

BIOTECHNOLOGY PATENTS AND STARTUPS

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6.931 Final Project

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1. Abstract

1 The purpose of this project was to attempt to determine the effects of patents on startup biotech companies. To understand this question fully, we decided that we had to look at the importance of patents throughout the life cycle of a biotech company, from their very inception to their success or failure. We tried to approach the problem from various points of view. We collected information from a plethora of sources including biotech companies (often startups), venture capitalists, angel investors, the MIT Technology Licensing Office, and MIT professors among other traditional research methods such as SEC filings and web and patent research.

2 Overall, we conclude that patents are absolutely essential to the success of traditional biotech startups as they provide the promise of monopoly profits in an extremely risky industry. However, this model is changing with the advent of the newer genetics technology.

2. Introduction and Background

2.1 Overview

3 To discover the role of patents in biotech companies, we decided to look at different stages of biotech companies and attempted to determine how influential patents are on their success and failure. The first section of the paper gives some background information about the biotech industry and discusses various features and issues involved in this industry. The next section looks at what it takes to start a biotech startup and what should be taken into consideration. Following that is a section about the inception of biotech companies and how that normally occurs. How biotech companies approach VCs and the role of patents in approaching them is also discussed. After biotech companies receive funding, they engage in research and development for a period of time during which they develop a suite of patents and have to protect them. The last section discusses how companies become successful and gives a few case studies. The last section consists of our conclusions.

2.2 Background

4 Within the last few decades, our understanding of biology reached a point where we can use cellular and molecular processes to solve problems and make products. The molecules most often used in this technology include nucleic acids (such as DNA) and proteins. Because of the specificity of the interactions between cells and molecules, biotechnological tools and techniques are precise and operate predictably. Thus, biotechnology targets specific problems in specific, precise and predictable ways(1).

5 The following list depicts various types of biotechnology and the ways in which they are employed. A good portion of information for this list was from Editor's and Reporter's Guide to Biotechnology(1) which is associated with the Biotechnology Industry Organization.

- **Monoclonal Antibody Technology**

6 Antibodies are extremely specific and can be used to locate miniscule amounts of substances and measure them with accuracy. They can be used to distinguish between cancerous and normal cells, to locate pollutants, to detect harmful microorganisms in food and diagnose infectious diseases.

- **Cell Culture Technology**

7 This technology involves growing cells outside living organisms. This allows us to engage in specific biocontrol (growing microorganisms to eliminate specific pests without affecting other insects) and to replace animal testing with cell testing. Cell cultures are also used to produce compounds of therapeutic value that are otherwise naturally occurring. In the future, this technology may be able to reproduce malfunctioning cells with normal cell culture grown cells.

- **Biosensor Technology**

8 This technology combines our understanding of biology and microelectronics. Cells or molecules can identify and measure substances with great accuracy and the devices use this accuracy to produce the appropriate signals. This type of technology is employed in measuring such things as the nutritional value of something, locating and measuring pollutants, providing accurate measures of blood components, and measuring glucose levels.

- **Genetic Modification Technology**

9 This type of technology involves combining genetic material from different sources. This type of technology is an extension of selective breeding. Because particular organisms have traits that are valuable, genes are combined on the molecule level using genetic modification. Genes with specific traits are moved from one organism to another and results in precise manipulations and outcomes. This technology results in such things as new and safer vaccines, treatments for genetic diseases, new and better medicines, and increased productivity with crops and animals.

- **Antisense Technology**

10 This type of technology is used to block the expression of particular genes. Small nucleic acids block the production of specific proteins by these genes. This type of technology can slow food spoilage, control diseases and inhibit inflammation and even possibly control cancer.

- **Protein Engineering Technology**

11 This technology is used in combination with genetic modification to improve and create new proteins. These proteins help improve the efficiency of industrial processes and allow for renewable and biodegradable resources. Enzymes trigger particular biochemical reactions and since they produce less unwanted by-products than chemical catalysts, they are environmentally

advantageous.

3. Facts and Statistics

12 The following statistics and facts were collected over the past year and a half by the Biotechnology Industrial Organization. (1) .

- There are more than 90 biotechnological drug products and vaccines approved by the FDA
- There are more than 350 products in clinical trials and hundreds more in early development. These drugs include treatments for cancers, Alzheimer's, heart diseases, diabetes, AIDS and other conditions.
- Biotechnology is used in hundreds of diagnostics tests that are involved in keeping the blood supply safe and in pregnancy tests.
- Biotechnology has already affected the production of various foods. In addition, hundreds of biopesticides are currently employed.
- Environmental biotechnology products make it possible and more efficient to clean up certain types of hazardous waste
- Biotechnology has led to cleaner processes and less waste and energy consumption in the production of chemicals, pulp and paper, textiles, food, and energy.
- DNA fingerprinting has aided in criminal investigations
- There are 1,283 biotechnology companies in the U.S.
- In 1998, the amount of money invested in the Biotech industry increased from \$93 billion to \$97 billion
- One third of biotech companies have less than 50 employees. Two thirds have fewer than 135 people.
- The biotech industry employs roughly 153,000 people in high-wage and highvalue jobs.
- The biotech industry spent \$9.9 billion in research and development in 1998.
- The biotech industry is regulated by the FDA, the EPA and the USDA.

4. Summary of Legislative Issues in Biotech

13 Biotech companies have to take various factors, that are beyond their control, such as legislative issues and markets, into consideration. Under legislative issues are concerns such as

price controls, changes in patent laws, government financing and grants and other legislation that may result from ethical or political issues.

14 In general, price controls and restrictions in health-care reimbursement are opposed by the industry. Many companies typically do not have any products on the market and thus no revenue stream as they research and develop new technologies. Price controls limit investments into the Biotech industry because development and research costs tremendous amounts of capital and is extremely risky. Thus, if the returns are not high, then investors are likely to put their capital in other industries.

15 As biotech companies depend primarily on private investments, patents are extremely important for various reasons. They are benchmarks into the progress of the development of a new product by a company. (1) In addition, they provide limited protection and monopoly profits. Without the protection and monopoly profits, investors would once again be unwilling to take the risks and move into other industries. They are also critical in raising capital to fund research and development of new products.

16 The National Institutes of Health Small Business Innovation Research Program (SBIR) provides substantial capital for start-up and emerging companies in the biotech industry. In 1999, over \$300 million was available through NIH for SBIR grants and the biotech industry received roughly fifty percent of this amount. Phase I grants were typically \$100,000 while Phase II grants received from \$750,000 to \$1.25 million. The Department of Defense, Department of Energy, the EPA, the Department of Agriculture and the National Science Foundation also award SBIR grants to biotech companies. (1)

17 Having looked at some of the background of the biotech industry and legislative issues regarding this industry, we will now look at what startups need to take into consideration as they begin their first steps.

5. What Considerations are involved in a Startup?

18 To investigate what goes into a startup biotech company, it is important to understand the conditions in which biotech companies develop. In addition to legislative issues mentioned above, there are other various factors that must be taken into consideration. This section gives an overview of what the market is like, the drug approval process and ethical considerations.

5.1. The Market

19 First, one must understand the conditions in the biotech market. Often, market enthusiasm in the biotech industry comes in waves. For instance, interest in the biotech markets in the late 80's and early 90's was very high and a great deal of capital poured into the industry. However, that interest died down but was revived again in the mid 90's and again in later 90's. One theory is that venture capitalists are on roughly a three to four year cycle where they invest in various companies at once and receive the returns in three to four years where they once again invest those returns thus creating the cycle. Public enthusiasm is also an important factor. Recently, enthusiasm in the industry resulting from the human genome projects and its potential

has driven the biotech industry but ethical and political considerations brought it back down.

5.2. The Drug Approval Process

20 Essentially, Biotech is one of the riskiest industries. To see why it is so risky, we'll discuss what it takes to market a successful drug. Much of the information concerning the approval process of a drug is from Bill Mann's article "The Life Cycle of a Drug". (2) From the inception of the idea of a drug to moving it to market is a long and treacherous path. Drugs have defined ending dates which are delimited by the expiration of its patent. However, before even that, most drugs do not even make it to market because of various issues. These issues include efficacy, side effects, obsolescence, commercial viability and regulatory scrutiny. (2) Overall, the process of moving a drug to market is grossly expensive and takes a very long time. This causes companies to only select those products that are most effective and likely to succeed. Problematically, the returns on R&D are difficult to track as results do not show up until often more than ten years afterwards.

21 On average, it takes twelve to fifteen years for a drug to make it to market. For certain types of diseases like AIDS and cancer however, there are "fast-tracks" that are pathways that can speed the approval process. Statistically speaking, only one of every thousand compounds that are evaluated even make it to human testing. Of these, only one of every five drugs gets approved. Looking at the time it takes a drug to get approved and the probability of getting a drug approved, the management of R&D at biotech companies is a crucial factor in its success. Before any revenue is seen, companies invest in drugs for over twelve years and even after these investments, its unlikely that they will even a dime will result. Thus, how R&D is managed at a company is very important. Which drugs receive further study, what the possible returns are, what capital gets reinvested in what research, which ones will likely receive approval, etc. are all very important for the survival of a biotech company.

- **Preclinical Testing**

22 During this stage, companies conduct laboratory and animal studies to determine what are the effects of a potential drug. In addition, the safety of the drug is also evaluated. This process takes roughly three-and-a-half to six years. Roughly around this state, a company can patent the drug. As patents are good for 20 years after the application date or 17 years after the issue date, an 11-year approval process will eat up 55% of the time the company can exclusively use a drug.

23 If the results look promising from this state, the company goes ahead and applies for an Investigational New Drug Application from the FDA. At this point, they must include the chemical structure of the drug, how it works and the result of the testing. The results must include toxic side-effects, how future human studies will be performed and how the drug will be manufactured. The FDA has 30 days to evaluate and deny it. If it has not been denied within 30 days, the IND becomes effective.

- **Phase I Clinical Trials**

24 This phase involves somewhere between 20 and 80 healthy volunteers who are sometimes paid for their participation. This phase tests the safety of the drug and the effects it has when it enters the human body. This includes how it is absorbed, processed and excreted. The range of dosage is also determined in this state. This involves measuring the intended effect of the drug and investigating side effects at different dosage levels. These trials generally take from several months to a year. Roughly 70% of drugs that reach this stage pass onto the next stage.

- **Phase II Clinical Trials**

25 This phase involves somewhere between 100 and 300 volunteers. This stage is primarily interested in testing the efficacy of the drug (determine proper dosage is also important). This means the drug is tested for whether it actually does what it is supposed to do. These tests are randomized and the volunteers are normally separated into three categories. The three categories are those that receive the potential drug, those that receive a placebo and those that receive the standard treatment. This test is often blind in that neither the volunteers nor the doctors know who was administered what. This stage should result in information about the safety and efficacy of the new drug and lasts roughly anywhere between several months to two years. About 33% of drugs pass both Phase I and Phase II.

- **Phase III Clinical Trials**

26 This phase involves somewhere between 1000 to 3000 patients from clinics and hospitals. This phase is designed such that the drug can conclusively be proven to work and that it works better than the standard treatment. These studies are also randomized and blind. Patients most indicate side effects that result from the testing and this stage takes roughly three years to complete. During this stage, many "surrogate endpoint" questions, such as whether the drug will improve life span or the overall quality of life, are addressed. 80% of drugs that enter this stage complete it successfully.

27 This last stage is extremely costly to the company. Thus, drugs that have marginal efficacy or have indications of costly side effects are likely to be abandoned after Stage II. These should be abandoned to avoid the expensive Phase III trials.

28 After these tests are completely, the data are compiled and analyzed. If the data support the safety and effectiveness of the drug, an NDA is filed with the FDA.

- **New Drug Application (NDA)**

29 The average review time for an NDA is two-and-a-half years. If the FDA approves the drug, the company has exclusive rights to market the drug under a trademarked name for the rest of the duration of the patent life.

- **Phase IV Studies**

30 This last phase involves collecting any additional information and data from patients after FDA approval. This stage looks primarily at symptoms and side effects.

- **Recalls/Restrictions**

31 Sometimes, various side effects or reactions may result that went undiscovered during the clinical testing. The FDA must deem the reactions excessive compared to the benefits or other available treatments. Often, restrictions will be placed upon the usage of the drug.

32 Overall, after examining the amount of time and costs that go into developing a drug several important conclusions can be made. Companies need excellent R&D management in determining which potential drugs to pursue. (3) Companies cannot blindly pursue potential drugs but after much evaluation must decide whether or not to pursue particular drugs. This involves various aspects of the drug. What problem the drug solves and what is the market for the drug is very important. If the drug is very efficient but solves a very small market or irrelevant market, then companies have to decide whether or not the returns will be great enough to pursue the development of the drug. In addition, the efficacy of the drug needs to be evaluated. How well does the drug solve the problem is very important. Finally, what are the side effects of the drug. If the side effects are enormous, then the potential drug may face problems from FDA approval. Ultimately, the process of bringing a drug to market is a long, expensive and arduous process. Most compounds that are evaluated never even come close to FDA approval. Thus, companies need to know which compounds to pursue and have to be capable in managing their resources.

33 The next section looks at the ethical considerations that must be taken into account.

5.3.Ethical Considerations

34 As witnessed by the human genome companies recently, ethical considerations cannot be ignored. Companies such as Celera and the Human Genome Project are driven by decoding the sequences that make up the human genome and are even patenting these sequences. However, political powers have declared that this information will most likely be made public as no company should really own this information. This has driven their valuations down. More ethical considerations will be discussed later as appropriate.

35 Now that we have looked at various considerations startups must take into account, we will actually look at the initial stages of a biotech startup and exactly what happens during those stages.

6. How do Startups get Started?

36 Essentially, as we have already seen, there are various important factors that a biotech startup needs to take into consideration when starting a company. After taking these factors into

account, how does the process of getting started work?

37 Many startup companies develop as a consequence of certain research that occurs in universities. Universities have relationships with other companies and often receive grants from the government to engage in particular research (for instance, the SBIR grants mentioned previously). Often, students or professors are employed in basic or pure science that may not have any particular applicable value. When possible, applications for patents are filed concerning that research. Depending on the relationship the particular university has with its research staff, their technological licensing office may appropriate the rights to the patent. Often, universities have clauses in their contracts with students that grant them a certain percentage of the royalties that result from the patent.

38 At some point, either the students or someone else realizes the potential applications that can result from the research. At that point, they can continue to develop the technology within the university confines or take their ideas and try to start a company based upon them. In the first case, when something applicable does result, patents are applied for that technology also. From that point, the researchers can license the technology from the university (depending on who has the rights) and then try to start a company. The university is at liberty to license the technology to whom it desires. In most cases, they will attempt to determine whether those seeking the license are capable of accomplishing their goal

39 Students may try to form a team of scientists and managers focusing upon that idea or technology. Sometimes they will present that idea to potential investors in order to receive seed money to purchase licensing rights from the university. From there they can approach venture capitalists. Or they can present the idea to venture capitalists and from that funding purchase licensing rights to the technology. Sometimes the university itself may be involved in bringing students and business managers together to form a team. (3)

40 In essence, the technology is often owned by the university and licensed to the student or the team that will try to develop it further as a company. Often, the instigating individual forms a team of business majors, researchers and research managers as the core of the company. This team will develop the business plan that they will use to seek venture capital. (3) Starting a company in the biotech industry is a very tedious process. As we have seen from above, the risks involved are quite enormous, thus biotech startups undergo greater scrutiny than most other industry startups. At this point, it is important to point out what exactly a biotech company has that is valuable compared to other companies. First of all, a biotech startup does not have any money or resources (compared to the deep pockets of successful companies like Amgen). Its scientists are not any more talented than scientists at other startups. Although they may have some very intelligent scientists, other companies also have very intelligent scientists. They mostly have no market for their product as they usually develop technologies and drugs in new markets. Essentially, they have nothing else but an application for a patent that promises monopoly profits in the far future and some individuals that may or may not be able to carry it to that point. (3)

41 Thus, when viewed from this perspective, the application for the patent and the individuals that are driving the ship are of utmost importance. In essence, the patent application

promises potential monopoly profits in the future. Thus, the patent itself needs to be sound. Although most companies do not capitalize on their very first IP, they attempt to build a suite of patents around it in the hopes for success. (3) Because of their limited resources though, they cannot pursue many other ideas but must keep their focus on this one particular goal. Thus, managing research and development is an important aspect of a startup. A startup company needs to know which projects to discontinue and which projects to further development. Managing relationships with capitalists is also important. However, without the initial promise for those monopoly profits, all the management in the world will not save the company. (3)

42 Thus, as we have seen so far, this is a rough sketch of the initial stages of a biotech startup. The conceptions of the company normally reside within the confines of a research institution such as a university. From that research, either the students or professors take that research and develop a core team of managers and scientists. From there they license the technology from the university and at some point approach venture capitalists for funding.

43 After the initial group of individuals is formed and they have their idea formed, they draw up a business plan. At this point, they have an idea of usage for a particular technology that has been developed, though they may or may not have any licensing rights to it yet. After they have written their business proposal, they take it to find capital to fund their research and development which is discussed in the next section.

44 A quick side note is that our paper does not discuss individual scientists. Although they cannot be ignored, biotechnology is an industry where the complexities and resources involved in the research are incredible and thus not as favorable to the individual researcher (though that is not to say there are none, but we did not come across any). Thus, that is why much of the research is normally done at large institutions such as universities and then licensed from the university.

7. Biotech Funding Environment

45 Once a biotech startup decides to enter the field, one of its foremost concerns is to secure initial funding. This section takes a look at how biotechs secure funding and what are the important factors in their success. It is important for them to understand the cyclical nature of the biotech funding environment in order to pick the right time to enter the market or to do an Initial Public Offering (IPO).

46 It is clear from the figures for 1987 to 1998 that biotech has experienced two fabulously rosy waves of great interest evidenced by large capital investments in this industry in 1991 and in 1996. Up to 1990, biotech had generated little interests on Wall Street and in mainstream America, but the situation dramatically changed in 1991. Several new drugs were coming on to the market while the potential of biotech industry was vastly exaggerated. The combination of these two factors led to the first wave of interests in biotech.

47 Then, three years of dullness in the field followed suit before the second wave of interest rose again spanning from the second half of 1995 into 1996. The third wave of interest not shown in the figure took place just last year, from 1999 to February of 2000. Starting from early

March of 2000, nearly all biotech firms were hit hard in terms of their stock prices, which contributed to nearly 30% of the decrease in NASDAQ.

48 One plausible reason for these periods of retreat in biotech funding is that the news media frequently portrays biotech as an industry that can develop wonder drugs" at an amazingly high pace. As a result, many investors are drawn into the loop. When their patience grows thin on the companies due to the company's inability in realizing these unrealistic expectations, investors just run off with their investment and stay away from the industry until their unpleasant memories fade. Hence, understanding of funding environment is extremely important for biotech startup to maximize their chance of survival and growth in this intensely competitive field.

8. Biotech Funding Sources

49 Now that we have a better understanding of the cyclical nature of the market, we will look at the sources of funding themselves. In terms of funding sources for biotech startups, there are mainly two places to turn to for large capital investments.

50 The first source is from venture capitalists (VC). VCs are people who invest in small startups that they think hold great potentials. The upside for startups is that funding from VCs is usually fairly large, ranging from one million USDs to ten million USDs. The funding enables startups to purchase the necessary equipment and materials to start research and development from just an idea in the mind or a patent sitting on a piece of paper. This funding also allows startups to hire enough highly motivated people to reach a critical mass. However, VCs generally also place several fairly stringent limitations on the startup company to protect their investments. Some of these demands from the VCs include taking a stake in the companies' equity (ranging widely depending on VC, but could reach well beyond 50%) as well as having the final say on how the company should be run, who should be running the company and so on.

51 The second source of funding for biotech startups is through collaboration, or alliance (6), with large, established pharmaceutical companies (pharmas). Because, these startups are usually limited by funding, it is almost impossible for them to take their product all the way to the market. They will have to rely on big pharmaceutical companies' resources and expertise in going through animal testings, human clinical trials (Phase I, Phase II a and b, Phase III), filing for FDA approval, and finally, sales and marketing of the drugs to physicians and the general public. Usually, big pharmas will invest millions of dollars in their biotech partner to get them off the ground and to churn out products as quickly as possible. The downside however is mainly two fold. First, these big pharmas will also demand an equity share of the biotech startup, leaving significantly less equity available to the executives to attract highly competent people. In addition, lawsuits are frequently involved between the big pharmas and small biotech startups. Several big, well-established biotech companies today, such as Amgen and Biogen, all litigated with their pharmaceutical industry partners. Litigation can take a huge toll on biotech startups since they have to divert their valuable capitals for non-research oriented activities. Despite of these downfalls, biotech startups do frequently collaborate with big pharmas.

52 Three examples are given below. The first one is the partnership between Sonus

Pharmaceuticals and Abbott Laboratories. Sonus's first product, the fluorocarbon-based ultrasound contrast agent, has gained marketing approval due to the marketing efforts of Abbott Labs. The second example shows the collaboration between GelTex and Chugai Pharmaceutical, a leading drug company in Japan. When GelTex completed its IPO in November 1995, its non-absorbed polymer hydrogel-based-drug, used to treat patients with end-stage renal disease by reducing their serum phosphorus level, was in Phase II of human clinical trial. Since GelTex wanted to break into the Japanese market, it was reasonable for them to enter into an agreement with a Japanese firm. Chugai Pharmaceutical then agreed to develop, sell and market the product in Japan and in the Pacific Rim. The last example shows the partnership between Pharmacoepia and Schering-Plough. Pharmacoepia was one of the first combinatorial chemistry companies to specialize in using combinatorial chemistry to vastly boost the pace of new drug discovery. This area was red-hot in 1995 and major drug companies were keenly interested in it. This collaboration turned out to be a very positive experience for Pharmacoepia as it still manages to maintain pre-eminence in the field. They used their proprietary technology to create libraries of custom-designed compounds for their partners, which they then leased to those partners.

53 Thus, the two major sources of funding for biotechs are VC's and big pharmaceutical companies. VC's normally provide substantial financial assistance along with help in management and coordination. Big pharmaceutical companies provide a wide range of assistance as they view startups somewhat as research bouquets. (3). Along with these two major sources are other sources that are not as significant. Angel investors also provide funding in a very similar manner to VC's. In addition, startups can apply for grants, such as the SBIR grants mentioned above, from the government to fund their research.

54 Now that we have looked at the sources, we will discuss the importance patents play when startups approach their funding sources.

9. Importance of Patents for Biotech Startups

55 Securing funding from either venture capitalists or large pharmaceutical companies is by no means trivial and straightforward. Biotech startups have to tell their potential investors a very attractive and appealing story in order to draw their interests. The most important factor in this story is what proprietary information (mainly patents) the companies have in order to gain an edge or a niche over their competitors. Hence, the role patents play in obtaining funding and launching biotech startups is nothing less than instrumental. It is fair to say that patents are the cornerstones of biotech startups and they can make or break a young, fledgling company.

56 Most of these biotech startups hold less than five patents and their core business evolves around their patents. For example, Exelixis (12) has only one patent it licensed from Carnegie Institute; it was a patented gene called P-element from *Drosophila*, a geneticist's favorite fruit fly. The company was able to manufacture and market their product based on just this one patent and recently grew to be a company with annual revenue of \$230 million. This is merely one example of how biotech startups survive and thrive. These startups obtain patents via three venues, namely, companies' own inventions, licensing from universities or other companies and acquisition by acquiring other companies. Although they initially startup with some IP, they will continue to build a suite of patents around that initial IP using these methods. As they grow and

mature, they will continue to use these methods to get more IP. Most of these patents are in very specific fields and treat specific diseases with smaller markets. However, profit margins of these specialty drugs are very high due to lack of alternative drugs in the same field.

57 A typical biotech patent takes about 3-5 years to obtain a patent from start to finish. Companies usually file for patents during the very early stage of development. There are both pros and cons for doing this. The pros for doing this is that companies can secure their market share and capitalization as well as discourage any competition in the early stage. However, they will also lose a couple of years of the patent life of their drugs. Despite drawbacks from filing patents early, all companies file for their patents in the initial development stage to protect them from other competition.

58 Patents are an instrumental part of the biotech startups' portfolio that is presented to the venture capitalists. These startups need to convince VCs that their ideas, based on patents, give them an edge over all of their competitors. In addition, startups have to paint a rosy picture to show VCs great returns on their investments. During our research for this project, we contacted hundreds of biotech companies, some startups and some established, to ask them whether they could survive without patents when they are at startup phase. Of those that responded, the answer we got back was a unanimously "NO". Some of the companies we contacted include MBG Tech, Mosaic Tech, Enzyme Systems Products and Bio Transplant. The complete list of companies who responded to our survey can be found at <http://plu.mit.edu/6.931/>.

59 In addition, patents for biotech startups serve two other functions. First, patents help companies secure an initial clientele base by presenting the uniqueness of their products. Second, patents serve as a competitive barrier of entry into the same field. As mentioned earlier, small biotech startups usually focus on specific drugs for specific diseases. Since the markets for these diseases are fairly small, it is imperative for them to have a dominant position in their respective fields.

60 Therefore, patents play a pivotal role in startup companies and their ability to receive funding. Ultimately, investors are gambling on the company's future potential for profits. The only way to receive high profits for such a risky business is through monopoly profits, and patents secure these monopoly profits. Next, we will take a look at the business models in which startups are engaged.

10. Business Models

61 Once biotech startups obtained their patents and secured their VC funding, how they want to capitalize on their patents depends on the business model of various companies. In general, business model can be broken down into two main categories. They are the model followed by pharmaceutical and therapeutic biotech companies and the model followed by genomics and genetics biotech companies. In the former case, companies focus their research and development around their core patents and try to develop more ensuing patents. The genetics case is a newer breed of biotech companies that take the shotgun approach towards patents and attempt to patent almost everything in sight.

62 First we will take a look at the more traditional biotech companies that focus on a suite of core patents. These companies are the ones who target specific diseases with smaller markets. A few examples of this type of companies which became successful include Genentech, Amgen, Biogen and Chiron.

63 In the case of Amgen (4), it was founded in Thousand Oaks, Ca, in 1980. It has three main products on the market today. They are EPOGEN, NEUPOGEN and INFERGEN. EPOGEN stimulates and regulates the production of red blood cells. Amgen received its first patent on the DNA used in producing EPOGEN in October 1987. This product received marketing clearance from FDA for the treatment of anemia associated with chronic renal failure in 1989. NEUPOGEN is a recombinant granulocyte colony-stimulating factor (G-CSF) that selectively stimulates the growth of infection-fighting white blood cells known as neutrophils. Amgen received its first U.S. patent for recombinant G-CSF in March 1989. NEUPOGEN received marketing clearance in the U.S. from the FDA in February 1991 for broad use in the cancer chemotherapy setting to decrease the incidence of infection associated with some forms of chemotherapy. In June 1994, NEUPOGEN was licensed for use in conjunction with bone marrow transplantation to reduce the incidence of neutropenia, and in December of that same year, for chronic administration to treat severe chronic neutropenia. INFERGEN is a bioengineered non-naturally occurring type 1 interferon used to treat chronic hepatitis C viral (HCV) infection. It received marketing clearance from FDA in October 1997. Thus, as seen from this example, companies may choose to build a suite of patents around their core patent or idea and from their continue developing other patents and ideas depending on their funding.

64 However, the recent boom in the Human Genome Project resulted in a different business model for biotech companies. For companies like Celera or Human Genome Science, they are in the business of rapidly mapping the entire human genome. Along the way, thousands of patents were issued in the fields of specific genes and methods of identifying certain genes. Celera, for example, strives to become the definitive source of genomics, proteomic and related biological and medical information. Celera uses this information for an integrated information and discovery system available to researchers in pharmaceutical, biotechnology, and academic institutions on a subscription basis. The discovery and information system includes software tools that provide the ability to view, browse and analyze this information in an integrated way to facilitate discovery. Celera also offers a variety of services to customers to assist in the analysis and interpretation of the data. Currently, Celera is developing new databases and services in the emerging fields of functional genomics proteomics. Their information, along with related services and tools, will enable researchers throughout the world in their efforts to improve our understanding of the biological world, the human body, and to accelerate improvements in health care. In this case, they are competing with other companies to map the human genome and are trying 10 patent everything in site. Often, they do not have a specific application for the genetic sequences they are patenting but are taking a shot gun approach instead. In addition, future political intervention may hurt their current endeavors, thus, their patents may not be as essential as the previous business model.

65 In conclusion, it is imperative for the biotech startups to understand the funding environment in the field to maximize their chance of survival and growth. Patents are vital to these startups as they can help carve out a market for these company to survive and thrive.

66 The next section takes a look at biotech companies after they have been developing their patents for sometime and need to protect their IP against infringers. As biotech companies grow and mature, patents also play as important a role as they did during their startup stages. In the startup stages, patents were pivotal in getting the company formed and securing funding. As biotech companies develop, they become important in maintaining profits and preventing infringement and abuse by other companies.

11. Protecting the Patent

67 As biotech companies grow, much of their progress is based on exclusive access to proprietary technology. The patents that they develop and acquire in the early stages of starting the company are crucial to the company's continued success. In order to maintain a patent's legitimacy, a company must police other companies to make sure that the patent is not being infringed upon. In addition to actively policing others, a company may have to defend its own patents from claims of invalidity. All of this requires extensive and costly litigation. In addition to litigating, public relations will also become critically important, as ethical considerations may also play a role in the granting of biotech patents.

11.1 To Sue or not to Sue

68 Many biotech companies find themselves in a quandary when they discover that other companies are illegally using their technology. Clearly, preventing competition from stealing technology is important to any company's survival; however, prohibitively expensive legal fees are required to bring the offenders to justice. This requires companies to make case by case decisions to determine if the extent of the damage caused by an infringement is worth the legal fees to seek restitution.

69 Some of the companies surveyed indicated that policing and litigation were worthwhile. Enzymes Systems Products indicated in the survey that they have successfully litigated over patented technology. The results were that the violator ceased manufacturing their product. Such success can effectively eliminate competition and allow a company to maintain a strong hold on market share.

70 Amgen, a global biotech company focusing on secreted protein therapeutics, is also in the midst of a lawsuit against Transkaryotic Therapies Inc. (Tkt). Amgen alleges that TKT has infringed on Amgen's patents that claim an erythropoietin product and processes for making erythropoietin. Both Amgen and TKT are large, well-funded companies with significant revenue at stake over the patents. Despite being expensive, the cost of litigation is warranted in this case since Amgen only has three major products and one of them is threatened. If successful, Amgen may drive away Tkt, currently a major competitor.

71 Even universities in combination with biotech companies have seen success pursuing patent infringement cases. Johns Hopkins licensed technology to biotech companies and reaped the reward when a jury awarded \$2.3 million to Johns Hopkins University, Baxter HealthCare Corp. and Becton Dickinson & Co., finding that defendant CellPro Inc. had willfully infringed

on two Johns Hopkins biotechnology patents. One of these patents covered monoclonal antibodies used in bone marrow transplants, a cancer treatment. Cell Pro had previously tried to prove that the patents were invalid but a court dismissed their case in 1993. CellPro continued to use patented technology without a license despite the dismissal, and the \$2.3 million dollar loss was the result. CellPro is appealing on the basis that current cancer patients are depending on access to CellPro's FDA approved technology, whereas Baxter's competing technology has not yet received approval. If Johns Hopkins and Baxter had not gone to court, CellPro could be profiting through a deliberate abuse of patented technology.

72 The remainder of the companies, a strong majority of those surveyed, either has not litigated or prefers not to litigate. The costs are so prohibitive that even guaranteed success does not necessarily provide substantial cause for litigation. As MBG Technologies indicated in the survey, a typical minimum expected profit for defending a patent would be \$500K. This means that the infringement must generate approximately \$10 million in revenue in order to provide enough incentive for going to court. With such a high cost of litigation, it makes sense for companies to find an alternative solution. Two companies, Medarex and Abgenix, have found a compromise. They both produce cutting-edge technology that enables the rapid and inexpensive generation of high-affinity, fully human antibodies through the use of transgenic mice that have

human antibody genes rather than mouse antibody genes. With so many similarities, the companies often found themselves in legal battles over intellectual property rights and patents. Instead of continued litigation, they thrive on the use of cross-licensing their patents, which has effectively resulted in a "duopoly" of the market. They essentially share the market and drive out all other competition instead of allowing competition to grow as they trap themselves in legal battles. Sometimes, litigation is not even an option. Celera, a well-known biotech company leading the way in discovering the human genetic code, is obtaining patents for the discovery processes and the code itself. It plans to license the information to other pharmaceutical, genetic, and biotech research companies. However, the United States government, also on pace to discover the entire human genome, will make all the information publicly available. Though Celera may discover it first and have legal rights to the patent, it is essentially nullified if the government makes all the information freely available.

11.2 Defending The Patent

73 Aside from actively policing other companies, biotech companies must be ready to protect themselves from attacks on their patents' validity. Even dominant market shares are no protection from any little company that wishes to enter the market by challenging the larger company's patents. One company in the survey, which wished to remain anonymous, complained that any patent, no matter how long it has been standing, can be challenged even by the most outlandish statements and by falsified data and dates. The result of one such challenge was a seven-figure lawsuit. Despite the company's success in court, the plaintiff was penniless and so the company had to absorb all the costs. IDEXX, a biotech company specializing in veterinary products and services, particularly immunoassay kits and veterinary drug development, has a dominant share of their market. However, IDEXX has experienced legal trouble due to its extreme success in driving out all competition. They have endured accusations that they take unfair advantage of their monopoly. CDC Technologies has complained that IDEXX's dominance is based on exploiting its exclusive dealing agreements, which violates the Sherman Act and Clayton Act. The court ruled in favor of IDEXX, but repeated claims against IDEXX continually drain the company of revenue. One well-known lawsuit currently in the courts is between biotech companies Promega and Hoffman-La Roche. The controversy surrounds the use of Taq polymerase in the process of Polymerase Chain Reaction (PCR), a significant invention that makes it possible to take a small amount of DNA and make many copies of it. Kary Mullis of Cetus Pharmaceuticals had developed PCR and received the patent in 1989. In 1990, Cetus granted a license to Promega Corporation to sell Taq for uses other than PCR. In 1992, Hoffman-La Roche purchased the rights to the use of Taq polymerase for PCR, including all licenses, from Cetus. Hoffman-La Roche then sued Promega for breach of contract, alleging that they were using the license to sell Taq for the use of PCR. In an effort to keep a tight hold on its patents and licenses, Hoffman-La Roche may have created more trouble than it had before. Promega filed a counter-suit, which challenged the validity of the patent on using Taq in PCR. Courts found that Cetus had withheld information when applying for the patent and have yet to determine its validity. Hoffman-La Roche has forced itself into a position where it must defend its patent, a patent for which it paid a high price.

74 Another company participating in the survey, Protein Polymer Technologies, has never appealed any ruling but has endured an interference proceeding in which two other companies

claimed an overlapping invention with the same priority date. PPT proved its case by revealing lab notebooks that indicated they had conceived and reduced the invention to practice first. As a result of winning the proceeding, no litigation was necessary. However, tens of thousands of dollars were spent on patent counsel for the interference proceeding alone.

11.3 Ethical Considerations

75 An issue that some biotech companies may have to deal with in the near future is public opinion of the ethics involved in current biotechnology. Although many biotech companies sell to research labs rather than selling directly to consumers, some pharmaceutical and genetics companies have raised concerns in the public sector. The media has expressed concerns that many people have regarding the patenting of human DNA. The patenting of human DNA raises fundamental ethical questions about how much DNA truly defines an individual and if an individual has the right to own their own DNA. In light of recent protests against the World Trade Organization (WTO) and other organizations attempting to control matters on a global scale, individualism may have an impact on how much ownership corporations will be allowed.

76 Already, the global arena is affecting corporate biotech patents. The Coordination of the Indigenous Organizations of the Amazon Basin (COICA) had its fifth General Convention during which it complained about the presence of US biopirate pharmaceutical laboratories on their territory. US labs have already obtained patents for ayahuasca, "una de gato", and "sangre de drago", which are all medicinal plants that the South American tribes have been using for generations. Negative publicity about such piracy may ultimately be detrimental to the leniency corporations have been given in receiving patents.

77 In March 2000, US President Clinton and British Prime Minister Blair issued a joint statement calling for free access to information on the human genome. Although such a decision does not necessarily fall under their jurisdiction, it may affect those who do have control over patents. The main concern is that the betterment of human health must be of primary importance, rather than the profits of research. Some American physicians are already concerned that patents and exorbitant licensing fees will prevent physicians and clinical laboratories from performing genetic tests and limit access to medical care. This would jeopardize the quality of medical care and unreasonably raise its cost.

78 For example, labs in Massachusetts are experiencing trouble with performing tests for diagnosing Alzheimer's disease because Athena Diagnostics has exclusive rights to the test. Athena Diagnostics has written letters to labs informing them that testing anywhere else would infringe the patent, but they would perform the test for a \$195 fee per sample. Since that is twice the price previously given by university medical labs, some researchers who operate on government grants and need hundreds of samples tested can no longer afford to have the tests done. Similarly, Myriad Genetics has acquired exclusive licenses based on patents for genes linked to breast and ovarian cancer and has sent out letters to labs, ordering them to stop screening women for the mutations (Borger 1999). With practices that clearly interfere with quality health care, social and political reprisal against biotech patents may be impending. Biotech companies will need to be prepared for all possible threats to their patents, whether it comes from other companies, or negative publicity generated by questionable business practices.

79 In this middle stage, it is important for biotech companies to understand that the battle for patents is not over. The development and acquisition of patents is only the first step as competitors will infringe upon and seek to invalidate these hard fought patents. Knowing when to litigate, when to compromise, and when to buyout competition can be key to surviving in the long run.

80 Now that we have looked at biotech companies in their maturation process and the role patents play there, we will take a look at companies that make it and become successful. How do these companies become successful and why are they successful?

12. Successful Companies

12.1 Background

81 In a brief yet informative timeline of biotechnology companies, Access Excellence [20] gives a rather accurate description of how the biotechnology companies came about:

"Genetic engineering became a reality when a man-made gene was used to manufacture a human protein in a bacteria for the first time. Biotech companies and universities were off to the races, and the world would never be the same again. In 1978, in the laboratory of Herbert Boyer at the University of California at San Francisco, a synthetic version of the human insulin gene was constructed and inserted into the bacterium Escheria coli. Since that key moment, the trickle of biotechnological developments has become a torrent of diagnostic and therapeutic tools, accompanied by ever faster and more powerful DNA sequencing and cloning techniques."

As we can see from this quote, biotech companies have only been around for slightly more than twenty years. Most of the companies base their survival on the products they produce. For the successful companies, receiving patents for their products are the most essential component of success.

82 In the following sections, the paper will discuss particular case studies of successful companies such as Millenium Pharmaceuticals, Genentech, Biogen, and Amgen. The paper will include a brief introduction to each company, product(s) in which the company hold the patents for, and what are the reasons for their success.

12.2 Case Study 1 - Millennium Pharmaceuticals [21]

83 Millennium Pharmaceuticals, Inc was founded in 1993. The company seeks United States and international patent protection for the genes, proteins, and drug leads it discovers, as well as therapeutic and diagnostic products and processes, drug screening methodologies and other inventions based on such genes, proteins and drug leads.

84 Currently, Millennium has not received any revenue from the sale of any products.

However, they derive substantially all of their revenue from strategic alliances with major pharmaceutical and biotechnology companies. They also receive United States government research grants. As of September of 1999, Millennium and its subsidiaries had more than 500 pending U.S. and international patent applications and forty-four issued U.S. patents.

85 From studying their financial information, we see that the money they place into Research and Development is as high as their revenue.

12.3 Case Study 2 - Genentech [22]

86 Genentech, Inc. is a leading biotechnology company using human genetic information to develop, manufacture and market pharmaceuticals that address significant unmet medical needs. As early as 1977, Genentech has made remarkable progress in the field of biotechnology. In 1977, Genentech reports the production of the first human protein manufactured in bacteria, somatostatin, a human growth hormone-releasing inhibitory factor. For the first time, a synthetic, recombinant gene was used to clone a protein. Many consider this to be the advent of the Age of Biotechnology.

87 Genentech currently manufactures and markets seven products in the United States: Protopin, Nutropin, Nutropin AQ, Activase, Pulmozyme, Rituxan and Herceptin. They are preparing to launch their eighth product, Nutropin Depot.

88 The success of Genentech can be seen from its financial profile. In 1999, there was a 45% increase in sales and 33% increase in earnings over 1998. We can also see that Genentech reinvested approximately 26% of its revenue into research and development.

12.4 Case Study 3 - Biogen [23]

89 Biogen, Inc. is a biopharmaceutical company principally engaged in the business of developing, manufacturing and marketing drugs for human health care. The interesting fact about Biogen is that its existence depends on one patent (AVONEX, which was introduced in 1996).

90 Biogen currently derives its revenues from the sales of AVONEX (Interferon beta-1a). AVONEX is used in the treatment of relapsing forms of multiple sclerosis. Biogen also receives revenues from royalties on worldwide sales by the company's licensees of a number of products covered under patents controlled by the company, including alpha interferon and hepatitis B vaccines and diagnostic products.

91 Biogen knows that it is in a very unsafe situation due to the fact that they only have one viable patent. The company's 5 long-term viability and growth will depend solely on the successful development and commercialization of other products from its research activities and collaborations. This is also the reason that 28% of the company's revenue goes into research and development.

12.5 Case Study 4 - Amgen [24]

92 Amgen Inc. is a global biotechnology company that discovers, develops, manufactures and markets human therapeutics based on advances in cellular biology. It manufactures, markets, and holds the patents for four human therapeutic products, EPOGEN, NEUPOGEN, INFERGEN, and STEMGEN.

93 From the studying of the company's financial data, we see that 25% of its revenue goes into research and development.

12.6 Reasons for their successes

94 From the case studies above, we can draw some general conclusions about the major factors that make a biotech company successful. The factors are as follow:

- They must be able to obtain and maintain necessary patents and licenses.
- They must demonstrate safety and efficacy of drug candidates at each stage of the clinical trial process.
- The must be able to meet applicable regulatory standards and to receive required regulatory approvals (from FDA).
- The must be capable of producing drug candidates in commercial quantities at reasonable costs.
- They must be able to compete successfully against other products. They must market products successfully.

95 On top of these factors, they must also constantly expand their development efforts related to other potential products in its pipeline. Methods of doing this include increasing spending on internal projects, acquisition of third party technologies or products, and other types of investments. Biotech companies have a higher R&D expenditure ratio than almost any other industry. From this, we know that they are heavily engaged in developing new IP and are actively engaged in protecting it also. Although increasing spending on internal projects seems to be the most effective answer to expanding developmental efforts, the company also needs to be concerned with the fact that product development involves a high degree of risk. From examples of many companies, only a small number of research and development programs actually result in the commercialization of a product. Which means that success in pre-clinical and early clinical trials does not ensure that later stage or large scale clinical trials will be successful (refer to Figure 1 below).

Figure 1: Product Development Pipeline

Research	Pre-Clinical	Clinical Trials (Phase I, II, III) Depending on the company	Preparing Regulatory Filings	Awaiting Approval	On the Market
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13. Survey Results

96 During the research of biotech companies, we were able to get 16 biotech companies from all over the world to fill out our surveys. The web based version of the survey results can be found at <http://Dlu.mit.edu/6.931/>

97 In the survey, we have asked the following questions relating to patents and the most common results we receive. Please refer to the web for the complete survey results.

13.1 During what stage were patents acquired?

98 Most of the companies acquire their patents during the development phase. Also, most of the companies agree that acquiring patents is an on-going process.

13.2 What effect did they have on the company growth? on VC funding?

99 The majority of the companies feel that patents were responsible for their initial funding, and their protection position convinced VCs of the application and exclusivity of their technologies

13.3 How long did it take to get patents? Did delay affect growth and allow for competition?

100 This answer ranges from one year to five years.

13.4 Have there been any cases of litigation over the patent? What were the costs and the results?

101 Since most of the companies we surveyed were startup companies, the majority answered no. However, we were privileged to get a response from a pretty large biotech company, Transkaryotic Therapies, Inc. They are currently involved in litigation with Amgen over their Gene-Activated EPO.

13.5 Could the company survive without patents?

102 The unanimous agreement here is no. Patent portfolio is critical to attracting corporate partners and investors.

103 As we can see from the result of the surveys, patents play a pivotal part in the formation and survival of a biotech company. They are normally acquired in the very early stages of the biotech's companies life as they are responsible for funding from various sources. Most startups are not engaged in litigation however as they do not have the funds and are usually in a very new field where there are no other companies to litigate with. Finally, there was an overwhelming response that indicated that they could not survive without the patents that grant them protection against other companies.

14. Conclusions

104 To understand the role of patents in biotech companies, we looked at various aspects of a biotech company's life cycle and examined where and how patents were crucial in its success. Overall, we concluded that patents are essential for the success of biotech companies. We first looked at the early stages of a company and how patents are important for receiving funding as they provide the future promise of monopoly profits in a very volatile and risky industry. As the company develops, it builds a suite of patents around their initial idea and patent but they have primarily one focus due to the lack of resources. As their technology becomes more successful or starts bringing in revenues, they can use that capital to pursue other technologies. We then looked at the protection of a company's IP. Sometimes they may need to litigate against other companies that are infringing on their patents and offend need to defend their own patents also. Finally, we looked at successful companies and what they had in common in respect to patents.

105 In conclusion, patents are the cornerstone for biotech companies and are essential for their survival. Without the promise of the monopoly profits in the future, biotech companies cannot get off the ground or protect themselves later in their life cycle. Thus, they must pursue and protect their IP vigilantly.

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