company. The traditional rationale for mergers and acquisitions (M&A) is to maximize the efficient use of corporate resources (Jensen and Ruback 1983). The efficiencies can arise through technological synergism's, economies of scale, economies of scope and vertical integration. In addition, M&A can generate efficiencies through the elimination of poor management teams (Jensen and Ruback 1983).

**Hypothesis:** Biotechnology companies that pursue the Service Model as a business strategy are dependent for their survival on the rents retained by their technology platforms. The rate of technological diffusion often dictates how well a company can harvest the value of these rents for their investors. Constant innovation is critical in replenishing the rents of a technology platform. Therefore, executives of service-oriented biotechnology companies will use acquisitions of complementary technologies to shore up the value of their technology platforms.

### **Building Value Through Mergers and Acquisitions**

The last several years has witnessed a large increase in the M&A activity in the biotechnology industry (Van Brunt 1997). The number of pharmaceutical company acquisitions of biotechnology companies has increased from 4 in 1994 to 21 in 1996. There has also been substantial growth in the numbers of acquisitions between biotechnology companies, with an excess of fifty such deals occurring in 1996 alone (see Figure 14).

**Figure 14**



Source: (Van Brunt 1997)

Some of the notable deals between pharmaceutical and biotechnology companies included American Home Product's acquisition of Genetics Institute for \$1.25 billion in 1996 and Glaxo Wellcome's acquisition of Affymax for \$539 million in 1994 (Van Brunt 1997). The rationale for the acquisition of Affymax was to gain access to an important platform technology. At the time, the head of Glaxo Wellcome R&D, Jim Nidel, suggested that,

“We want Affymax to continue doing its own thing; but we want to see the result on every research bench of [Glaxo Wellcome]” (Hodgson 1995).

It appears that at some of the major pharmaceutical companies are buying up pieces of the Drug Discovery Triad. These innovator companies have derive tremendous benefit from these early acquisitions and these early successes may lead to future acquisitions.

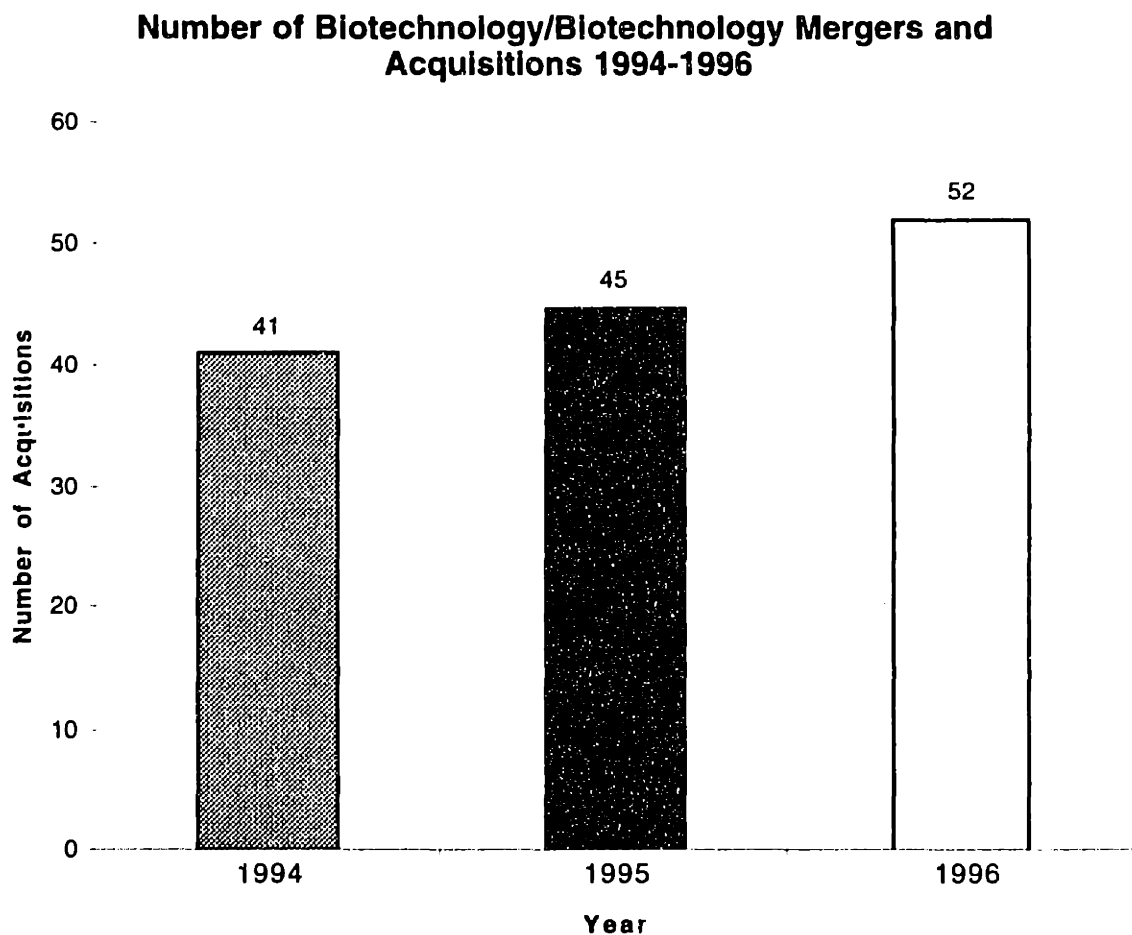
“A lot of people in the industry don’t realize how a handful of large pharmaceutical companies are in the process of automating drug discovery. Look at what we have done with high-volume screening and combinatorial chemistry: we acquired Sphinx, took its original combinatorial chemistry and screening operation, and have significantly enhanced its capabilities and productivity. We’re going from discovery as an individual scientist painting a single picture over a long period of time to many scientists working together to produce a gallery of pictures every day” (Longman 1997).

However, a much higher level of M&A activity is occurring between biotechnology companies rather than with big pharmaceutical companies. Here, the rationale for M&A activity centers around combining technology platforms and pooling financial resources of these small companies.

“You have to be prepared to integrate new pieces of technology into your drug discovery platform,” said John Walker, president and CEO of Arris Pharmaceutical Corp. “For example, the new genomics tools are target discovery tools. But having a target is a long way from having a drug. You need to combine target identification with the chemistry necessary to get to a small molecule compound” (Bernstein 1997).

Many biotechnology companies start out by developing a specific technology platform or research tool. This is sufficient to fund the company over the short term. However, as the technology rents dissipate through the industry, this tool company must acquire new technologies to remain competitive. There has been a substantial increase in M&A activity between biotechnology companies during the past three years (see Figure 15).

**Figure 15**



Source: (Van Brunt 1997)

Some of the notable acquisitions between biotechnology companies include Chiroscience Group plc's acquisition of Darwin Molecular Corp. for \$120 million, Elan Corp. plc's

acquisition of Athena Neurosciences Inc. for \$635 million, and Genzyme Corp.'s acquisition of PharmGenics Inc. for an undisclosed valuation (Van Brunt 1997). In each of these cases, the acquiring company was buying access to technologies that were mission critical in sustaining competitive advantage in the marketplace. For example, Chiroscience's drug chemistry program is complemented by Darwin Molecular's genomics program. The case of the three way merger leading to Aronex Pharmaceuticals illustrates many of the issues driving the wave of acquisitions in the biotechnology industry. The outcome of this merger points out some of the ways that a merger or acquisition can enhance the prospects for all of parties at the table.

### ***Case Study: The Formation of Aronex Pharmaceuticals***

Argus, Triplex and Oncologix merged in September of 1995 to form Aronex in response to the pharmaceutical industry pressures outlined above, and because of the poor reception of biotechnology companies by the capital markets in the period leading up to the merger (Sutter, 1995). Prior to the merger, each company had a unique strategy for succeeding in the pharmaceutical industry through the use of biotechnology. The following section will examine the strategy of each of the companies prior to the merger, the reasons for a merger, and an evaluation of the current strategy of Aronex for competing in the pharmaceutical industry.

### **A Tale of Three Companies**

**Argus** was established in 1986 with the goal of becoming a leader in the discovery, development and commercialization of novel therapeutics for treating cancer and life-threatening diseases (Sutter, 1995). Under the direction of CEO David M. Leech, the publicly-traded company developed a conservative product development strategy of licensing therapeutics that are effective against cancer or fungal infections, but exhibit

toxicity and dosing problems in humans that mitigate their usefulness as therapeutic agents. The company reformulated the compounds in proprietary lipid carriers that either reduce or eliminate toxicity while retaining or increasing the effectiveness of these compounds against their respective diseases. Two lead compounds from this approach, Nystatin and Tretinoin, were both in Phase II human clinical trials by the end of 1994, and six other compounds were under pre-clinical development. This product development strategy hedged the risk of product failure by using well-characterized compounds as the basis of its therapeutics, and created value by developing a core competency in lipid carrier development. However, the core competency in lipid carrier development was being simultaneously developed across a large number of biotechnology and pharmaceutical companies. Argus used a public equity markets, outsourcing agreements, and strategic alliances to competitively position itself in the pharmaceutical industry.

First, Argus was a publicly traded company on the NASDAQ stock exchange (Sutter, 1995). This was an important accomplishment because it allowed the company to have access to capital through trading vehicles such as stock warrants and secondary stock offerings. The SEC regulations also forced the company to be accountable to shareholders, a stress that usually results in a better management team.

Second, Argus utilized outsourcing agreements to leverage its limited resources. Argus maintained a close alliance with a team of scientists at the University of Texas M.D. Anderson Cancer Center (MDACC) that specialize in lipid carrier development and immunology (Sutter, 1995). The company was granted an exclusive worldwide license to numerous patents through this relationship. These agreements allowed Argus to have access to basic research being performed by MDACC scientists. This enabled the company to focus on pre-clinical and clinical drug development. Argus outsourced manufacturing in order to focus its resources on pre-clinical and clinical product development. However,

Argus did retain in-house the capability to develop formulations, analytical methods, process controls and manufacturing technology for products under development. Argus outsourced some aspects of the clinical trial programs to a contract clinical research organization (CRO). The CRO provided support in data processing and monitoring of clinical trials.

Finally, Argus participated in a number of inter-firm alliances that were critical to its product development strategy (Sutter, 1995). A strategic alliance with Genzyme Corporation was used to help fund and commercialize the Tretinoin compound. Argus helped to found and support R Gene Therapeutics, Inc. (RGene), a company devoted to developing pharmaceuticals based on gene therapy. Rgene and Argus were jointly developing a number of early-stage therapeutics.

**Oncologix** was founded in 1987 as a private biotechnology company that functioned as a cancer diagnostic reference laboratory under the name Molecular Oncology, Inc. (Sutter, 1995). In 1993, the company changed its focus to developing novel therapeutics that kill cancer cells under the name Oncologix, Inc. Under the direction of Charles N. Blitzer (CEO), the new company developed a two-prong strategy of performing in-house R&D to create new therapeutic compounds, and in-licensing exclusive rights to therapeutic technologies from pharmaceutical and academic institutions. The company used this strategy to rapidly develop a broad, unfocused, array of technologies that attack specific cancer and vascular diseases in unique ways. Linking cancer cell killing agents to molecules that can transport the killing agent to cancer cells might be considered a core competency of the firm because two of the five products under development were based on this technology. However, the remaining products under development were based on completely different technologies, with no obvious synergistic effects between them that

might accelerate the product development cycle. Oncologix was attempting to use economies of scope as a strategy to hedge against product failure.

Oncologix utilized licensing agreements with academic institutes or pharmaceutical companies for each therapeutic compound under development (Sutter, 1995). One of the compounds, OLX-102, was previously tested in Phase II clinical trials by Boehringer Ingelheim before Oncologix secured the marketing rights and the burden of an expensive Phase III clinical trial for this compound. A key cancer killing agent was licensed from Merck & Co. for use in developing the compound OLX-103. A technology called SCA, that was required for developing OLX-209, was licensed from Enzon, Inc. and Creative BioMolecules, Inc. Patents critical for protecting the compounds OLX-501 and OLX-514 were exclusively licensed from the Ohio State University Research Foundation for a period of time. Finally, Oncologix had entered a manufacturing agreement with Bio-Intermediar, B.V. to produce OLX-209 for clinical trials, and the company expected to outsource manufacturing for all future therapeutic compounds. In short, the company appears to have been following a business strategy that focused on rapidly assembling a broad range of technologies at substantial expense through licensing agreements, with the hope that this unfocused technology platform would serve as the basis of a public equity offering to fund future clinical development.

**Triplex** was founded in 1989 to commercialize the triple helix technology developed by a scientist at Baylor College of Medicine (BCMT) (Sutter, 1995). The business strategy under CEO James A. Chubb, Ph.D., was to develop pharmaceuticals based on triple helix technology for the treatment of viral infections and cancer. Triplex planned to use strategic alliances with established pharmaceutical companies or biotechnology companies to support the clinical development and marketing of pharmaceuticals based on triple helix technology. However, the company expected to develop a marketing organization by retaining North

American co-promotion rights for pharmaceuticals under joint development. Finally, the company planned to outsource the manufacturing of all pharmaceutical compounds under development.

Triplex had two lead compounds, T30177 for HIV and T01132 for CMV, under pre-clinical development by the end of 1994 (Sutter, 1995). Both of these compounds were obtained through a licensing agreement between Triplex and BCMT, and continued research collaborations with BCMT were being used by Triplex to boost its research capabilities in triple helix technology. In addition, Triplex had established a strategic alliance with Hoechst A.G. to develop pharmaceuticals based on triple helix technology. The initial viral disease targets listed above were switched, by Hoechst, to disease targets involved in acute inflammation.

Triplex was a young company with a highly focused technology platform and close ties to the university experts who pioneered this technology. The company created value through its core competency in triple helix technology. However, the focus on a single, high risk technology platform greatly increased the likelihood that the firm would cease to exist if the lead compounds failed in the clinics.

### **Reasons for the Merger of Argus, Oncologix and Triplex**

The benefits of a merger can be realized when there are synergy's between the companies involved in the merger. Upon close examination, all of the parties involved could benefit from a merger of Argus, Triplex and Oncologix. Argus had both public equity and therapeutic compounds in clinical trials, but its core competency in lipid carriers was being devalued by competing pharmaceutical companies. Oncologix had some promising technologies under clinical development, but it failed in its efforts to raise working capital

through a private equity placement or an IPO. This forced the firm to all but cease operations and lay off 46 of 52 employees. Finally, Triplex had an innovative and unique technology platform, but no products in clinical trials and a heavy dependence on one strategic partner for research funding and guidance in clinical development.

The companies had established technology platforms that should have strong synergy's if placed under one roof. The lipid carrier technology developed by Argus could provide an ideal delivery system for the triple helix technology under development at Triplex, and for a number of the compounds under development at Oncologix. The research programs at all three companies were targeting similar diseases such as cancer and inflammation, allowing for economies of both scale and scope following the merger. This is important because little remained of the research staff at Oncologix.

The strategic alliances developed by each company should be more valuable following the merger. The scientists at MDACC might benefit from working more closely with scientists from BCMT. The research at Rgene may benefit from the research at Triplex because both projects have a similar need for experts in DNA technology. The strategic alliances between Hoechst A.G. and Triplex, and between Argus and Genzyme, should provide valuable expertise in clinical trial development to the other two companies in the merger. Finally, the technologies licensed by Oncologix could be beneficial in improving the drug development efforts at the other two companies.

The three companies had similar research cultures that could be easily synchronized following the merger. Both Argus and Triplex fostered a research culture with close ties to an academic research institution. All of the organizations were focused exclusively on research, with a policy of outsourcing marketing and manufacturing functions. While not

explicitly stated, it is likely that each company utilized some form of a matrix organization, with a strong emergent strategy that fostered innovation.

Finally, the financial situation for each of the companies should improve following the merger. Oncologix and Triplex could gain access to the public equity markets via Argus. Argus could benefit financially from the strategic alliance between Hoechst A.G. and Triplex. In addition, there should be enough cash and investments to fund the combined operations through the third quarter of 1996, or about one year. Future cash need could be satisfied through the public equity markets using stock warrants and secondary stock offerings.

#### **Aronex Pharmaceuticals, Inc.: Strategies Going Forward**

Aronex is in a much better position to compete in the pharmaceutical industry than any of the firms that entered the merger. Under the direction of James M. Chubb, President, and Martin P. Sutter, Chairman, Aronex has developed the “critical mass” necessary to compete in the pharmaceutical industry (Sutter, 1995). The new company will focus on developing compounds that treat fungal infection, cancer and AIDS. Going forward, Aronex should carefully consider the corporate impact of outsourcing of manufacturing, strategic alliances with established pharmaceutical companies and managing resources over a diverse product line.

Aronex has continued the strategy of outsourcing the manufacture of drugs in clinical trials. This practice will be continued if these compounds reach the market. Outsourcing of manufacturing puts the company at risk if a contract manufacturer is unable to keep up with demand for a drug. This is the classic case of a “hold-up” because Aronex would be reliant on the contractor for commercial quantities of the drug. The stiff manufacturing regulations

imposed by the Food and drug Administration (FDA) would make it very difficult for Aronex to change to a different manufacturer. The Crown Equipment Company provides an example of the difficulties that can ensue when managers realize that they can no longer rely on a sole supplier. Aronex would be wise to line up several manufacturers for each drug to help reduce supplier power, but it is doubtful that manufacturers would agree to this approach because of the large expenses necessary to establish the manufacturing process. However, several of the drugs being developed by Aronex have two components, a lipid portion and a chemical portion. It might be possible for Aronex to manufacture these two components separately, and reconstitute them together in-house. This might provide a little more leverage for Aronex in its dealings with the manufacturers. Recent research indicates that early integration of process design in the drug development cycle can reduce the time to market for drugs based on synthetic chemistry (Pisano, 1997). Many of the drugs under development at Aronex fall into this category.

The drug development process at Aronex is dependent on a number of technical strategic alliances with university laboratories and pharmaceutical companies. Aronex outsources its early research to teams of academic scientists that it controls through exclusive licensing agreements. This strategy provides Aronex with a way around the strong internal research facilities present at most established pharmaceutical companies. These research facilities have traditionally acted as barriers to entry to the pharmaceutical industry. The key is to avoid alliances where the goal of the partner is to internalize core capabilities present at Aronex. The best case scenario is when the alliance creates value based on core competencies that lie with each of the partners.

Managers at Aronex must be careful to focus resources on projects that have a good shot at being the first therapeutics to treat a specific disease market. High competition for market share in the pharmaceutical industry suggests that late entrants to a disease market may have

a difficult time in just recouping R&D costs, let alone making a profit. It is clear that Aronex has more products in its pipeline than it can afford to develop at one time. So the company will have to get at least one of them to the market in order to support the development of the rest. Fortunately, the company has a nice assortment of conservative therapeutics in late stages of clinical development that have a good shot of making it to the marketplace. These drugs are closely followed by a number of innovative compounds that may prove to be market leaders in their respective disease markets. No more than four compounds should be in clinical trials at one time.

## **Conclusion**

The three-way merger between Argus, Triplex and Oncologix presents an excellent case study of the divergent strategies that are being used by biotechnology companies to enter the pharmaceutical industry. The conservative drug development strategy pursued by managers at Argus may have been just as flawed as the risky technology strategy pursued by managers at Triplex. The competition could have dealt Argus a severe blow at the marketplace. Under all circumstances, managers should avoid throwing together a technology strategy purely through licensing agreements. There was little value added to the projects assembled by Oncologix once the costs of the licensing agreements were taken into consideration. The case of Oncologix brings up another problem that plagues the biotechnology industry. The capital markets are not very receptive to the idea of waiting for ten years or more to get a return on an investment. This forces struggling young biotechnology companies into strategic alliances with established pharmaceutical companies until they have a product close to market. There is a current trend toward delaying a biotechnology IPO to a much later point than the norm of five years ago. In some respects, a window of opportunity for entering the pharmaceutical industry may be slipping away.

## **VI. Conclusion**

### A New Drug Discovery Platform

The advent of genomics, combinatorial chemistry, bioassays and bioinformatics has caused the re-engineering of the process of drug discovery. A new paradigm, called the 'Drug Discovery Triad', is dramatically increasing both the quantity and quality of pharmaceuticals. The rate of change of the underlying technologies makes it difficult for any one firm to obtain maintain mastery of the entire platform. While the technology is evolving out of the biotechnology industry, few biotechnology companies have been able to obtain access to all of the technologies in the Drug Discovery Triad.

### Adoption of the Drug Discovery Triad by Pharmaceutical Companies

The main consumers of the Drug Discovery Triad technologies are the established pharmaceutical companies. Early adopters, such as SmithKline Beecham, are likely to be in a stronger competitive position in the long term than late adopters of the Drug Discovery Triad. At the very least, the early adopters have enjoyed the benefit of negotiating better deals with the biotechnology companies for access to key technologies. For example, Hoffman La Roche negotiated access to Millennium's genomic database for two major disease categories, giving up relatively little in the way of therapeutic rights or cash to Millennium. Contrast this deal with the one struck recently with American Home Products/Wyeth-Ayerst, where the pharmaceutical partner obtained access to only one disease category, paid high upfront fees, and retained rights in a restricted number of therapeutic categories. The likelihood of a firm adopting an innovative new technology or product is correlated with the strength of the CEO (Cockburn and Henderson 1995). The early adoption of the Drug Discovery Triad by SmithKline Beecham indicates that the company is run by a very talented management team and CEO.

Studies of the adoption rate of new technologies by the pharmaceutical industry argue against the theory that R&D investments choices are driven by the R&D investments of competing companies, so-called racing behavior (Cockburn and Henderson 1993). The data presented in this study depicts a very rapid adoption of the Drug Discovery Triad, suggesting that pharmaceutical companies may engage in racing behavior if a new technology platform is perceived to be of critical importance to the industry. There are only a finite number of disease-related genes, and firms that lock up access to these genes through patents and early drug development will achieve a significant advantage on the marketplace relative to their competitors. These results also suggest that there are few spillovers of technology between firms investing in the Drug Discovery Triad (Cockburn and Henderson 1994). The tremendous investment in the Drug Discovery Triad indicates that pharmaceutical companies eagerly seek new ways to improve the productivity of their pharmaceutical research.

The growing number of strategic alliances in the pharmaceutical industry may be in response to a rapid change in the industry “clockspeed” (Fine 1996). The clockspeed of an industry refers to how relatively dynamic an industry is across variables such as the rate of new product introductions, the obsolescence rate of firm-specific knowledge, or the useful lifetime of fixed industry assets. The pharmaceutical industry has traditionally had a slow clockspeed relative to other industries such as the semiconductor industry. The biotechnology industry clockspeed is significantly faster than the pharmaceutical industry clockspeed because it is populated by more flexible and entrepreneurial organizations. However, the productivity of the biotechnology is only slightly better than that of the pharmaceutical industry based on the generation of NCEs (Drews 1996). The advent of the Drug Discovery Triad has dramatically increased the rate of NCE generation. The increased rate of NCE generation combined with reduced product lifetimes due to intense competition between similar drugs is driving down the pharmaceutical industry clockspeed.

The rate limiting step holding back dramatic reductions in the clockspeed of the pharmaceutical industry is the clinical development process. Regulatory hurdles and resource constraints impede the rapid movement of new pharmaceuticals to market.

The combination of genomics and pharmacogenetics has the potential reduce this logjam through careful management of clinical trials and patient populations. As the pharmaceutical industry clockspeed increases, firms may find it necessary to modify their organizational structure (Fine 1996). The recent wave of mergers between established pharmaceutical companies may be a response, in part, to a change in the clockspeed of the industry. A reduction in the clockspeed of the biotechnology industry might explain the recent increase in merger activity between biotechnology companies, obsolete or unsustainable companies are being acquired by successful firms.

Organizations most adapted to a fast clockspeed are likely to be found in the biotechnology industry. For example, the spin-out strategy being pursued by Millennium Pharmaceuticals may be an adaptation to a rising industry clockspeed. The spin-out strategy was pioneered by Thermo Electron Corporation, a company that competes in fast clockspeed industries such as the electronics industry.

#### The New Service Model for Biotechnology Companies

Studies on R&D productivity identified three key determinants of innovative performance across pharmaceutical companies: size, scope and focus of the R&D effort; the embedded firm knowledge of drug development; and the quality of the R&D management team (Cockburn and Henderson 1996). While there are significant industry-wide benefits for economies of scope, these benefits were found to be firm specific (Cockburn and Henderson 1996). A new business model for the biotechnology industry is the Integrated Service Model. Many of the biotechnology companies with technologies supporting in the

Drug Discovery Triad are following this new model. One of the key benefits of the Integrated Service Model is that it encourages biotechnology companies to focus on obtaining economies of scope, and harvesting these benefits through multiple alliances with pharmaceutical companies. The rationale underlying the benefits of this approach is that pharmaceutical research in one disease area may be synergistic with pharmaceutical research in a different disease area. There is also the obvious benefit of reducing the risk of product failure through multiple approaches at product development.

Critical to success along the new Integrated Service Model is gaining access to cutting edge technologies. For some biotechnology companies, strategic alliances may fill gaps in their technology platforms. For many other biotechnology companies, acquisitions may prove to be the method of choice for building out technology platforms. This may lead to considerable consolidation of biotechnology tool companies in the near future, as the best management teams and technologies take leadership positions in the industry. This type of industry consolidation around a dominant design or technology platform is predicted by the Abernathy & Utterback model for innovation (Utterback 1996).

## VII. References

Anonymous (1995). Cor Therapeutics: Dealmaking for the Marketplace. In Vivo-The Business and Medicine Report: 8.

Anonymous (1996). "The genome rush of 1996." Nature Biotechnology 14: 1199.

Anonymous (1996). Strategic Alliances and the Value of Consolidation. MarketLetter.

Anonymous (1997). The Future of Genomics at SmithKline Beecham. Marketletter.

Arora, A. a. G., Alfonso (1994). "Evaluating technological information and utilizing it: Scientific knowledge, technological capability, and external linkages in biotechnology." Journal of Economic Behavior and Organization 24: 91-114.

Bernstein, K. (1997). "Who Survives?" BioCentury: The Bernstein Report on BioBusiness 5(14): A1-A5.

Blumenthal, D., N. Causino, et al. (1996). "Relationships between academic institutions and industry in the life sciences-an industry survey." N Eng J Med 334: 368-373.

Brown, J. S. a. D., Paul (1991). "Organizational learning and communities-of-practice: Toward a unified view of working, learning, and innovation." Science 2: 40-57.

Brown, K. S. (1996). "Biotech Companies, Researchers Venture into Functional Genomics." The Scientist 10(23): 1-3.

Brown, K. S. (1996). "Drug, Biotech Firms Beginning to Embrace Combinatorial Chemistry." The Scientist **10**(10): 1-5.

Cockburn, I. and R. Henderson (1993). *Racing to Invest: The Dynamics of Competition in Ethical Drug Discovery*. Cambridge, MA, Massachusetts Institute of Technology.

Cockburn, I. and R. Henderson (1994). *Racing or Spilling? The determinants of Research Productivity in Ethical Drug Discovery*. Cambridge, MA, Massachusetts Institute of Technology.

Cockburn, I. and R. Henderson (1995). *Do Agency Costs Explain Variation in Innovative Performance?* Cambridge, MA, Massachusetts Institute of Technology.

Cockburn, I. and R. Henderson (1996). *Scale and Scope in Drug Development: Unpacking the Advantages of size in Pharmaceutical Research*. Cambridge, MA, Massachusetts Institute of Technology.

Cockburn, I. and R. Henderson (1996). "Scale, Scope and Spillovers: The Determinants of Research Productivity in Drug Discovery." RAND Journal of Economics **27**(1): 32-59.

Cohen, J. (1997). "Genomic's Wheelers and dealers." Science **274**: 774-775.

Cohen, J. (1997). "The Genomics Gamble." Science **275**: 767-772.

Davidson, S. (1996). "Hidden biotechnology worth over \$7.5 billion a year." Nature Biotechnology **14**: 564.

Deeds, D. L. and C. W. L. Hill (1996). "Strategic alliances and the rate of new product development: An empirical study of entrepreneurial biotechnology firms." Journal of Business Venturing [JBV] ISSN 11(1): 41-55.

Delinassios, J. G. (1996). "The Four Key Trends in Pharmaceutical Alliances, Part 2." In Vivo, the Business & Medicine Report(September): 36-40.

Delinassios, J. G. (1996). "GI Goes Fishing, Part I; Plans to join Genentech and Chiron in first genomics deal involving major Biotechnology companies." In Vivo: The Business and Medicine Report October, 1996: 17.

Doz, Y., L. (1996). "The Evolution of Cooperation in Strategic Alliances: Initial Conditions or Learning Processes?" Strategic Management Journal 17(Summer Issue): 55-83.

Drews, J. (1996). "Genomic Sciences and the Medicine of Tomorrow." Nature Biotechnology 14: 1516-1518.

Edwards, M. (1997). Recent Trends in Pharma/Biotech Alliances: Alliances of Top 20 Pharmas. Allicense 97-Biotechnology Comes of Age, San Francisco, CA, Recombinant Capital.

Erickson, D. (1996). "Incyte Serves Up Information." In Vivo-The Business and Medicine Report 14(5): 32-41.

Fine, C. H. (1996). Industry Clockpeed and Competency Chain Design: An Introductory Essay, The International Center for Research on the Management of Technology, Massachusetts Institute of Technology.

Fischman, J. (1996). "Working the Web With a Virtual Lab and Some Java." Science **273**: 591-593.

Fisher, L. M. (1996). Biotech Counterattack on Resistant Bacteria; Small Companies Leading Research. New York Times: Section D, Page 1.

Friedrich, G. A. (1996). "Moving beyond the genome projects." Nature Biotechnology **14**: 1234-1237.

Ghodsian, F. F. (1995). "Technology: A safety net for high-wire acts." Biotechnology **13**: 1154.

Goffeau, A. and e. al. (1996). "Life with 6000 Genes." Science **274**: 546-567.

Gold, L. and J. Alper (1997). "Keeping pace with genomics through combinatorial chemistry." Nature Biotechnology **15**: 297.

Haber, E. (1996). "Industry and the University." Nature Biotechnology **14**: 441-442.

Hodgson, J. (1995). "Biotech's Platform Technologies Lure Big Pharma." Bio/Technology **13**: 945-947.

Hofstaetter, T. (1997). Licensing/Alliance as Strategy Implementation Tools. Allicense 97-Biotechnology Comes of Age, San Francisco, CA, Recombinant Capital.

Hogan, J. C. (1997). "Combinatorial Chemistry in Drug Discovery." Nature Biotechnology **15**: 328-330.

Jensen, M. C. and R. S. Ruback (1983). "The Market for Corporate Control: The Scientific Evidence." Journal of Financial Economics **11**: 5-50.

Koberstein, W. (1995). "An insider's story of Merck's transformation into a global industry leader by someone who helped build it." Pharmaceutical Executive(July): 40.

Kolassa, E. M. a. B. I., B. F. (1995). Growing Competition in the Pharmaceutical Industry: A Response to the PRIME Institute Report., Research Institute of Pharmaceutical Sciences, The University of Mississippi.

Kolassa, M. (1993). Reductions in Pharmaceutical Price Growth: An Assessment of List Price Changes in the U.S. Pharmaceutical Market 1989-1992., Working Paper, The Pharmaceutical Marketing and Management Research Program, Research Institute of Pharmaceutical Sciences, The University of Mississippi.

Lee, K. B. and G. S. Burrill (1996). Biotech 97 Alignment, Ernst & Young.

Levin, M. (1996). Millennium Annual "Rapport". Cambridge, MA, Millennium Pharmaceuticals.

Levin, M. (1996). Prospectus for Initial Public Offering of Stock for Millennium Pharmaceuticals. Goldman Sachs & Co. and Robertson, Stephens & Co, Underwriters. Cambridge, MA, Millennium Pharmaceuticals.

Levin, M. (1997). Company Workshop, 17th Annual Cowen Health Care Conference.

Levin, M. (1997). Millennium Pharmaceuticals, Inc. Allicense 97-Biotechnology Comes of Age, San Francisco, CA, Recombinant Capital.

Longman, R. (1995). "Millennium: Genes are not Enough." In Vivo: the Business & Medicine Report(October).

Longman, R. (1997). "Biotech Models, Part II: Early Stage Companies." In Vivo: The Business and Medicine Report(January, 1997): 71-79.

Marshall, E. (1997). "Companies Rush to Patent DNA." Science **275**: 780-781.

Marshall, E. (1997). "Is Data-Hoarding Slowing the Assault on Pathogens?" Science **275**: 777-780.

Merck (1995). Annual Report.

Mullin, R. (1996). "Rajen Dalal: Biotech the broad way." Journal of Business Strategy [JST] ISSN **17**(5): 40.

Palsson, B. O. (1997). "What lies beyond bioinformatics?" Nature Biotechnology **15**: 3-4.

Parkhe, A. (1993). "Strategic Alliance Structuring; A Game Theoretic and Transaction Cost Examination of Interfirm Cooperation." Academy of Management Journal 36(4): 794-829.

Persidas, A. (1995). "Enabling Technologies and the Business of Science." Biotechnology 13: 1172-1176.

Persidis, A. (1995). "Enabling Technologies and the Business of Science." Bio/Technology 13: 1172-1176.

Persidis, A. (1996). "Innovation: Building molecular value." Journal of Business Strategy [JST] ISSN 17(2): 18-20.

Pisano, G. A. (1989). "Using equity participation of support exchange: Evidence from the biotechnology industry." Journal of Law Economics and Organization 5: 109-126.

Pisano, G. P. (1990). "The R&D boundaries of the firm: An empirical analysis." Administrative Science Quarterly 35: 153-176.

Pisano, G. P. (1997). The Development Factory: Unlocking the Potential of Process Innovation. Boston, MA, Harvard Business School Press.

Poste, G. (1997). "Managing discontinuities in healthcare markets and technology; Creativity, cash and competition." Vital Speeches of the Day 63(10): 309-313.

Powell, W. W., K. W. Koput, et al. (1996). "Interorganizational collaboration and the locus of innovation: Networks of learning in biotechnology." Administrative Science Quarterly [ASQ] ISSN 41(1): 116-145.

Reid, L. (1997). Personal Communication.

Rodriguez, R. (1997). Personal Communication.

Roush, W. (1997). "Whitehead, Three Firms Splice a Deal." Science 276: 891.

Shrader, S. (1991). "Informal technology transfer between firms: Cooperation through information trading." Research Policy 20: 153-170.

Simon, S. (1996). "Cellular probes on the move." Nature Biotechnology 14: 1221.

Stipp, D. (1997). "Gene Chip Breakthrough." Fortune 135: 56-73.

Taubes, G. (1996). "Software Matchmakers Help Make Sense of Sequences." Science 273: 588-590.

Tushman, M. L. a. A., Phillip (1997). Managing Strategic Innovation and Change: A Collection of Readings. New York, Oxford University Press.

Usdin, S. (1997). Lehman's reply on DNA patents. BioCentury. The Berstein Report on BioBusiness: A4.

Utterback, J. M. (1996). Mastering the Dynamics of Innovation. Boston, MA, Harvard Business School Press.

Van Brunt, J. (1997). "Mergers and Acquisitions Validate Biotechnology." BioWorld 5(9): 1-8.

Velculescu, V. E. (1995). "Serial analysis of gene expression." Science 270: 484-487.

Ward, M. (1996). "Europharmas increase stakes in U.S. biotechs." Bio/Technology 14: 21-22.

Williamson, O. E. (1991). "Comparative economic organization: The analysis of discrete structural alternatives." Administrative Science Quarterly 36: 243-259.