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Turning Research into Gold

An in-depth look on the life and structure of biotech ventures.

In his book, *Fantastic Voyage*, inventor Ray Kurzweil speaks of the explosion in life sciences discoveries in the 21st century. If the progress of medical science is plotted on a timeline, he observes, the pace of technology is accelerating. Mankind will discover as much in the next 14 years, as it did in the entire 20th century.

Suffice it to say that the world we know will be dramatically changed by the coming big bang in the life sciences universe. And with this new age will come an ocean of opportunity for four groups. First there are the universities and academic medical centers that have the brain trust to develop new technologies. Then there are the researchers themselves, who the federal government now allows to profit commercially from the research they do with federally-funded research grants. Next, there are the pharmaceutical companies, many of which have realized that a strategy of buying adolescent biotechnology companies is more cost-effective than conducting early-stage research and development in-house. And lastly, there are the private investment funds which have learned how to structure their investments in promising biotech start-ups.

But experience also has shown that many biotech companies have flopped with resounding vigor. In almost all cases, the science behind these failed ventures was sound. The money backing them was real, but where many fell short was in their failure to appreciate or account for the vast and complex web of relationships that must exist for a biotech venture to succeed. The divergent interests of the players (academia, scientific researchers, pharmaceutical and device manufacturers, private investors, and the federal government) require a delicate balancing that is easy to upset. Understanding the balance and structure of a biotech venture is the first step in turning scientific research into gold.

Birth of the biotech venture

Biotech ventures that grow out of research institutions have three common goals as start-up companies. They must: (1) license patented technologies that have economic value; (2) develop the proper relationships among academia, investors, and pharmaceutical and device manufacturers; and (3) imple-

ment a legal structure that leverages the technologies and relationships.

• Protecting Technologies-

Every biotech venture's primary business objective is to develop and own a unique technology that has economic value because of its uniqueness. If the developers of a new technology do not properly protect the technology, others can exploit it. If others are exploiting it, it is no longer unique, and the economic value of the technology diminishes. A well-groomed and aggressively protected patent portfolio is essential for a company that wants to commercialize a new technology.

Many patentable new technologies are owned by the research institutions which received federal research grants to develop the technologies. Even the most august research institutions in the world, however, can make mistakes in patenting new technologies. In some cases, the mistakes do not come to light until long after a biotech venture has been formed and funded. An essential step in setting up a successful biotech venture is conducting detailed legal and scientific due diligence to ensure that the technologies that will be licensed to the start-up company have been properly patented, and their uniqueness assured.

• Proper Relationships-

Start-up companies in the life sciences industry often grow out of research institutions which receive federal research funds.

These research institutions have an incentive under applicable law to attempt to commercialize a new technology and to share any license fees it receives with the researchers who developed the technology. The easiest way to do this is to license a new technology to a start-up biotech company that is owned in part by the researchers. The research institution can then take an equity stake in the new venture, a license fee for the technology, or both.

A second essential element of the successful start-up venture is a critical mass of researchers who are interested in taking pre-clinical work out of the laboratory into a translational setting. Most researchers who spend their career studying a discrete area of technology or medicine will be interested in pursuing relationships that allow them to derive an economic



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benefit from their work. Despite this, biotech ventures often fail in the birth stage because they do not have the critical mass of researchers to successfully commercialize a technology. This most often occurs when there are multiple groups of researchers at a research institution whose work contributes to a new patented technology. When the new biotech company is formed to exploit the technology, one group may be interested in participating in the venture, while other groups may be more interested in focusing their energies on preclinical research in other areas. When evaluating the odds of a venture's success, it is therefore important to determine which researchers contributed to the patented technology that will be licensed to the venture. If one or more critical researchers are missing and his or her contribution is not one that can easily be replicated, it is preferable to delay the formation of the venture until the missing groups can be persuaded to participate in the venture.

Once the biotech company has been formed and the license agreement with the research institution is in place, the start-up company has the raw materials it needs to commercialize a new product. But raw materials are not all that is needed. A January 2004 report issued by the FDA and the Association of American Medical Colleges estimated the cost of bringing a new drug to market to be \$800 million. As the biotech venture grows, so will its appetite and need for capital. Private investment in the venture is therefore essential. This capital can come from a variety of sources, and often comes from more than one source. In some cases, pharmaceutical companies and device manufacturers will invest directly in the venture, taking an equity position. More often, however, these companies prefer to minimize their investment risks by purchasing more mature companies whose products have been developed and successfully tested. Most biotech start-ups will receive funding from private equity and angel investment groups.

A new biotech venture backed by a prestigious research institution with researchers who have previously developed and commercialized life sciences technologies will attract investors, particularly if the venture is designed to produce tests or treatments with broad commercial appeal. These types of ventures also will be in the best position to demand limitations on the percentage of the company given to the investors in exchange for their capital contributions, as well as the amount of overall capital the investors will be required to contribute over the life of the venture. A technology that is developed by a lesser-known research institution, by a group of researchers with no prior track record, or in connection with an obscure disease or subject matter, will have greater difficulty in attracting investors and less leverage in their negotiations with the investors which are willing to fund the venture.

This being said, the amount of the capital that will be required to fund a biotech venture will, in large part, depend on the venture's business strategy. If the goal of the venture is to successfully demonstrate a product's success in clinical trials, with the expectation being that the company will be sold before manufacturing begins, the venture will have different capital needs than a venture that plans to develop, test, manufacture and distribute the product. As a general rule, private equity companies and angel investment firms invest in ventures which plan to develop only up to a point, and then position themselves for sale to larger companies that focus on the same specialty areas or alternatively, large pharmaceutical and device companies that have greater resources for bringing new products to market.

• **Leveraging Technology through Licensing-**

The license agreement between the research institute and the start-up company must be structured in a way that assures that both the research institution's and the start-up company's needs are met. From the research institutions perspective, the license must ensure that all funding restrictions placed on technologies developed with federally-funded research are passed on to the start-up company. To further develop their academic expertise in a given area, the research institution will likely want to retain the rights to publish the results of its research at a time that does not interfere with the commercial value of products derived from the research. The research institution also will require that the license contain an indemnification from the start-up company in the event that a third party asserts that the technologies infringe on its intellectual property, or in the event the testing of products derived from the institution's technology results in personal injury or death.

From the start-up company' perspective, the license must clearly articulate the scope of the license. The research institution may desire to enter into exclusive licenses with more than one start-up company, if the uses that each start-up company hopes to make of the technology are different. For example, one start-up company may hold an exclusive license to develop and commercialize a technology for use in the treatment of animals. A second company may hold the exclusive license to develop and commercialize the same technology for applications in human beings. Problems sometimes arise when the scope of the licenses are unclear and potentially overlap. From a start-up company's perspective, the best license is a broad license that covers a wide-variety of potential uses. The start-up company must then carefully negotiate the scope of the appropriate license with the technology transfer office of the research institution and must be assured that the license it is being given truly is exclusive.

A good license agreement will do more than just define the scope of the licensed technology. It will also address many of the operational matters that must be addressed if the start-up is to succeed. For example, a license agreement also should allocate the responsibility and costs for maintaining the patent portfolio that is subject to the license. It also may describe in detail the resources that the research institution will make available to the start-up venture and the cost that the venture must bear for these resources. Because a start-up company may be relying on space, equipment or services owned by the research institution, it is essential that the research institution contractually commit to continue to make these items available to the venture for as long as the venture will continue to need the items to grow and expand.

The adolescent biotech venture

A biotech venture that has established a corporate and capital structure, negotiated a license for a promising technology, and received some initial funding to further develop the technology has survived the birthing process and has entered the adolescent stage. The company is no longer speculative in that all the proper relationships among the players (e.g., research institutions, researchers, private investors) have been established, and there is no risk that the venture will crater as a result of a failure to strike a balance among these conflicting interests. There no longer is a risk that the venture will fail to attract investment to fund its immediate capital needs. The company begins to outgrow the laboratory space it was leasing

from the research institution. Technical employees will often leave the employ of a research institution and go to work for the start-up company. The company moves into new office and laboratory space. And work begins in earnest on the clinical development of products.

As a biotech venture moves from the birth stage to the adolescent stage, the venture's reliance on the research institution progressively weakens. At the outset, a new biotech venture may lease laboratory and office space, employees, equipment and services from the research institution. Because the research institution typically is a tax-exempt entity, it cannot provide goods or services to a private biotech venture for less than a fair market value return. Although the biotech venture gets no break on the cost of equipment, space and services, it at least has the security that these critical things will be provided for. As the venture grows and hires more employees, it will require less personnel support from the research institution. As it outgrows its laboratory, it will move into its own space and no longer lease space or equipment from the research institution. As it begins to develop an array of relationships with technology and bioinformatics vendors, it will require less services from the research institution.

If a venture is well-capitalized and has the critical mass necessary to begin testing new products directly, it usually will move into office and laboratory space that it will build to suit its specific needs. It will hire a full-time staff and enter into contracts with service providers to support its operations. When companies are less-well capitalized, they may not have the resources to immediately lease their own space, hire a full-time staff and otherwise incur the overhead associated with running a business. In many cases, these companies are too big to continue to lease space from their sponsoring research institution, but too small to go it on their own. Many of these companies will turn toward biotech incubators (a.k.a accelerators) as an answer.

• Understanding the Incubator-

Often times, new biotech ventures do not have the capital to build out their own laboratory space. The founding researchers may have never run a business before. The company may need outside service providers to assist them in conducting clinical research, but may not have developed relationships or contracts with these outside vendors. They may not have the regulatory approvals to operate some of the equipment they must use to conduct their research. And they may not have developed the sophisticated information technology infrastructure that they will require to operate successfully. In this case, the company may need to look to an incubator for assistance.

Historically, incubators were run by state or municipal governments in collaboration with research institutions. Increasingly, companies like LaunchCyte, Inc. and a variety of private equity companies are acting as incubators for biotech ventures. An incubator is an entity that spreads its investment in fledgling biotech companies by providing critical operational assistance to help the company mature. In exchange for an equity stake in the biotech venture or a portion of the sales generated from products the company eventually develops (or both), the incubator provides an adolescent biotech venture with a variety of services that can include:

- Laboratory and or office space
- IT infrastructure

- Legal assistance
- Grant-writing assistance

Apart from these critical services, the incubator also offers a biotech venture other intangible benefits. Often times the incubator has relationships with investors which are looking for opportunities to invest in biotech ventures. The incubator also introduces the founders of the biotech venture to other researchers, and allows them to develop relationships with technical service providers which can assist them in conducting their research.

But the incubator is not intended as a long-term fix. Incubators have a financial incentive to churn as many promising biotech venture though the incubator as possible. The average length of stay in an incubator is between one and three years. The incubator provides incentives to move the company through as quickly as possible. In many cases, the rent paid by the biotech company for office space increases the longer the company remains at the incubator. If the company does not attract sufficient capital to move into its own facilities and set up its own operations after several years, the company will be expelled so that new companies can use its space.

• Building a Compliance Infrastructure-

When a biotech moves out of a research institution, it leaves behind a compliance infrastructure that must be completely rebuilt. A research institution, unlike a fledgling biotech venture, is accustomed to operating in a heavily-regulated environment. It has developed sophisticated policies and procedures that define the manner in which it conducts scientific research, protects patient data and makes required regulatory reports and filings. The biotech venture that moves out of the research institution is a separate legal entity. It cannot rely upon or adopt by association the compliance policies of the research institution out of which it emerged. Even though the venture is a small business, it is held to many of the same scientific and legal strictures as the research institution. It must develop the same complex web of relationships that a large research institution develops when it conducts research.

Because a biotech venture's success is judged in large part by whether it can produce a drug that tests successfully, the venture cannot be successful if the scientific research that supports the testing is tarnished. The first part of an effective compliance infrastructure is the development of conflict of interest and scientific misconduct policies. If the venture will be sponsoring clinical trials or conducting clinical testing, it must closely scrutinize each of its many financial relationships and take great pains to ensure that the financial interests are not influencing the outcome of its research. In June 2005, the Public Health Service issued rules addressing research misconduct. The rules, which set new standards which a research institution should follow in investigating allegations of research misconduct, underscore the growing scrutiny that scientific research is receiving from regulators. To comply with these new standards, research institutions will require detailed certifications from their researchers. Pharmaceutical and device manufacturers also are required by the FDA to disclose certain financial relationships. To meet these reporting obligations, these companies will impose their own reporting obligations on researchers and biotech ventures. The only way to meet these reporting obligations and to produce scientific data that is untarnished is to implement policies and procedures designed to ferret out and manage conflicts of interest, investigate allegations of misconduct, and meet industry-standard reporting obligations.

A second critical element of an effective compliance program is developing HIPAA policies and procedures. The Health Insurance Portability and Accountability Act of 1996 prescribes the manner in which patient identifiable data may be stored, disseminated and used. If a biotech venture will be sponsoring or conducting clinical trials on patients, the venture must assure that its information technology infrastructure can track and generate an accounting of each person who viewed a patient's medical information. HIPAA also tightly restricts the parties to whom the patient-specific information can be disseminated. Most importantly, HIPAA does not allow protected health information to be used for purposes of conducting research unless the patient signs an authorization form. The scope of these authorizations must be crafted carefully, narrowly enough to comply with applicable law, but broadly enough to allow the data produced from the clinical trial to be used again for secondary research.

The mature viotech venture

When the biotech venture has successfully taken a technology through clinical trials and has one or more products capable of being commercialized, marketed and distributed, it has reached maturity. Companies that reach this plateau pursue one of two paths. They either sell the company to companies who have the resources to manufacture and distribute the product, or they seek the funding necessary to do so themselves.

• **Putting it on the Block-**

Ninety percent of mature biotech ventures choose sale as their strategic path. Sale has many advantages. It allows the researchers and investors to cash out, thereby giving them the capital necessary to start and build other ventures. It also allows researchers whose primary interest is scientific discovery to turn-over responsibility for managing the business to the buyer. These management responsibilities would increase if the company decided to manufacture and distribute products itself. Private equity firms which have invested in the biotech venture will likely push very hard to sell a mature biotech venture. The sale gives the private equity company an immediate return on its investment, eliminates future risk and, most importantly, forecloses the possibility of the firm

having to raise and contribute additional capital that would be necessary to take the company to the next stage.

If a company has developed and tested several marketable products, it may attempt to sell non-core technologies, and manufacture and distribute its core products itself. The proceeds derived from the sale of the non-core technologies can be used to fuel the expansion efforts needed to take the core products to the next level.

The path less traveled

The small percentage of companies that do decide to go it alone fall into two categories: specialty companies and platform companies. Specialty companies tend to have a limited product portfolio, or a broader portfolio with limited application. Specialty companies typically outlicense their technologies and products to other companies (platform companies, large pharmaceutical and device companies, etc.). The revenues of a specialty company are in large part derived from the license fees it receives for its technologies. A new trend among these companies is to securitize the revenue streams derived from their license fees, thereby allowing them to realize current value for technologies that are designed to pay off over time. Because the specialty company has no need to mass-market a product publicly, its operating costs are also lower than a platform company's costs.

Platform companies have a broader product portfolio with greater marketing potential. Platform companies that seek to fully commercialize a product all have one thing in common. They need to raise capital; a lot of capital. Although there are private equity companies which specialize in mature biotech ventures and which have the resources to take a platform company's products to market, this capital is relatively scarce. If the biotech venture has developed a revenue stream or has a product with obvious mass appeal, it can go public. The initial public offering or "IPO" is the most common way to go public. The IPO gives the company an immediate source of capital and also allows the company the ability to make strategic acquisitions using its own stock as currency. Still, biotech IPO prices have been deflated in recent years and many have raised less capital than anticipated.

—*John M. Callahan*

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