SOLUTIONS FOR CHALLENGES MEDICAL ENTREPRENEURS FACE WHEN CREATING BIOTECHNOLOGY STARTUPS

Presented by Yuqing Xiong

in partial fulfillment of the requirements for completion of the
Evidence and Inquiry certificate, the
Polymathic Scholars honors program in the College of Natural Sciences, and
Plan II Honors Program at
The University of Texas at Austin

Spring 2017

_____

Jonathan Sessler, Ph.D. Date
Supervising Professor
Department of Chemistry

_____

Rebecca A. Wilcox, Ph.D. Date
Second Reader
Honors Center, College of Natural Sciences

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Yuqing Xiong Date

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Jonathan Sessler, Ph.D. Date
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Department of Chemistry

Acknowledgements

I would like to express my appreciation for Dr. Jonathan Sessler,
for his mentorship and encouragement throughout my thesis project.

I would also like to express my gratitude for Madison Searle, for
guiding me through my undergraduate career leading up to this thesis.

I am grateful for the guidance and encouragement given to me by Dr. Rebecca Wilcox.

Finally, I would like to thank my parents, Shunbin Xiong and Liangzhen Zhu, for
providing me with the support and opportunity to be where I am.

Abstract

Many obstacles impede the success of biotechnology startups. The Food and Drug Administration's (FDA) clinical trials is one of the primary challenges. The FDA currently imposes rigorous standards before a biotechnology company's product is approved for dissemination to the public. A result of FDA standards is a costly 7.5-year average product development pipeline that hinders companies, already limited in cash and resources, from quickly generating steady streams of income to sustain their businesses. After a literature review, several important areas of focus were highlighted by individuals who successfully started biotechnology companies or have expertise in the area. They advocated best-practice policies in areas for securing funding, navigating the FDA's clinical trials, utilizing local resources, and testing products. In addition, a case study was conducted on a Texas-based biotechnology company called Mirna Therapeutics Inc., to highlight some of the best-practices endorsed from literature, as well as to show their limitations. This research could potentially foster a new way of looking at biotechnology startups and provide insightful techniques which entrepreneurs could utilize for their current or future businesses in the field.

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Introduction

With the rise in the number of startups across the U.S., it is little wonder that this expansion has reached the healthcare industry as well. Naturally, many people equate startups with small businesses or corporations. However, in reality, startups have unique attributes that differentiate themselves from small businesses and corporations. They are also comprised of individuals seeking to create new value with scarce resources in high-risk situations. Startups working with biotechnology have additional high-risks associated with them since they work with the human body. However, they offer innovation, job growth, and a reduction of healthcare costs. Their biggest problem is the ability to transition from an idea to a startup and finally to a sustainable business. In order to do so, biotechnology startups must face multiple obstacles such as raising money to do research and development, conducting numerous lab testing, and passing the Food and Drug Administration's stringent clinical trials by performing human subject testing before marketing their product.

This thesis will be discussing the issues surrounding fledgling biotechnology startups and how these seemingly insurmountable obstacles lead many medical entrepreneurs to fail in their attempts to create a sustainable business. A literature review on the subject will be presented from those whom have succeeded in creating biotechnology companies to shed light on the best-practices advised by experts in the field. These best-practice protocols will be applied to the Austin Texas based company, Mirna Therapeutics Inc., to not only highlight their merit but also showcase their limitations.

The Formation, Logistic, and Importance of Startups

The line between a startup and a small business or corporation can become blurred; both have few employees and are for-profit. Upon closer inspection, startups have unique attributes to their nature. Startups differ in the characteristics of the people working in them and the nature of their business models. Academics have defined startups as a group of individuals who are trying to create new value with scarce resources in high-risk situations (Beverley). These individuals engage in entrepreneurship, a creative destruction process of new goods and services, markets, improved production processes, and organizational structures, leading to competitive barriers and economic profit (Montanye 7). Entrepreneurs in a startup are also seen as individuals who specialize in taking "judgmental decisions about the coordination of scarce resources while engaging in creative destruction" (Casson 19-20). They see a need to be filled in the market and take the risk of creating something to meet that void (Beverley). Usually, the formation of such a group is due to the recognition of a problem, whether personal or societal, in the market place that they believe can and need to be addressed by them.

The second difference between the two business entities is in their predictability. Whereas traditional small business owners and corporations have businesses which are usually run with relatively smaller risks and a constant, steady stream of revenue, startup founders are operating with little ability to see where their next source of revenue will be coming from. The business model of a startup is starkly different from others. Most academics would agree that startup is a phase of the future business or a "temporary organization used to search for a repeatable and scalable business model" (Blank). A startup is not an ongoing business that lasts for years, rather, it is a stage in which the business either attempts to "grow up" and become a company or fails to do so and dies (Beverley). It attempts to "grow up" in risky and not well

understood market conditions. During this phase, it tries to establish a business model or strategy to stabilize its source of revenue and continues to find ways to scale the business. However, because of the limited resources at the startup's disposal, many will fail and die before becoming companies.

Many startups fail because of their inability to secure capital or funding from investors (Tsai and Erikson 49). If it cannot secure funding, the startup will not be able to acquire initial adopters or early customers to test their product or service. Some may not have the funds to even produce their idea. However, sometimes a startup does not fail due to their inability to secure initial funding, but rather on the basis of what their future company is premised upon or what hypotheses are made about the business.

Many startups have adopted a lean approach by becoming what are called "lean startups." These companies minimize their initial need for capital by manufacturing their idea or service in the most efficient and crude way possible in the hopes of putting their idea out into the market as fast as possible (Ries 45). These startups are built upon three guiding principles or hypotheses that dictate the foundations of their business. These hypotheses include problem, value, and growth (Ries 64). When these hypotheses are not validated by the entrepreneurs, their entire startup business could falter and subsume substantial losses in time and resources, which could ultimately lead to failure.

The problem hypothesis is the assumption entrepreneurs have that there is a problem in the market place, also known as its market niche, in which the startup will fill. The problem is usually from their potential customers. Entrepreneurs in lean startups are advised to reach out to their potential customers for their business models and solicit information firsthand by asking if the assumed problem exists. If the consumers do have a problem, then the entrepreneurs are said

to have validated their problem hypothesis for their business. Many startup founders neglect the importance of asking their potential customers if they actually have the problem. Entrepreneurs can potentially become engrossed in the process of creating a service or product that looks polished and refined but does not actually solve the problem or there was no problem in the first place. This leads to the production of unnecessary features and, in the worst case, an unwanted product. Because of the time, money, and energy placed into producing such a product or service, the startup may not have the necessary resources in their already scarce arsenal to survive through the loss. Morale would also be low, leading to higher tensions and potential failure of the fledgling startup.

The second hypothesis is the value hypothesis. In this hypothesis, entrepreneurs are now positing that the problem they have identified actually has value in it, meaning the customers or consumers with the problem are actually willing to pay for their problem to be solved by the entrepreneurs. Similar to the first hypothesis, entrepreneurs who do not validate this hypothesis will accrue heavy losses by producing a product or service that consumers will not necessarily pay for. With no streams of revenue to support or keep the startup afloat, it will quickly fail. As one professor with experience in multiple startups puts it, "cash is king" and the blood or life support of a startup (Beverley). Validation of the second hypothesis is a bit trickier than the first. Customers who say they will pay for the startup's service or product upfront may not actually pay when the product or service is delivered to them. Rather, they may be reluctant to pull out their wallets. One way to offset this, which many lean startups have begun testing, is the use of an MVP or minimal viable product (Ries 96). The MVP is the most basic form of the idea with little features and add-ons, thus requiring the least amount of resource, energy, and time to build. Entrepreneurs then target their MVP at their potential customers and observe whether or not they

are willing to purchase the MVP while collecting consumer feedback. Based on the feedback collected, entrepreneurs use the information they learned, called validated learning, to iterate on or modify their MVP and create the product or service that the customers actually want and are willing to pay for (Ries 99).

The final hypothesis, the growth hypothesis, hinges upon the continual iteration of the MVP by entrepreneurs. During this process, entrepreneurs are constantly looking for ways to acquire more customers and grow their customer base. In this hypothesis, the founders are testing and validating which engine of growth will allow their startup to accelerate the most in size. Without finding a suitable engine of growth for the startup, the business model is not scalable. These engines of growth can either be sticky, meaning it has low attrition rates, viral, word-of-mouth, or a few others. For example, the viral engine of growth is built on the premise that the product or service will become very attractive to potential customers based on its popularity with initial adopters. This will potentially lead to streams of people who will flock to use the new product or service. The exponential growth of tech companies, like Facebook, highlight the growth ability of the viral engine. Once the company has successfully achieved and sustained growth and revenue, it is usually no longer called a startup (Hall).

Startups also play a large, important role in the economy. Entrepreneurs create wealth through new services or products which foster economic growth through their startup companies (Kolympiris 227). These startups help generate economic growth by creating more jobs in the economy, accounting for up to 50% of new jobs created in 2016 (Fetsch). In addition, startups provide new services and products to the public that meet needs and improve quality of life while generating huge amounts of revenue. As a result, they also bring in tax revenue for the local area since companies are obligated to pay taxes. For example, the Austin Technology Incubator (ATI)

was able to produce more than $20 million in local tax revenue from 2003 to 2012 (UT News). At the same time, the incubator, a workplace for startup companies, was able to generate $880 million in economic output and created 6,520 jobs in the area. In 2015, due to the rising number of startups located in Austin, the number of dollars invested in Austin was $911.3 million. The number of incubators, institutions which provide the infrastructures, people, and resources for entrepreneurs to get started, have increased to 46 (Austin Chamber of Commerce). While many of these benefits are relevant to almost all startup companies, biotechnology startup companies have a few extra benefits and disadvantages that are unique to them—the topic of the next section.

The Biotech Company

A. An Overview of a biotechnology company

In general, biotechnology startup companies are very similar to other startups. They address a need in the market. However, as the name implies, their market focuses specifically in healthcare and medicine. Startups working with biotechnology deal with high-risks due to the inherent challenges of working with the human body (Tsai and Erickson 50). These companies try to develop new solutions to tackle health issues or provide novel technologies to expedite treatment and efficiency within the healthcare system. In theory, the benefits these startups provide to the economy are tremendous, as they stir innovation, create new jobs, and reduce healthcare costs.

While the problem and value hypotheses are evident, as there are a multitude of problems in healthcare currently and huge amounts being spent in the industry, the hardest one is sustainable growth (Grohn 67). In order to transition into a sustainable business, the startup must pass the FDA clinical trials, an extensive quality check on their product, before it is released into the public for use.

Once a biotechnology company starts growing, the amount of benefits it generates include: economic growth, local revenue, goods and services for the public, new jobs and wealth, and many others.

B. Exclusive Benefits from Biotechnology Companies

One important aspect of startup biotechnology companies is their ability to reduce healthcare costs in a number of ways. Entrepreneurs, by their nature, look for new, creative solutions to existing problems. They help tackle existing issues of healthcare such as rising cost

of care with innovative solutions (Brenner 28). With a national annual expenditure of over one trillion dollars and one of the lowest health outcomes across Western countries, the U.S. has an extremely poor rate of return from their healthcare spending (Bodeneimer and Grumbach 143) (Davis et al. 7). Currently, healthcare is not sustainable and still operates with outdated technologies such as paper records and old equipment (Chowdhury 32). Top-down methods by the government and corporations have failed to provide newer, digital technologies to help modernize healthcare (Chowdhury 31). New biotechnology companies could step in and meet the demand for quicker and efficient solutions by delivering better quality healthcare at a lower price with their solutions. These startup companies invent methods to reduce the costs to develop their MVPs, thus giving the public solutions which cost less than the ones in the status quo. An example is the lean startup, Inchor Therapeutics Inc., which developed a novel way of working with stem cell technologies in an affordable laboratory to combat age-related diseases (Grohn 62).

Another important aspect that biotechnology companies provide is the increased sense of control for consumers in the healthcare industry (Sage). New technologies developed by these companies would provide more and better options for consumers to take control of their own health while limiting the need for physician visits. For example, biotechnology companies which develop digital or mobile medical applications allow consumers to run diagnostics with Do-It-Yourself (DIY) technologies. One biotechnology called WellDoc uses an FDA-cleared, physician-prescribed, and reimbursed digital medicine product called BlueStar (Steinberg 915). BlueStar is a software application which can be accessed on a mobile device and aids diabetic patients in monitoring and managing their blood glucose levels (Steinberg 915). There are many other companies which have created DIY technologies for the consumer to monitor their

biomarkers and generate feedback. Other groundbreaking mobile health applications include an iPhone-powered electrocardiogram (Fellay 1). Not only do these devices empower the consumer by allowing them to do some of the easier medical tasks themselves, but they also reduce healthcare costs with fewer visits, provide greater data accessibility, and up-to-date information (Fellay 1). While these benefits are certainly welcoming for the economy and the general public, biotechnology startup companies face many challenges before their innovative solutions hit the general public and markets. Some of these obstacles are ones which startups in other industries face, while some are unique to startups operating in healthcare.

Issues Surrounding Biotechnology Startups and Best-Practices from Literature

Many of the problems faced by biotechnology startups are the same ones startups in other industries face. These include obtaining funding capital, management of human resources, and public relations. Furthermore, biotechnology companies have a whole host of issues exclusive to them. One such issue is the regulatory frameworks set by the FDA (i.e. clinical trials). These are long, expensive, and have low success rates (Rose). Another problem is of location for a biotechnology startup. Without the availability of wet labs or the scientific experts within their location, biotechnology companies will have a hard time flourishing (Kolympiris 228). Issues in regards to the product or service such as: research and development, manufacturing, sales and marketing strategy, are all areas the company has to solve before it generates even its first stream of revenue (Durai 6). This highlights the necessity for management to cautiously manage the changes a biotechnology company must go through from the startup growth phase to a company (Rafferty 479). Each of these issues will be discussed in more detail in the following sections.

I. Biotechnology Startup Issues

A. Capital Funding

All startup companies require funding to begin, either for acquiring new customers or for developing their MVP. Biotechnology companies are no different. However, venture capitalists (VCs) and angel investors, groups and individuals who invest in startup companies respectively, have invested more in other industries such as technology platforms than biotech. Numbers dating to 2005 indicate VCs have invested only $300 million versus $20 billion into other technology platforms (Moran). Furthermore, securing funding from VCs is much harder for a biotechnology than a technology company due to the science and risks involved, such as working with the human body (Durai 7). However, a recent report has shown a significant increase in the

past decade in capital investment into biotech. In 2015, $71 billion was invested, a record high (EY 4). However, the report indicated several signs of a slowdown such as decelerated funding in every category and a lack of initial public offerings (IPOs) (EY 5). An IPO is when a company goes public to collect public funding to continue their strong business. The lack of investment may be due to researchers' incomplete understanding of the sciences involved in biotechnology companies, such as those working on developing new drugs and treatments and the failure to pass FDA clinical trials to gain approval (Moran). Some biotechnology companies, such as WellDoc, require less capital since their product incorporates more digital technology rather than the synthesis of new biological drugs and treatments. Thus, they do not need to undergo the FDA clinical trials, lessening their financial burdens and increasing their chance of success.

The lack of complete scientific knowledge in biotechnology companies that are developing new drug therapies carries high risks for investors because of the uncertainty on where the intellectual property will go (Moran). In other words, there is a high probability the company's proposed solution of a therapy or drug may not pan out as they allegedly expected it would when they tried to raise capital from VCs and angel investors. This lack of confidence in the startup decreases its chances of securing funding for its venture. No money or capital equals no product or business. Unfortunately, the initial round of funding called the "seed round" is the riskiest because the biotechnology company has only just began developing their idea (Durai 7). Seed investment represented only 0.03% of venture capital funds around the mid 2000's for biotech companies working on drugs and therapies (Durai 7). A significant worry is that low seed funding may stifle biotech innovation.

One of the highest barriers to entry for a biotechnology company startup is the significant amount of cost in procuring a basic laboratory to begin research and development. Historically,

the acquisition and maintenance costs of equipment have been prohibitive (Grohn 61). Without the initial seed funding, biotechnology companies face a roadblock in simply getting started. However, once they do, additional issues subsequently arise to challenge the fledgling company.

B. FDA Regulatory Frameworks

I. Drugs

As mentioned earlier, the most notable obstacle is the FDA guidelines and policies for biotechnology companies. Pharmaceutical active ingredients, biological items such as tissues or cells, and any invasive medical treatment therapies are classified as drugs under FDA's statutory definitions (FDA, "Conducting Clinical Trials"). This indicates these products must undergo clinic trials to test the safety and efficacy against a placebo and the current standard of treatment in a double-blind test with a sufficiently large patient pool.

Before the procedure or drug is tested on a human population, a preclinical study phase is conducted in the lab on animal test subjects. The animal and laboratory studies phase usually takes about 4.5 years (MD Anderson). Afterwards, the treatment is then moved to Phase I of the FDA clinical trials where it is tested for safety, dosage, proper administration of treatment, and initial response to the treatment in fewer than 100 healthy volunteers or patients with the disease for several months (MD Anderson) (FDA, "Step 3: Clinical Research"). On average, the FDA lists about 70% of drugs or treatments moving to the next phase, Phase II (FDA, "Step 3: Clinical Research"). Phase I is generally for monitoring the treatment or the drug's interaction with the human body (FDA, "Step 3: Clinical Research"). Phase II tests up to several hundred patients from several months to two years on the efficacy and the potential side effects from the treatment (FDA, "Step 3: Clinical Research"). 33% of treatments move to the next phase (FDA, "Step 3: Clinical Research"). Phase II provides additional safety information from patients. In

Phase III, the treatment or drug testing recruits roughly 300 to 3000 patients with the illness. The test is conducted for a length of one to four years. Phase III provides the most data on clinical safety and efficacy. It tests whether the new treatment is more effective than the standard and reveals any uncommon or long-term side effects in patients. Generally, only 25-30% of the drugs and treatments move on to the next phase (FDA, "Step 3: Clinical Research"). At this stage, the FDA collects all the data received from the first three clinical trials and evaluates the safety and efficacy of the treatment before it decides whether or not to approve it (MD Anderson). The fourth and final clinical trial, Phase IV, tests already approved FDA treatments to gather more information on long-term effects in several thousands of volunteer patients (FDA, "Step 3: Clinical Research") (MD Anderson). Each of these stages can last anywhere from a few months to a few years, with the total average to be about 7.5 years (Sertkaya). Preclinical research by itself can take many years before it is deemed favorable enough to undergo clinical trials. This makes the total amount of time from discovery to approval by the FDA to be between 10 to 15 years for a typical drug (Sertkaya). For example, the Texas-based Mirna Therapuetics company spent roughly five years on preclinical research before being ready to undergo clinical trials (David Brown). The stages themselves, when combined, can last anywhere from five years to ten years (FDA, "Step 3: Clinical Research").

In addition to a substantial amount of time invested in the trials, a significant amount of capital is also necessary to go through the trials. An estimate of between $161 million and $2 billion is required to bring a new drug to market, with the bulk of the cost being from phases two and three due to greater patient volume and time needed (Sertkaya). The biotechnology startups face tremendous difficulty in procuring the necessary funds to pay for the compliance costs of running large FDA clinical trials to test their products or treatments (Epstein).

II. Devices

The FDA's policies for regulating medical devices are different than biologicals. Overall, they are much shorter and less expensive. The FDA's categorization of medical devices is large. It includes applications that offer medical reminders, provide information about drug interactions, use Global Positioning System to alert potential dangers, equipment for surgery, diagnosis, and treatment (Fellay 4). Medical devices and applications are separated into three groups based on their risks to the user. Class I devices pose little threat to users if they malfunction and are therefore subject to the most limited set of regulations (Fellay 4). If the device is similar to a device currently on the market, it will be cleared for marketing. Some Class I devices may need a 510(k) premarket notification. The 510(k) premarket notification is a letter which compares the proposed device to ones in the market and tests performance (Faris 4). Class II devices are almost always subject to a need for 510(k) premarket notification to the FDA with around 10-15% requiring clinical data to support its performance and safety (Faris 4). These devices have the potential to result in a mild to medium injury in cases of malfunction (Fellay 5). They also have special controls by the FDA (Faris 3). Finally, Class III medical devices are ones which could result in death or serious injury in the case of malfunction. These devices must obtain FDA premarket approval similar to a biological drug instead of just a premarket clearance (Fellay 5). Much of the steps for a Class III device is similar to drug development but the path to approval by the FDA is not through four clinical trials but through an investigational device exemption for premarket approval (FDA, "The Device Development Process"). It is almost synonymous to a Phase III clinical trial for a drug. The data is then aggregated for FDA review and approval. The process usually takes a few years and can be anywhere from $1 million to $10 million (Fellay 2) (Hogan).

As these numbers and the 7.5-year timeline show, the process to become FDA approved is long and time consuming. Much can go wrong within the timeframe. To avoid potential delays in the process and further downstream costs, medical entrepreneurs must learn to navigate through these regulatory frameworks. Otherwise, a failure to understand and comply with regulations will scare away potential venture capitalists, angel investors, or partners (Rose).

C. Product Testing

In addition to the regulatory frameworks and funding requirements, there is the actual matter of the testing itself. There is the issue of test site selection, as in where the test will be conducted and where patients will go to be part of the clinical trial, and the need for recruitment of medical personnel to handle and administer the drug or device being tested (Deb 5). Delays in either part can significantly increase the time-to-market. In addition, a patient pool must be assembled and the patients' medical data must adhere to clinical trial protocols by the FDA and be coherent for interpretation (Deb 6). Conventional clinical processes require extensive monitoring, creating lag time between data gathering and analysis (i.e. physicians receiving the results from exams at a much later date). This could potential cause a delay in profitability and incurring further regulatory sanctions from the FDA.

II. Best-practices and Potential Solutions from Literature

D. Startup Environment

The location of a biotechnology startup company for initial operation is a very crucial decision in its business plan. As mentioned earlier, initial biotech startups require seed capital for basic laboratory equipment to develop their product as well as experts to help them navigate the intricate, maze-like regulations of the industry from the FDA. Therefore, the location selection

must consider both the personal characteristics of the entrepreneur or entrepreneurs and the environmental factors which can potentially play a role in the success of the company (Kolympiris 228). A study followed 187 venture-capital backed biopharmaceutical firms that were started by 275 entrepreneurs in the U.S. Using an empirical model developed in the study, researchers were able to show certain patterns in the decisions these entrepreneurs made when deciding where to start their companies (Kolympiris 233). The research indicated the proximity to knowledge assets, such as a medical school, hospital system, universities as well as access to capital, from venture capital firms or large pharmaceutical companies, were important factors in the entrepreneurs' decisions on where to begin their startups.

One of the critical factors for selecting a location to start is the startup's proximity to resources, such as capital, to help it get started. As already mentioned, unlike software technology companies, biotechnology companies require large overhead expenses to produce a minimum viable product to even begin testing in the FDA's clinical trials (Steinberg 914). Entrepreneurs should, and usually do, have a high probability of picking a location where there's a venture capital firm nearby, as mentioned in the Kolympiris study. Aside from capital, biotechnology companies require specific equipment, such as quality lab space to develop and test their products when conducting preclinical animal experiments. Biotechnology companies may have to relocate to different areas in order to acquire sufficient space to either retrofit it into a wet lab workspace or rent out wet lab space from pharmaceutical companies, hospitals, or medical schools (Kirkpatrick 130). Therefore, proximity to existing healthcare or medical infrastructures and organization is beneficial when attempting to acquire lab equipment and start a biotech company.

Another key component in the decision on location is the knowledge assets within a location. Since biotechnology founders have to be familiar with the regulations and guidelines within their industry from the FDA, it would be wise to not only know who the large players are in the field, but to also make an effort to collaborate with them (Lorenzetti). Large players in the field of healthcare are pharmaceutical companies, hospital organizations, and the FDA. One unique, initiative model is the collaboration between the pharmaceutical industry with small life science biotech companies (Styhre and Remneland-Wikhamn 256). The small firm can capitalize on the mature pharmaceutical company's expertise, their capital resources such as labs, equipment, funding, in exchange for a share of the potential profits and sometimes intellectual property rights. Industry experts from mature pharmaceutical companies would be extremely beneficial to startups to help in navigating the complex and lengthy clinical trials, saving time and money by avoiding mishaps. Medical schools and hospital organizations could also serve similar functions for a biotech startup company. For example, the University of Texas Health Science Center in Houston has a fully functional wet lab space, limited used equipment (e.g. refrigerators, freezers, biohazard hoods, incubators, and centrifuges), and a suite of offices with furniture to help companies get started (Kirkpatrick 130). In addition, the Austin Technology Incubator recently partnered with Austin Community College to launch a startup business mentoring service with state-of-the-art biotechnology equipment, specialized wet lab space, conferencing areas, and an expert staff (IC^2 Institute).

E. Staffing, Management and Employment

Similar to all businesses, biotechnology companies face challenges in accessing adequate capital, managing limited resources, handling partnerships, ability to make wise go or no-go complex decisions, and correctly making appropriate risk assessments in a realm of uncertainty.

One of the pivotal moments in a biotechnology company is the transition from the research discovery phase, when the initial discovery of a new drug, technique, or equipment was made, to product development and safety testing (Rafferty 480). Thus, priorities and objectives change from getting the science down to making the product viable for testing and being effective and safe. This requires a need for new skills and talent. There may be an increase in hiring and rapid expansion of staff and the purchase of new infrastructures to accommodate the new needs.

Research has shown that company leaders should be open in communication about changes and what to expect in transitions. Individuals and teams are advised to be patient during decision making times and seek information to understand the changes that are happening (Rafferty 479). Much of the burden of running the biotechnology company in its early stages fall on the founders or upper management, as they strategically plan for the company. For example, management has to decide whether to build, license, or sell their idea and scientific research (Tsai and Erickson 50). At times, all three may come into play depending on the environmental factors of the industry. Management must also decide if it is favorable to seek a corporate alliance with large pharmaceutical companies when times are tough and capital is low. Strategic alliances could help salvage a biotechnology startup when faced with difficulties from clinical trials. Other tasks of equal importance include generating and maintaining free cash flow, planning and executing a viable financing strategy to fund daily operations and research and development, and securing intellectual property rights on their scientific research (Tsai and Erickson 53). These all must be managed and dealt with to maintain the company and have a successful run in the FDA's clinical trials. Therefore, it is imperative that the leaders of the company are seasoned managers with vision and business acumen in dealing with high-risks and many difficult challenges.

F. Technology

In order to conduct an accurate and successful clinical trial, the sponsor or biotech company conducting the trials must assemble an adequate patient pool to test their new product on (Deb 7). The public health data in internal databases, such as from the U.S. Centers for Disease Control and Prevention, can be used to select locations with adequate patients of the right condition to test. Large hospital networks or those who cater towards specific patient groups could also be potential areas of test sites.

Finally, the use of technology can drive this process more quickly and smoothly. With the advent of many technological innovations, biotech entrepreneurs can leverage such advantages in their tests. For example, sponsors can implement a centralized control mechanism and a cloud-based platform to regulate quality control and access and retrieve information readily instead of using paper (Deb 7). This would speed up communication between teams and reduce human errors during the trials. A digital platform can further help in streamlining data collection such as the Electronic Data Capture (EDC) system which can upload information to the cloud platform and be readily available in real-time. This aggregated pool of data from the study can then be analyzed and generated into reports by either data analysts or the use of machine learning algorithms.

Case Study on Mirna Therapeutics Inc.

In the subsequent sections, research findings on Mirna Therapeutics Inc. will be presented to assess the biotechnology company's strategy and success in navigating through the challenges listed above. It should be noted that not every company will face all of the problems listed above and certain information on the companies will be limited due to the scarcity of literature on company decisions and information that are usually reserved for the board of directors or leadership of the company. Nevertheless, in the following sections, an attempt to extrapolate and assess how well the company's strategy embodied the best-practices from literature mentioned earlier will be made, and whether the practices were able to help circumnavigate the issues which plague biotechnology companies.

History and Background

Mirna Therapeutics Inc. was founded in Austin by Dr. Matthew Winkler, who first founded Ambion in Austin Texas (Stoudemire). Ambion synthesized chemical reagents and tools that were used to work with oligonucleotides and RNA-related research applications (Thermo Fisher Scientific). Dr. Winkler was very successful with his initial company, Ambion, and later sold it for $300 million (Stoudemire). Eventually, he used a portion of his money to start another company in Austin called Asuragen Inc., which developed diagnostic kits for cancer, genetic diseases, and generated a lot of information on the potential therapeutic value of oligonucleotides, specifically micro-RNA. Over the years, the company developed a portfolio of micro-RNAs and their potential clinical use. Dr. Winkler used the information from the RNA portfolio and his personal resources to form a branch company called Mirna Therapeutics Inc.

The Science

The science behind Mirna Therapeutics Inc. is the novel method of using micro-RNAs as oligonucleotide-based therapies for cancer treatment. Oligonucleotides are short nucleic acid polymers used in research that are usually 13-25 nucleotides in length and designed to hybridize to DNA or RNA. These short oligonucleotide micro-RNAs are important in the regulatory network of cell development and function as individual micro-RNAs can control several hundred genes across multiple pathways (Brown). Micro-RNAs also function in cancer pathways as they are expressed inappropriately in tumors. The therapeutic application of oligonucleotides is these short fragments typically are comprised of nucleotide analogs that enhance the stability, delivery, tolerability, and/or potency of the drug candidate (Brown). They can also be used as drugs themselves under the label of so called siRNA-based drugs which act as antisense strands that bind to the sense strand of DNA (coding strand) to stop the production of certain proteins or activities that are causing the cancer.

The production of these short oligonucleotide strands is very simple. The sequence of the messenger RNA strand believed to be the cause of the disease can be referenced or searched in genome databanks. With the sequence information, the information can be inputted into a computer such as a GenFab Automated Gene Design machine or used in wet-lab methodologies such as polymerase chain reaction (PCR) mediated gene assembly to create the therapeutic oligonucleotides (Ellington). These strands are theoretically supposed to be highly specific due to the complementary base-pairing between nucleotides.

Despite their ease of manufacturing and high specificity, the biggest challenge oligonucleotide therapies face is delivery, getting the strands into the cells. They do not go through membranes easily due to size and therefore need to be encapsulated (Brown). High

concentrations of the strands are easily thrown out by the cell. Furthermore, the use of liposomes, a structural carrier made of lipids which encapsulates the strands, often accumulate in the liver, spleen, and bone marrow, affecting normal function and induces toxicity in patients (Brown). Sometimes these strands bind to inappropriate regions of the cell and trigger innate immune responses from the patient or affect the expression of other genes rather than the target.

Funding

After the company first began in December 2007, it received seed funding of $3 million capital from its parent company, Asuragen Inc., in April 2008. While most startup companies don't form from branching off of a parent company, Mirna Therapeutics Inc. was fortunate to be connected to Asuragen Inc., allowing it to receive immediate funding to begin its research and development of microRNA products.

With its advantageous location in Texas, Mirna was able to secure government funding from two different sources. In 2009, Mirna received a $5 million award from the Texas Emerging Technology Fund, created in 2005 by Governor Rick Perry to provide Texas with unparalleled advantages in research, development, and commercialization of emerging technologies here in Texas (Life Science Analytics 15). Following that year, Mirna was also able to secure $10.3 million dollars in funding from the Cancer Prevention and Research Institute of Texas (CPRIT) (Life Science Analytics 15) (Mirna, "Form 10-K" 4). The institute was established in 2007 with the goal to expedite innovation in cancer research and product development, giving better access to prevention based programs and methods across the state (CPRIT). The money received from CPRIT was essentially free money because the funding was non-deluded or "no strings attached" (Stoudemire).

In some cases, government funding could potentially add uncertainty to a company's research and commercialization due to requirements and limitations of actions placed on the company from the agency giving the federal or state grant (Mirna, "Form 10-K" 6). For instance, the powers given to the government could entail repayment of all the grant proceeds, termination agreements, claims rights, and other obligations. For Mirna's case, their 10-K report, a comprehensive summary report of the company's performance submitted annually to the U.S. Securities and Exchange Commission, indicates there were requirements to continue operating in Texas to prevent penalties. There was also the requirement to pay CPRIT less than 10% of a portion of their revenue from certain products until they met a certain portion of their grant money amount (Mirna, "Form 10-K" 4).

Aside from the money received from state grants, Dr. Matthew Winkler, the founder, also invested $36 million of his personal fortune, money he received when he sold his first company Ambion, into the company. In addition, the company went through multiple funding rounds with venture capital groups such as Pfizer venture, Baxter Ventures, and Sofinnova Ventures among the many others (Life Science Analytics 15) (Stoudemire). After raising funds from venture capitals, the company went on to launch an Initial Public Offering or IPO to raise money from the public by selling stocks or ownership of the company. On October 1, 2015, the Mirna Therapeutics Inc. offered 6,250,000 shares at a price of $7 to the public and generated approximately $43.8 million in proceeds. At the same time, it offered 2,395,010 private shares to CPRIT to raise an additional $16.8 million (Life Science Analytics 15). While Mirna went the route of financial fundraising like most startup companies, it was able to take advantage of its affiliation with its parent company, Asuragen Inc., and its location here in Texas to secure initial funding in its early days.

FDA Regulations and Clinical Testing

Mirna Therapeutics Inc. initially discovered their microRNA product, miR-34, in 2011 and published its findings in scientific papers (Life Science Analytics 19). For the next couple of years, it continued to conduct research in animal models, such as mice, and published its findings in scientific journals. The product was tested in mice to inhibit cancer growth in lung, liver, and lymphatic system (Life Science Analytics 16). MicroRNA-34 serves as a master regulator in tumor or cancer suppression, thus a vital component in preventing the development of multiple types of cancers (Bader 1). In 2013, Mirna presented these preclinical data to a Keystone conference in Vancouver, Canada. The results were superb, as mice who were affected by late stage cancers showed significant signs of remission (Brown). Later that year, Mirna submitted its preclinical trial data to the FDA in order to begin conducting Phase I clinical trials on humans (Life Science Analytics 18).

Mirna outsourced its clinical trials testing to a CRO or contract research organization to offset costs and manufacture expenses for the MicroRNA product (Stoudemire). These organizations have all the necessary equipment, medical personnel, and resources to conduct clinical trials for biotechnology companies. The company began its Phase I clinical trial study by enrolling in a small number of patients that fit specific health requirements for the trial, such as having acceptable liver function based on vital sign measurements of bilirubin among other factors (Mirna, "A Multicenter Phase I Study of MRX34"). The trial recruited 25 patients in April 2014, which increased to 50 by November of that year, and 75 patients by July 2015 (Beg et al.). Before the trial was terminated early, it had a final enrollment of 155 patients (Mirna, "A Multicenter Phase I Study of MRX34"). The main focus of the trial was find the best dosage

amount for MicroRNA-34 for patients with liver cancer, lymphoma, melanoma, multiple myeloma, and renal cell carcinoma while minimizing the MicroRNA's side effects (Mirna, "A Multicenter Phase I Study of MRX34"). Mirna's clinical trial with MicroRNA marked the first of its kind (Life Science Analytics 18).

Dr. Jay Stoudemire, Vice President of Preclinical Development and Regulatory and Quality Assurance for the company, was in charge of managing the paperwork and regulations surrounding the clinical trials (Stoudemire). Dr. Stoudemire has 30 years of experience working with biotechnology companies, such as at Genetech and Xoma, and getting their products from the bench to the bedside (Stoudemire) (Mirna, "Mirna Board of Directors"). The medical aspect or the principal investigator for the clinical trial was led by Dr. Vincent O'Neill, the chief medical officer who has served on various other boards in other biotechnology companies (Mirna, "Mirna Board of Directors"). These highly experienced individuals were responsible for coordinating the clinical trials with the CRO. Dr. Stoudemire explained that each patient had several thousand pages of medical health data documentation. The data was maintained in a very controlled and regulated fashion (Stoudemire). Clinical research associates ensure documentation occurs at the CRO test sites. Every single clinical site must be approved with documentation and the final clinical study report with all the drug and patient data must be completed while precisely following the FDA's guidelines and given to them. Dr. Stoudemire was in charge of the report.

Another important component of the study which had to be constantly monitored by Dr. Stoudemire was the labeling and shipping conditions of the drug being tested. Every label made for the drug had to be accounted for in case of mishaps that could be life-threatening to the patient. The shipping conditions of the drug from manufacturing companies must ensure product

safety and quality until the time of use in the trials in order to prevent adverse effects. This aspect was also managed by the expert, Dr. Stoudemire. Therefore, having at least one expert on the leadership panel of a company to conduct clinical trials is extremely important and beneficial to help mitigate a plethora of possible complications, delays, and fines in the process.

The dollar amount of the clinical trial was already high. Each patient's total cost was roughly $65,000 (Stoudemire). Part of the reason for the high cost was because it was an oncology study and cancer is highly complex in nature. According to Dr. Stoudemire, additional costs include the $1 million for manufacturing the drugs for testing, the CRO contract of $10 million, and the total cost was approximately $120 million dollars for an unsuccessful Phase I clinical trial with 155 patients. If the test was a phase II or III, with its larger patient sample and longer duration, it would have cost approximately $750 million.

The study was unsuccessful because of unknown causes of high toxicity in patients taking the test drug miRNA-34. The study was halted by Mirna last year. This topic will be elaborated in the limitations section.

Local Resources

Due to its connection with its parent company, Asuragen Inc., Mirna brought many scientists over to develop mircoRNA as a therapeutic agent for cancer (Stoudemire). It was a novel endeavor at the time, as there were no drugs that mimicked microRNA being tested.

The founder of Mirna, Dr. Winkler, is a resident of Austin, Texas. According to Dr. Stoudemire, Dr. Winkler has built "a community of strong connections and deep roots" at UT Austin. Dr. Winkler believed that Austin would become the next biotech hub like Boston or the Bay Area. He is not far from the truth as out of the four major cities in Texas—Houston, San

Antonio, Dallas, and Austin—Austin is the fastest growing startup city with the largest amount of newly financed startup companies (Egan 3).

Current Situation of Mirna and Limitations of the Case Study

As mentioned earlier, due to the unsuccessful Phase I clinical trials from the toxicity incurred in the patients using miRNA-34, the company had to halt and terminate its study. Despite the fact that Mirna had many advantages, such as adequate funding from various sources, resource capital from its parent company, and promising results from its animal, preclinical studies, it could not foresee the outcome in its Phase I clinical trial. Interviews with Dr. Stoudemire and Dr. Brown, both integral in the clinical trial study, expressed their surprise and disappointment in the study's results. They stated that the human body is much too complex to be modeled by only a mouse. Unfortunately, this is currently the best technology available to prescreen products before applying them in human studies. Even with the best possible starting position for a biotechnology company, there could be potential setbacks when dealing with the human body in clinical trials. Perhaps future research and methodologies will harness the computational power of technology to better predict the many variable outcomes before beginning human trials.

Since Mirna put all of its resources and high hopes into their one product, miRNA-34, its failure to pass the clinical trials has left the company in a tight predicament. With no product to enter the market to generate revenue on the horizon, and the fact that the company has been operating in debt since its inception, the company is now seeking to do a reverse merger. In other words, Mirna is looking for another company with the resources to buy their company and

assume leadership (Stoudemire). Mirna hopes the new company will be willing to pool resources, go back to the drawing board, and continue to do research (Stoudemire).

The case study represents only one of the many other biotechnology companies and thus by no means represent the end result for every biotech startup. However, the selected company provides a potentially unfortunate reality for those working or hoping to work in the field. Even with enough resource capital, stellar preclinical data, and the necessary management and means to operate clinical trials, the results from the trials may not always reflect the positive data obtained during the preclinical phase.

Conclusion

After conducting a literature review on mitigating issues for biotechnology startups, the importance of securing funding, the understanding of FDA regulations, the ability to test and conduct clinical trials, and the advantages of utilizing local resources were reoccurring areas of importance from authors who have successfully started their own biotechnology companies or have large amounts of expertise in this area. These four areas, if managed properly, can substantially help prevent a biotechnology startup from getting into trouble early on. As presented in the case study on Mirna Therapeutics Inc., the company was able to successfully achieve early funding, use the local university and its parent company's resources and workforce, contract with a CRO to conduct clinical trials, and successfully navigate Phase I clinical trials, albeit the trials themselves for the product was unsuccessful.

Despite Mirna's early successes of their product in preclinical settings on animal models, it did not preclude the possibility of bad results in the human studies in the trial. Furthermore, even though Mirna did everything right when getting started, no one could have predicted how patients would react to their product, highlighting the need for clinical trials in the first place. Therefore, it is important to note the limitations in following the recommended proposals offered by Tsai, Clarke, Durai, Kirkpatrick, and others in these areas of importance when starting a biotechnology company—it cannot guarantee long-term success but will prevent early failure.

In the coming decades, perhaps future research could explore the possibility of using machine learning techniques and other computation methods to better predict the probability of success for a given drug in clinical trials before actually conducting them. This would allow biotech companies to conserve more manpower, capital, and other resources and use them on a

clinical trial for a drug with the highest probability of success. Further research in this area may increase the success rate of biotechnology startups.

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Biography of Yuqing Xiong

I am a graduating pre-medical senior from the CNS Polymathic Scholars Honors Program and COLA Plan II Honors Program with degrees in Biochemistry and Plan 2. I am also a member of the Texas Alpha chapter for Phi Beta Kappa. My interests include technology, medicine, innovation, neuroscience, physics, philosophy of mind, space, video games, Chinese dramas, and basketball.