Strategic issues for biomedical technology development

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Health care remains a $300 billion driver of the national economy. Venture dollars invested in biomedical device and technologies and biotechnology in 2000 and 2001 were $5.7 billion and $3.5 billion, respectively. Public financing for these sectors totaled $20 billion and $5 billion, respectively, for the 2 years (Fig 1). Yet the transfer of technologies from academia to the public continues to follow a twisted path. Universities are often woefully unconnected to sources of nongovernment or foundation-derived capital, and the financial community has done little to facilitate the necessary trust and expertise in the university setting to smooth the translation of science to commercially applicable technologies.

By creating the Small Business Innovative Research (SBIR) program, the National Institutes of Health (NIH) demonstrated its recognition that commercialization of scientific projects funded by the federal government is an objective of the original grants themselves. Yet a knowledge gap and perhaps innate suspension exists within academia as to how best to introduce, protect, commercialize, and recognize economic rewards from technologies emanating from its faculties. The gap is cultural—the lack of recognition that private and public equity financing are as critical to the realization and dissemination of technology as NIH grants are to the discovery and nascent development of technologies—as well as practical (Fig 2). Although most universities have established offices to facilitate technology transfers, these offices are often ineffective in building robust relationships with the few investor groups that are comfortable mining the hall of academia for promising science that could be developed with experienced and appropriate management teams.

New technology diffusion in the life sciences depends on a variety of essential support structures. The introduction of a new medical technology begins ideally with innovation that responds to clinical need, progresses through engineering and scientific development, is fostered by financing from a variety of sources, and reaches the markets through disparate commercial structures. Along the way, the technology is subject to scientific, clinical, engineering, and regulatory scrutiny. The technology may be appropriately lost to the target community by demonstration of a lack of validity, safety, or effectiveness, or unfortunately derailed by mismanagement of its development.

The method by which new medical technologies are funded in the period between concept and product launch is a critical and dynamic part of any technology diffusion and application. Tied to strategic development, this funding starts with peer-reviewed or foundation support but ultimately can take the form of small-business grants from the government (SBIRs), angel investment, corporate strategic partnership, venture capital and mezzanine investment, and, finally, the public markets.

With revolutionary development in the methods by which vascular disease, and indeed all care, is delivered, commercial funding of clinical trials and device technology development has become a ubiquitous presence in community and university medical centers, with surgeons serving as investigators but also as inventors and developers of many of the technologies in question. To understand and thus interpret better the process of technology financing, this review will outline strategies and pitfalls in obtaining this funding and address the process by which private and public funding occurs.

STRATEGIC APPROACH TO RAISING CAPITAL

Initial investment in a promising technology often will come from private sources. “Angel” investors are typically high net-worth individuals who seek to deploy a portion of their capital in a high risk/high return vehicle. Although often sophisticated, the structure of these investments is less formal than that found with venture capital, which represents professional deployment of large pools of capital. The latter investors, regularly accountable to sophisticated limited partners, are typically far more stringent about valuation, ie, the purported worth of a company or its technology, board representation, and ultimately about control of the company as it is managed to a “liquidity event” (sale or public offering) for the investors, founders, and management. The balance between angel investment
and venture investment can be delicate, as companies benefit strongly from professional involvement at the board level but will inevitably give up a greater share of the company in the process if venture rather than angel investment is sought. Ultimately, more effective management leads to higher returns, a greater probability of success, and more effective dissemination of valuable technology, thus rendering a smaller percentage of ownership more valuable.

Alternatives and later stages for capital sources include the public markets, strategic partnerships with large corporations, which often include milestone payments for achievements along a path to commercialization and debt capital. Strategic partnerships can also provide research revenues and grants designed for business development which are separated from the potential conflict of interest of funds designed for use by the founder’s academic laboratory. Choosing among these avenues becomes a complex
and critical strategic consideration in the management of a promising technology.

Any capital raise must be tied to the projected use, the “use of proceeds.” It is impossible to raise capital without a clear business plan in mind—namely scientific, clinical, or commercial milestones to be achieved and the associated personnel, supplies, regulatory, legal, development, marketing, etc, costs along the way. The best approach for such companies involves setting an endpoint—a specific level of liquidity, for instance, or a future financing event—and then determining the amount of capital necessary to get there.

When deciding on a funding target, ie, an amount to be raised and the source of the capital, a young company should try to project its future needs in several categories:

- **Operating capital** is necessary to cover anticipated day-to-day and project-specific costs until the next financing event;
- a cushion of capital, or **opportunity capital**, is needed to enable both planned and unforeseen strategic initiatives, as well as to account for failures or changes in plans over this same period;
- **negotiating capital**—this cushion is provided to maintain a position of financial strength during protracted negotiations with potential strategic partners, which are generally larger and acutely aware of a young company’s “burn rate” (monthly or quarterly expenditures); and
- **protective capital** to provide sufficient protection against the old adage that anything that can go wrong, will go wrong—one of the abiding principles in technology-rich young companies.

All too frequently, private companies underestimate their needs and raise insufficient funds. This is often because of a fear of dilution, the reality that raising extra capital at a lower valuation will result in the original owners, the founders of the company, or the university that has rights to the patent, retaining too small a fraction of ownership. For companies raising capital, less is not more, it is usually less. Dilutive financings, while seemingly onerous, often provide the firepower to develop the technology, secure the intellectual property so critical to success, and pay for the management muscle necessary to withstand competition. Undercapitalization will threaten the survival of a new company, and frequently leads to the distracting cycle of a rapid need to raise more capital rather than allowing management to attend to the aggressive development of the technology. This translates into less being accomplished, milestones not being reached, and diminished valuation during a period of significant vulnerability. At the very least, it may simply ensure the need for painfully dilutive financing at a later date. It may also prove to be the death knell of the company, despite the promise of the technology.

Numerous financing options exist for companies (Fig 3). Companies should think strategically about the best source of capital for their particular needs. Short-term debt, such as lines of credit that provide working capital and enable equipment leasing and similar expenditures, is both necessary and useful. However, long-term debt often hurts a young company more than it helps, as it creates a periodic cost that can cause cash flow problems. Emergency debt arrangements can be even more perilous, if unavoidable at the time.

Equity financing, the issuance of stock in exchange for funding, requires its own balancing act. Angel investment—raising capital from nonprofessional high net-worth individuals who have an interest in but not deep expertise in a particular technology—is often the first path chosen by young companies or universities that are seeking to spin out technology. Although “angels” provide capital, there are dangers in this capital structure that private companies may rue later in their development. In general, angels are the least professional investors: they

- invest at valuations not linked to the market,
- often lack industry experience, and
- may make unreasonable demands of management.

The latter occurs especially with regard to valuation or business direction when the need for professional investment becomes apparent and appropriate. Financing beyond the reach of angel investment becomes necessary when technology and development milestones such as clinical trials, marketing efforts, and the recruitment of experienced management are approached.

In an ideal world, an investor should offer something of value other than money—be it the experience of the venture capitalist, the savvy market read of the hedge fund manager, the cachet of the crossover investor (one who invests in both public and private companies and is viewed as validation for private companies seeking access to public capital), or the technology validation of the strategic investor. Angels fall short here as well, as they generally bring little other than capital to the table and are not viewed by later-stage investors as proof of the worth of the investment under consideration. In fact, the presence of angels is often viewed by professional investors as a negative factor—a sort of prejudice that may sell short a promising technology at a critical juncture in its life cycle.

The issuance of common stock for employees and for angels is fine, but most financial investors (and many stra-
The company needs more capital than can be raised in the private markets.

- The company needs a public security underlying option packages to attract senior experienced management.
- The company needs a public security for currency in making acquisitions to either fuel growth or expand and protect its intellectual property position.
- The company needs to be public for credibility with its customers.

In addition, certain threshold criteria should be met. These criteria will vary by industry, but at the very least a company on the verge of a public offering should have its complete infrastructure in place, visible positive events in the near future, and an expected valuation that will be large enough to attract institutional investors. (At the moment, that means a valuation of at least $300 million.)

There is no denying that a “public to private” discount exists, justified primarily by the relative illiquidity of private vs public equity. Because private equity investors routinely apply this discount when valuing prospective investments, companies may be (somewhat rationally) tempted to favor the public markets. However, forcing an initial public offering (IPO) before a company is ready is not prudent, as any short-term valuation gains must be weighed against the liabilities associated with an under-performing public company, which resides under the scrutiny of its investors. This scrutiny relates directly to the important consideration that for most companies, the IPO is not the last financing event. Raising equity as a recently public company with a fallen stock price can be extremely disadvantageous as investors look to management to provide ongoing proof of ability to execute on a business plan that is in turn valued by additional investors competing for and thus driving up the share price. In short, a premature IPO can cripple future growth prospects.

The standards for migration of a private company to a public one can generally be viewed as:

- Compelling technology that will provide either incremental quality gains at reduced costs to medical consumers or that is so revolutionary (a “disruptive” technology) that adoption is inevitable given the marked improvement in clinical care that will ensue.
- An effective, experienced management team. This can not be overemphasized. The best technology or most advantageous clinical improvement can be lost to the public by virtue of mishandled trials, unethical behavior, or mismanagement of the funding process. Although clinical need and science/technology drive the inventive process, not recognizing the need for professional management can be construed as a moral failure in the inevitability of not delivering much needed technology to the population at large.
- A clean and strong intellectual property position—lack of protective elements to prevent rapid competition and devaluation of the offering will drive investors away.
- A significant market opportunity—large unmet clinical needs and/or an inadequate solution by current therapeu tic approaches are sought by investors at this time.
This is not to minimize the importance of smaller niches within the clinical world; however, differing financing and development choices rather than venture or public investment are usually needed for these important entities.

- A reasonable competitive environment, ie, one in which an overly powerful competitor, even with a lesser technology offering, holds too much sway with the decision makers of the relevant clinical technology purchases.

It takes time to raise money. Any investor of merit will perform extensive due diligence on the management, products, and market opportunity of a company under consideration for his portfolio. As a result, it can be dangerous for a private company to underestimate the time required to close a financing deal. If a firm waits too long to start the process, its balance sheet can weaken, eroding its negotiating power. Generally speaking (although subject to market conditions), a company should never assume it can complete a private financing in less than 12 weeks. Even when one is accessing the private markets, it is important to understand the tight linkage between the public and private capital markets. Waiting too long to raise money exposes the company unnecessarily to the whimsy of the capital markets. Further, it is wise to have an additional “buffer zone” of at least another 12 weeks cash on hand (or roughly six months cash in total) when initiating fundraising. Although this is relatively conservative advice, companies should never underestimate the utility of negotiating from a position of strength.

Although creativity in business and in science is always admirable and almost always imperative, creativity in designing capital structure is full of risk and rarely necessary. Young companies, especially those reliant on products or processes of technical complexity, should employ simple capital structures to counterbalance the business risks assumed by investors. Straightforward convertible preferred stock that surrenders as few added bells and whistles as possible, is best.

Stated differently, complexity has its costs. A company with a confusing or contorted capital structure, regardless of its stage of development, will always be penalized by investors. This phenomenon can be observed repeatedly with public companies that have been very creative in funding their technologies. Historically, the arcane financial statements of these firms have dragged their shares below those of their peers. If a private company is forced to employ unwelcome capital structures, it may be necessary to clean them up prior to an IPO. Extensive angel investment, with numerous investors each owning very small portions of the company, is a classic example of the type of complex capital structure that appears attractive in the short run but becomes detrimental during critical phases of a company’s development.

Even if a firm is raising money in the best of times, it is best to structure its financing positions for the worst of times. The need for simplicity is even more pressing when financing in difficult environments. At such times, there are three proven safeguards that will help a company avoid dangerous financing terms: (1) a healthy cash balance; (2) competition among potential investors; and (3) existing investors with enthusiasm and the ability to follow initial investments with further financing, both to protect the investors’ position and to protect the company from predatory financing terms.

Finally, there is a temporal dimension to the design of capital structure. Although an emerging growth company should target an optimum capital mix, its capital structure should be sufficiently elastic to respond to changes in the firm’s development and shifts in the capital markets. Capital markets should not alter the ultimate mix of a company’s sources of capital—only the timing of using those sources.

DILIGENCE PROCESS

Regardless of the origin of the funds, the evaluation of the potential for commercial success of an idea or a technology is known as the diligence process. Diligence, in assessing the benefit of the technology in question, the market, and, most importantly, the patients, carries certain overlapping responsibilities and methods. This section will explore in detail the concerns that must be accounted for in the development of any new technology from the commercial investment perspective, emphasizing both the strategic needs and thought process and the ethical responsibilities of the investors in the process.

The process includes but is not limited to the following:

- technology, products, and capabilities of the developing technology company;
- scientific due diligence;
- regulatory structure;
- evaluation of current existing therapies;
- manufacturing diligence;
- market dynamics and attractiveness;
- intellectual property;
- management capability, experience, and integrity.

Technology and anticipated products. The credibility of the inventor, scientist, or the company developing the technology is often the first barrier for an investor to pass in evaluating an opportunity. Any technology must serve a purpose rather than exist as an engineering solution in search of a market. Misapplication of scientific or engineering capability leads to either increasing cost in our health-care system without benefit of improved quality or safety, or leads to investment failure either financially or ethically with regard to promotion of an inappropriately supported technology.

Scientific due diligence. Scrutiny of the available data about the technology in question will reflect the stage of development and, therefore, the stage, size, and terms of investment. Nonetheless, diligence must demonstrate at least the following as organized by stage of investment.

- Seed stage: begins with a well-defined clinical problem and need for which current solutions remain imperfect, and is tied to a cogent scientific solution.
• Early stage: reduction of the scientific idea to some level of practical application either through computer modeling and prototype production or early animal testing.

• Pre-clinical stage: demonstrated safety and efficacy in animal models with progression to phase I testing demonstrating safety in humans.

• Pre-launch (PMA) stage: phase II and phase III trials demonstrating efficacy and ultimately effectiveness under tightly controlled circumstances.

Regulatory structure. Determination of the class of technology is critical to the time to market launch. Full analysis of predicate technologies will reveal whether the technology in question can be categorized either class I, II, or III (ranging from benign, harmless devices through implantable devices for which demonstrated safety and effectiveness must be statistically proven before market release). Subsequent submission of either the shorter pathway of a 510(k) appropriate device or a lengthy and costly PMA application demanding a randomized trial with sufficient statistical power, will have a significant influence on the type of investor sought and the ultimate terms of the financing.

Current standards of care. A thorough analysis of existing current therapies must be undertaken to determine whether the developing technology truly offers anything in a quality/cost/unmet need paradigm. This analysis entails review of:

• Efficacy and effectiveness of current interventional and noninterventional approaches to the disease, as published in reports of appropriate randomized studies or meta-analysis of high-level reviews of similar parameters. In the absence of such data, review of anecdotal literature may be undertaken with the caveat that current therapies may reflect long-standing clinical assumptions rather than demonstrated effectiveness, or that efficacy in tertiary centers may not have diffused sufficiently to prove effectiveness in the hands of the noninvestigative provider.

• Risk-benefit ratio for current therapies and a complete audit of complications, morbidity, and mortality associated with these current therapies must be established.

• Ease-of-use, learning curve, quality of life, discomfort level, required ancillary services for existing therapies and comparison to the proposed alternatives.

• Alternative therapies (eg, interventions replacing pharmacological solutions and vice versa).

These parameters will also be tied to the market dynamics: competitors, other projected developments, reimbursement patterns, previous failures in the same field with attendant analysis thereof, and distribution channels for competitive technologies.

Manufacturing diligence. Manufacturing standards must be established for the sites involved in producing the technology in question. This must include materials testing; appropriate fatigue, deformation, dysfunction, and breakage expectations based on well-engineered in vitro stress simulations; as well as sterility, packaging, labelling and adherence to international manufacturing standards.

Intellectual property. Intellectual property rights are critical to commercial success in most health-care related ventures. These rights ensure freedom to operate (not infringing on others' patents) and barriers to entry (disabling patents preventing others from competing in the same filed with similar technological solutions). Attention to intellectual property positions is an all to frequently ignored part of an early stage company's development or is lost in the rush to publish before the university or technology transfer group has appropriately secured its position for inventors and center of origin.

Management. By the time a biomedical technology has reached the maturity to attract outside investors, management of the project should be assumed by experienced business development. It is a common misconception that a technology's intrinsic capability will determine its success at the bedside. The process of fundraising, overall company vision, engineering, as well as the core, driving clinical or scientific competence that initiated the company in the beginning usually needs to rest with a management team that is differentiated from the scientific process or has significant administrative capacity and understanding of business dynamics. Founder-management combinations are possible; however, to justify funding, investors look increasingly to those with a track record in bringing biomedical technologies to market. Business judgement, like surgical judgement, involves recognizing one's limitations and seeking synergistic help, collaboration, and expertise to bring a project to a successful outcome.

SUMMARY

There is no magic to the capital-raising exercise for the young, technology-rich company. Most of the tenets and process expressed in this review are common sense. If a company has a clear vision of its ultimate goal, it will gain access to capital in form and amounts that will prepare it for that goal. The astute management team should also be able to avoid the traps that can stifle growth and ultimately prevent the technology from reaching the patient's bedside.

Despite the potential conflict that must be addressed when clinicians and investigators engage in commercial pursuits, it must be recognized that the very nature of medical practice and scientific discovery in our society is linked to material and personal reward that have long been tolerated and encouraged in both academic centers and community settings. Because the goal of all technology support and development, including the distribution of government grants, is to allow the fruits of intellectual labor to improve the lives and care of patients, responsible management of the process and effective communication among all responsible parties, rather than the stifling of entrepreneurship would seem to be a moral imperative on the part of both scientific founders and their university settings and the financial community. Understanding the process by which the goals of technology development are accomplished is one small part of this overall management.

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