

TRANSLATIONAL TOOLBOX

Entrepreneurialism in the Translational Biologic Sciences

Why, How, and However

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SUMMARY

Because they are perceived as distinct from the biological sciences, entrepreneurial pursuits may be daunting to the average researcher. In this report, we explain why academic scientists and in particular translational researchers should be naturally as well as rationally attracted to entrepreneurial endeavors. We go into some detail of how entrepreneurial achievements are actually accomplished and offer a few caveats for consideration when embarking down entrepreneurial pathways. We conclude that, although not for everyone, for translational investigators in the biologic sciences, entrepreneurial pursuits are desirable, accomplishable, and professionally rewarding. (J Am Coll Cardiol Basic Trans Science 2018;3:1-8) © 2018 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

The passage and signature into law in 1980 of the Bayh-Dole Act (1) is credited with transforming the U.S. economy from a manufacturing to an innovation-driven base (2). The basic thrust of the law was to transfer ownership of patents generated from federally funded research to the institutions under whose aegis the funding was awarded and where the work was conducted. The law was conceived and enacted in response to the recognition that taxpayer-supported research discoveries were not adequately benefitting the public, in a system where the federal government controlled patents and allowed only nonexclusive licenses to private sector companies seeking to develop the

intellectual property (IP) (2,3). The result of Bayh-Dole was an explosion in numbers of submitted and issued patents and their subsequent application (3,4). Part of the impact of Bayh-Dole legislation was the establishment of the U.S. biotechnology industry. In 2016, there were 2,772 biotechnology companies in the United States, approximately 50% of the world's total (5). Much of the industry is funded by venture capital (VC) investments in start-ups, the majority of which are scientifically founded by university-based researchers. Currently the U.S.-based biotechnology industry is at an all-time high in investment (6), and in terms of growth is outperforming the broader market (7). In this report, we discuss the basics of

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ABBREVIATIONS AND ACRONYMS

IP = intellectual property

VC = venture capital(ist)

VCFU = venture capital
fundable unit

why faculty-based translational scientists may want to participate as entrepreneurs in the biotechnology innovation arena, and how this is typically done. We also describe some of the caveats or “howevers” that should be considered before embarking on such a journey.

Although academically generated IP can be licensed to a third party for development, the emphasis in this paper is on the application of IP to found start-up companies where the IP inventor or inventors are playing important entrepreneurial roles. In addition, we are using a more expansive definition of biotechnology beyond the original description of “the use of living organisms to make products or run processes” (8) to include any IP discovered by a translational researcher working in the biological sciences that is entered into commercial development by a life sciences company, defined by a focus on development of biotech, pharmaceuticals, or medical devices.

Creating a life sciences start-up provides the means of realizing the full potential of a discovery or a new technology, which generally cannot be achieved in an academic lab where direction is typically driven by trainees seeking to make open-ended new discoveries. In this regard, it is worth highlighting the distinctions between the goals of academia and biotech. In academia, almost anything new can be interesting even when seemingly unrelated to a human disease or treatment, and the eventual connections between basic science discovery and a possible therapeutic might take decades to realize. In contrast, the primary goals of start-up companies are to optimize discoveries in a very directed way, which often translates into studies of toxicity, delivery, and pharmacodynamics. Such efforts are extremely important for therapeutic development and are not easily achieved in an academic laboratory.

WHY SHOULD TRANSLATIONAL SCIENTISTS CONSIDER ENGAGING IN ENTREPRENEURIAL ACTIVITIES?

POTENTIAL POSITIVE OUTCOMES. The reasons why academic scientists should consider becoming involved in entrepreneurial activities range from pursuit of positive outcomes to avoidance of some of the negative circumstances likely to be encountered in a typical career trajectory. **Table 1** lists some of these, in descending order of importance or encounter likelihood for positive or negative reasons, respectively. At the top of the positive list is to create a better chance of one’s discoveries entering into

commercial development, and ultimately being made available to improve human health. The alternatives to scientist-driven commercialization is to not have eligible discovery converted to IP, or to license IP to an outside organization such as a pharmaceutical or device company. In our opinion, it is the ethical if not legal responsibility of academic scientists to convert patentable scientific discoveries into IP that can potentially benefit the taxpayers who support research institutions and federally funded research. In other words, scientists should attempt to convert all eligible discoveries into IP. Once that is accomplished, the very difficult challenge of trying to move the IP into commercial development begins. Here the choice is between licensing the IP to an outside interest, typically a biotechnology, pharmaceutical, or device company, or attempting to develop the IP oneself. For various reasons, the latter option may have a greater chance of success.

If a scientist is able to use IP to found a company and then attract start-up investment, this will ordinarily be accompanied by research support to consolidate and extend the IP, some of which typically is done in the founding scientist’s laboratory. Depending on the strength of the IP, the licensing details of the IP, and the start-up characteristics, some of the funding may return to the scientist’s laboratory for general research support, in exchange for a first option of review or license of any new IP related to the research support. In an age of near single-digit National Institutes of Health pay lines, any type of additional research funding is generally viewed favorably. Another, less obvious potential benefit of successful entrepreneurial activity is that its recognition may influence other investigators or companies to invest in the research area, increasing the chance that something from the research sector will ultimately be available to society.

Regardless of the details of any entrepreneurial activity, once launched, the academic scientist will be exposed to new scientific and nonscientific perspectives and activities, none of which would likely have been encountered outside of the new venture. For example, in the science arena, it is likely that techniques beyond the scientist’s range of expertise will need to be employed, and to stay engaged in the IP development the founding scientist will need to become facile with them. Some of these might include high throughput screening and compound optimization, regulatory science, and clinical trial methodology. From the business side, the function of corporate governance, federal regulation, initial public offerings, and exit strategies will all become familiar to a scientist-founder.

Items 6 and 7 in the positives list in **Table 1** relate to 2 major regional favorable impacts of successful entrepreneurial activity. Job creation, often reaching substantial proportions, will stimulate the local economy and provide further impetus to the local biotech sector. And not to be ignored is the local stimulus to the regional economy of a successful company exit, where employees, local venture investors, and other regional stockholders recycle profits back into the economy and the sector. The last 2 entries on the positive side of **Table 1** relate to personal benefit to the scientist who successfully engages in entrepreneurial activity. The first (item 8 in the list) is based on our own anecdotal experiences, both personal and in observation of colleagues. There is a near-universal favorable effect of being involved in successful entrepreneurial activity that relates to its being interesting, challenging, and accomplishable. Any equity-based revenue accruing to the scientist is welcome but should not be a motivating factor in engaging in entrepreneurial activity. In our collective experience, the benefit of such revenue is more to defray or decompress the need to raise full academic salary support than to create personal wealth. This in turn allows more protected time for the scientist to pursue purely investigational activities, as opposed to supporting salary from administrative or clinical sources. The final point is that because most start-ups fail (see However section), the traditional pathway depicted in **Figure 1** is much more likely to result in economic gain. Stated succinctly, the gain of personal wealth is not a rational or valid reason to engage in scientific entrepreneurial activity.

Translational scientists are ideally positioned to engage in entrepreneurial activity in the biological sciences, because they are likely to be proficient in both basic and clinical research concepts and methods. Work in human systems may be particularly valuable because it may allow for earlier patentability of IP, based on the direct connection to therapeutic outcomes.

AVOIDANCE OF NEGATIVE CAREER OBSTACLES. On the negativity avoidance side of the ledger in **Table 1** are situations that may or may not concern an academic scientist. For some of us the “unicorn” career path portrayed in **Figure 1** is preferred to the standard academic career path, where after being a division or section director, one progresses to department chair, then dean, and so on, progressively gravitating away from personal research interests and activities in the process. The crossover from the traditional to the entrepreneurial path typically occurs at mid-career after a scientist is well established, but it can occur at any time during career development. The move into the entrepreneurial side does

TABLE 1 Selected Reasons for an Academic Scientist Becoming Engaged in Entrepreneurial Activities

| Benefits of Entrepreneurial Activities | |
|--|--|
| Potential Positive Outcomes | Avoidance of Negative Career Obstacles |
| 1. Improving societal health, through increasing the probability of commercializing discovery | 1. Potential release from the typical academic career path |
| 2. Creation of additional sources of funding, allowing for grant-independent research support | 2. Elimination of dependence on the academic system |
| 3. Potential of favorably influencing the scientific field | 3. Escape from monotonous and repetitive work routines |
| 4. Exposure to new research techniques and areas | |
| 5. Opportunity to experience and learn nonscientific skill sets | |
| 6. Job creation | |
| 7. Generation of investor and institutional return on investment | |
| 8. Positive effects on personal mental health through creation of an interesting, new challenge and an alternative career path | |
| 9. Source of personal revenue, relieving pressure to generate academic institutional salary support | |

not have to be and typically is not permanent, and the scientist may return to the traditional academic track while maintaining contact with the start-up company in the form of scientific advisory or other consulting arrangements. However, to maintain a meaningful impact on IP development as well as to extract maximum benefit from association with the start-up entity, it is advantageous for the scientist to maintain a formal management association with the company. Some universities allow this and some do

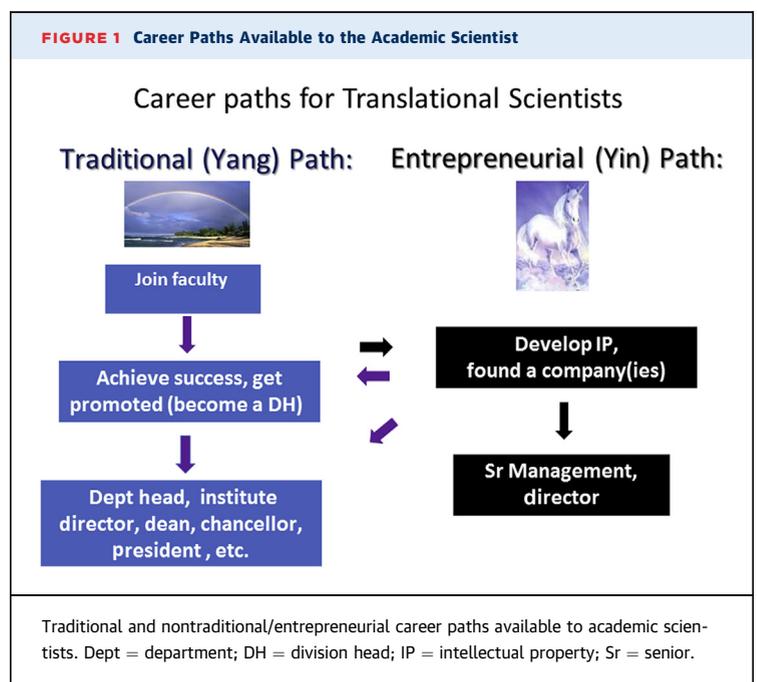


TABLE 2 Why Academic Scientists Are Natural Entrepreneurs

| |
|---|
| Thrive on uncertainty, do not require predictability for optimal function |
| Not bound by rigid goals, able to quickly adapt to changing circumstances |
| Effective in the <i>Iron Chef</i> (12) mode |
| Like to think big |
| Inherently optimistic |
| Not afraid to fail |
| Are essentially small businesspersons living by their wits |

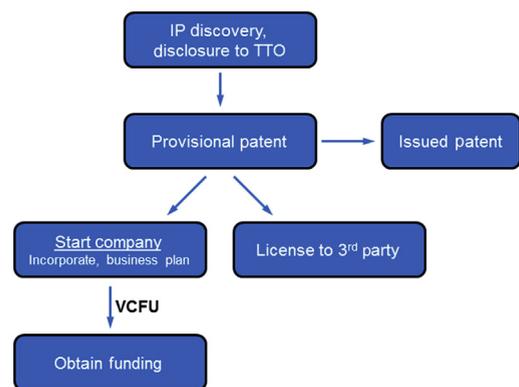
not, but we maintain it is in the best interest of a university to allow such arrangements.

ACADEMIC SCIENTISTS ARE NATURAL ENTREPRENEURS.

Potential benefits notwithstanding, another factor that should be considered when contemplating a move into or support of entrepreneurial activity is that by virtue of their nature (9), upbringing (10), scientific training and career experience, academic scientists are natural entrepreneurs (11). An entrepreneurial venture is basically a high-risk test of a hypothesis, in concept not unlike what is typically done in scientific laboratories. Table 2 lists some of the attributes that contribute to this natural entrepreneurial spirit. The typical academic scientist is comfortable with uncertainty, is capable of adapting quickly to a change in circumstances, and can function in the *Iron Chef* mode (11,12) to produce results with a minimum amount of starting material. In our experience, academic scientists like to think big, as the discipline selects for individuals who want to make a difference in terms of improving societal health. This is not simply a psychologically desirable trait, but it is also crucial to business tactics. The potential value of a venture is determined by its upside, because downside risk tends to be roughly the same across value propositions (13). The realities of scientific training and subsequent conditions for maintaining an academic laboratory eliminate pessimists and create an ecosystem where failure (of papers being accepted, grants being funded, and so on) is routine and is simply factored into tactics and strategy. And finally, because they have to balance budgets, hire and manage employees, and engage in high-risk and speculative discovery activities, academic scientists are essentially small businesspersons. All these factors favor a comfortable transition of academic scientists into entrepreneurial activities.

HOW TO MOVE BIOLOGIC DISCOVERY INTO COMMERCIAL DEVELOPMENT

GENERAL PROCESS OF CONVERTING SCIENTIFIC DISCOVERY AND IP INTO A VCFU. The process of creating a minimum venture capital fundable unit

FIGURE 2 Major Steps in Formation of a Biotech Start-Up

General process of converting intellectual property (IP) to a minimum venture capital fundable unit (VCFU) capable of developing the IP. 3rd = third; TTO = Technology Transfer Office.

(VCFU) of IP is straightforward (Figure 2), but execution of the component steps is not. The entrepreneurial “Valley of Death” for IP is the step of obtaining VC funding. VC groups vary tremendously in their appetites for investment, and if generally interested, all of them engage in extensive due diligence of variable quality. The challenge of obtaining VC funding is to convince a single fund to invest, because that investor will typically make a seed investment and then recruit other members of a syndicate into the series A round, the first major round of funding. The key to obtaining VC funding, assuming the IP has value and the founding scientist(s) are of high quality, is tenacity and willingness to continue engaging prospective investors in the face of serial rejection.

DETERMINANTS OF SUCCESS FOR BIOTECHNOLOGY START-UPS. Some major determinants of success for biotechnology start-ups are given in Table 3, in our estimated rank order.

Intellectual property. Assuming the founding scientists have no disqualifying characteristics, the most important determinant of start-up formation is IP. To

TABLE 3 Factors Influencing Success of Biotechnology Start-Ups

| |
|--|
| Intellectual property |
| Founders |
| Capital availability |
| Management and company strategy, including practicality of the scientific plan |
| Tactics and company execution |
| Geographic location |
| Sector and general economic cycles |
| Luck/serendipity |

TABLE 4 Favorable Characteristics of Academic Founders of Biotechnology or Device Start-Ups

| |
|--|
| Ideally should be at/close to the top or clearly headed for the top of their scientific field |
| Reputation for effective collaboration; should not be considered a difficult co-worker |
| Stellar ethical reputation; should not be controversial |
| Willing to commit long-term to the mission of the start-up |
| Open to sharing the responsibilities and recognition with co-founders and senior management; "team player" |

be of high value, the IP that serves as a platform for the start-up ("actionable IP") should be patentable, address an unmet medical need, have the potential for a large return-on-investment, and be amenable to a cost-effective and executable development strategy (14). Not only does IP need to meet these criteria, but the data and materials have to be developed to communicate these characteristics to potential investors.

Founder's qualifications. Scientific founders of life sciences start-ups are a diverse group who possess a wide array of backgrounds and strengths. Although the most important, critical path-enabling aspect of converting scientific discovery into successful entrepreneurial activity is the strength of the IP, the perceived quality of the founders is also heavily weighted by most investors. For some VCs, the value of founders' qualifications exceeds that of the IP, termed "betting on the jockey, not the horse". In any event, there are a few founders' characteristics that bear consideration (Table 4). Although not all of the characteristics listed in Table 4 are or need to be inherent in successful scientist-entrepreneurs, typically most of these attributes are present and major deficiencies in any of them are potentially disqualifying to astute investors. Note that the career trajectory position is not listed as a factor; provided that criterion 1 in Table 4 is satisfied, a founder may be an early-, mid-, or late-career investigator. Also, in device start-ups, criterion 1 is not applicable. For device development there is less of a funding requirement and a shorter development time, and it is not uncommon for cardiovascular junior scientists to found companies.

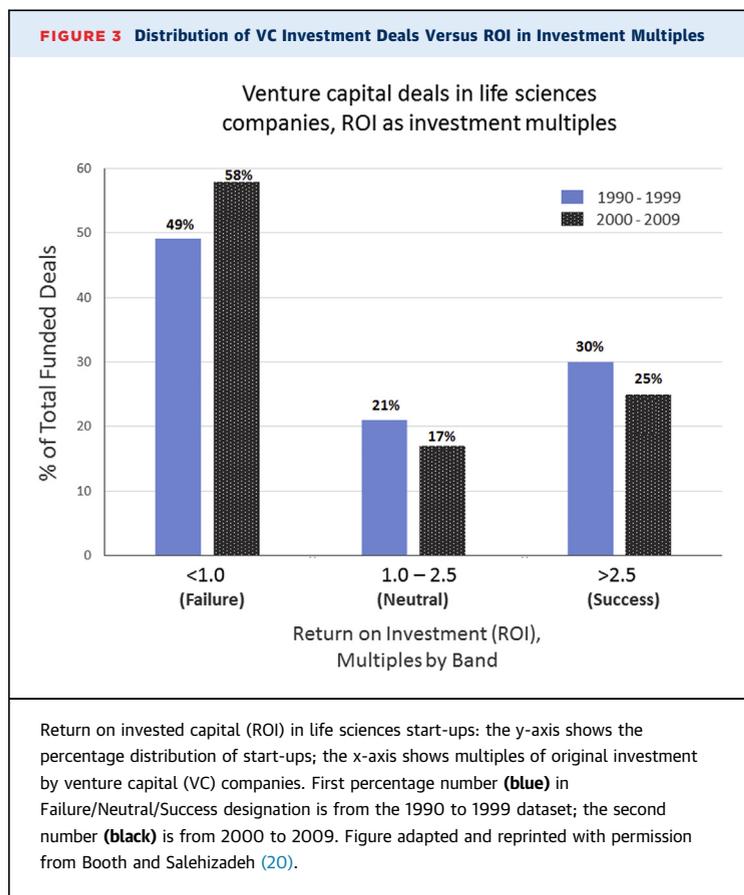
Capital acquisition. There are 2 general strategies for ongoing capitalization of a start-up company. At 1 pole is a strategy typically favored exclusively by some founders and management, which can be characterized as "raise all the capital possible, all the time, from any source." This approach may allow for developing multiple assets, thereby hedging risk of failure of any 1 program. However, the additional capital in-flow dilutes out early stage investors, who may prefer

hedging their own risk through single-asset investment in other companies. In addition, this model commits senior management to a continuous cycle of fundraising (15), which will necessarily be accompanied by less focus on the company's primary business. An alternate model at the other end of the spectrum and favored by some VCs is the capital efficiency model (16), where investment is typically limited to the initial asset on which the company was founded and financing stages are dependent on valuation step-ups to reduce capital cost. The more realistic and usual approach is typically something in between these 2 extremes. The fact is that scientific founders are usually not in a position to select one model versus another, given the exigencies of fundraising.

Company direction. Once a start-up company is founded and has secured its series A funding, there are a few "good business practices" that deserve mention. The first is that capital is precious, and operations need to proceed on the most parsimonious course that allows for meeting program objectives in a timely manner. The second is that to be successful in the context of finite resources, mistakes in direction or execution must be avoided, which means experienced personnel must be brought into management positions ranging from directors to company officers. The choice of board members is another critical step. Here the blending of multiple backgrounds relevant to the company's mission is the major challenge, followed closely by the choice of individuals with track records of working effectively with others. The board and senior management are responsible for setting strategy, but equally important are the execution tactics that are the major responsibility of mid-level and project managers.

Geographic location. We believe it is important to consider where to locate a life sciences start-up. Among the important factors are: 1) proximity to a major research university, typically that of a founder; 2) a region with enough ongoing sector business activity to have created a pool of qualified potential employees; 3) a locally favorable cost of living/quality of life index; and 4) a favorable business climate. Collectively we have founded or co-founded companies in Northern California; Boulder/Denver, Colorado; Boston, Massachusetts; and Dallas, Texas, all of which at the time of founding satisfied the above-mentioned criteria and were able to attract adequate human and financial capital.

External factors. Table 3 lists 2 factors beyond the control of founders, management, and directors; sector or general economic cycles; and good or bad fortune. For example, during the major recession in 2007 to 2008 it was not possible to raise capital, and



creative financing instruments such as reverse mergers had to be resorted to in order to maintain start-up viability. Luck and serendipity are always factors, at all levels of scientific activity. Serendipity plays a major role in scientific discovery as well as product development (17), and luck tends to favor a well-organized/opportunistic organization (18) as well as one that is unafraid of risk (19).

HOWEVER, ENTREPRENEURIALISM IN THE TRANSLATIONAL SCIENCES IS NOT FOR EVERYONE

FAILURE IS THE MOST LIKELY OUTCOME. The sobering reality of academic scientist entrepreneurial endeavors is that the vast majority of them fail, at least from a conventional business context. In a survey conducted by the University of Colorado Technology Transfer Office in 2013, of IP with provisional patents submitted deemed worthy of seeking seed or other start-up funding, only 25% were successful. A comparable figure from research universities in the Boston area (B. Booth, personal communication, October 4, 2010) was 33%. Figure 3 gives the outcomes

of VC investments from nearly 1,300 VC companies, by decade from 1990 to 2009 (20). Defining post-financing failure as a return multiple of <1.0 yields an approximate 49% to 58% failure rate, whereas success defined as a multiple of >2.5 gives a success rate of 25% to 30%. If a neutral rate of multiples between 1.0 and 2.5 (17% to 21%) is included with the failure subgroup, approximately 72% of funded start-ups will not have success as defined by investment metrics. Multiplying the odds of receiving seed funding for candidate IP of 0.30 yields a net probability of success of 0.30×0.28 , or 0.084. If the neutral band in Figure 3 is included with the success subgroup, the odds become $0.30 \times 0.465 = 0.14$. Therefore, the chance of failing to turn actionable IP into a successful start-up is in the 86% to 92% range. As daunting as these odds are, they are not dissimilar from the National Heart, Lung, and Blood Institute ROI pay line.

But there is another perspective on life sciences start-ups, from a founder's point of view. A <50% chance of success is factored into the calculus of venture investing, accepted as the cost of doing business. The VC perspective is that return on investment is not normally distributed, and they depend on the occasional large multiple (>5-fold) to generate net fund profit. For founders, a good analogy is major league baseball, where hitters fail at least 2 out of 3 times but sustaining this batting average over time qualifies them for the Hall of Fame. Although serial failure will lead to loss of investor confidence in founders, an early success will allow a certain degree of failure tolerance. In any event, the most effective way to become proficient in entrepreneurial ventures is to participate in them, and the experience gained increases the probability of success for subsequent endeavors. Failure to return a sufficient multiple therefore is not considered a disqualifier for future venture investment in founders and their IP, as long as the founder's participation in the start-up is viewed as positive.

ENTREPRENEURIAL ACTIVITIES MAY NEGATIVELY AFFECT ACADEMIC PERFORMANCE. Regardless of the role assumed by an academic founder in a start-up, these activities will be time-consuming to some extent. In our experience, meaningful full-time equivalent fractional contribution to a start-up will range from 0.25 to 0.50, requiring the academician to relinquish some academic responsibilities. For nonsystematic participation, full-time equivalent contributions of 0.05 to 0.10 are a reasonable estimate. In order for the founder-scientist to maintain

academic expertise, the activities that are abdicated need to be in nonresearch areas, and there needs to be adequate compensation from the start-up to compensate the academic unit and the founder for this loss of job effort and salary. In reality, these are not difficult issues to resolve if university leadership is flexible and in favor of faculty entrepreneurial activity.

CONFLICT OF INTEREST ISSUES. Although conflict of interest issues are of theoretical concern, in an era where most research universities aggressively endorse entrepreneurial activity (21-23), this has become less of a problem. In fact, a persuasive argument can be made that federally funded scientists and research institutions have a moral obligation to convert their discoveries into useful medical products or services (23). There are several keys to avoiding conflict of interest entanglements. The first is a transparent, fully informative, and accurate conflict of interest disclosure that is updated annually or whenever circumstances change. The second is to ensure that the university, the legal holder of the start-up IP in most cases, is directly involved in the start-up. This means that the IP license from the university to the start-up includes royalty and milestone payments, as well as equity with antidilution provisions. These measures essentially align the university's interests with the founding scientist's, eliminating any fundamental basis for conflict and avoiding a misguided "damaging solution in search of a problem" (24).

DISTRACTION FROM OR LOSS OF ACADEMIC RESEARCH FOCUS. Because a start-up is labor intensive and its activities are usually quite interesting to most founders, there may be a tendency to spend more time than is necessary on company issues. Unless a founding scientist leaves his/her academic position and joins a start-up full time, it is imperative the scientist maintain and ideally even accelerate his/her company-unrelated research activities. The main value of a founding scientist to the start-up is the index IP generated in the founder's laboratory, and the scientist's ongoing activities and reputation continue to factor into the IP's worth. Perhaps even more importantly, the potential for new or supportive discovery from the founding scientist's laboratory adds value to the company, which based on the licensing arrangement of the original IP is typically in first position to acquire rights to any additional discovery. How to balance these sometimes-competing interests may become a challenge, but the founding scientist should not forget that his/her value to the start-up is as a

successful independent scientist positioned on the cutting edge of an important field, and this status should be maintained or extended.

INADEQUATE TRAINING AND PREPARATION FOR ENTREPRENEURIAL ACTIVITY. Most academic entrepreneurs are self-taught and do not have business backgrounds or formal business school training, which is certainly the case for us. However, some formal instruction in relevant topics such as IP process, patent law, finance and business tactics and strategy as applied to the life sciences sector may be available in academic centers. If research universities want to maximize their entrepreneurial potential, they should offer or have access to these types of didactic programs, if for no other reason than to raise the faculty level of consciousness for IP development. However, it should be emphasized that the steps involved in entrepreneurial activity can be self-taught or sought from more experienced individuals, who typically are willing to be helpful.

CONCLUSIONS

Participation of translational scientists in entrepreneurial activities can be effectively woven into an academic career without major difficulty. Most technology transfer offices at research universities possess the expertise to assist investigators in these endeavors. However, successful outcomes in life sciences entrepreneurialism are low-probability events whose likelihood can be increased by the quality of the founding IP, the strength of the founding scientists, and other factors. By far the most compelling reason to engage in life sciences entrepreneurial activity is to attempt to shepherd one's discoveries into the marketplace, that is, to ensure that research progress translates into societal benefit. This principle is codified in U.S. federal law, and should also be considered a moral obligation of the research enterprise.

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