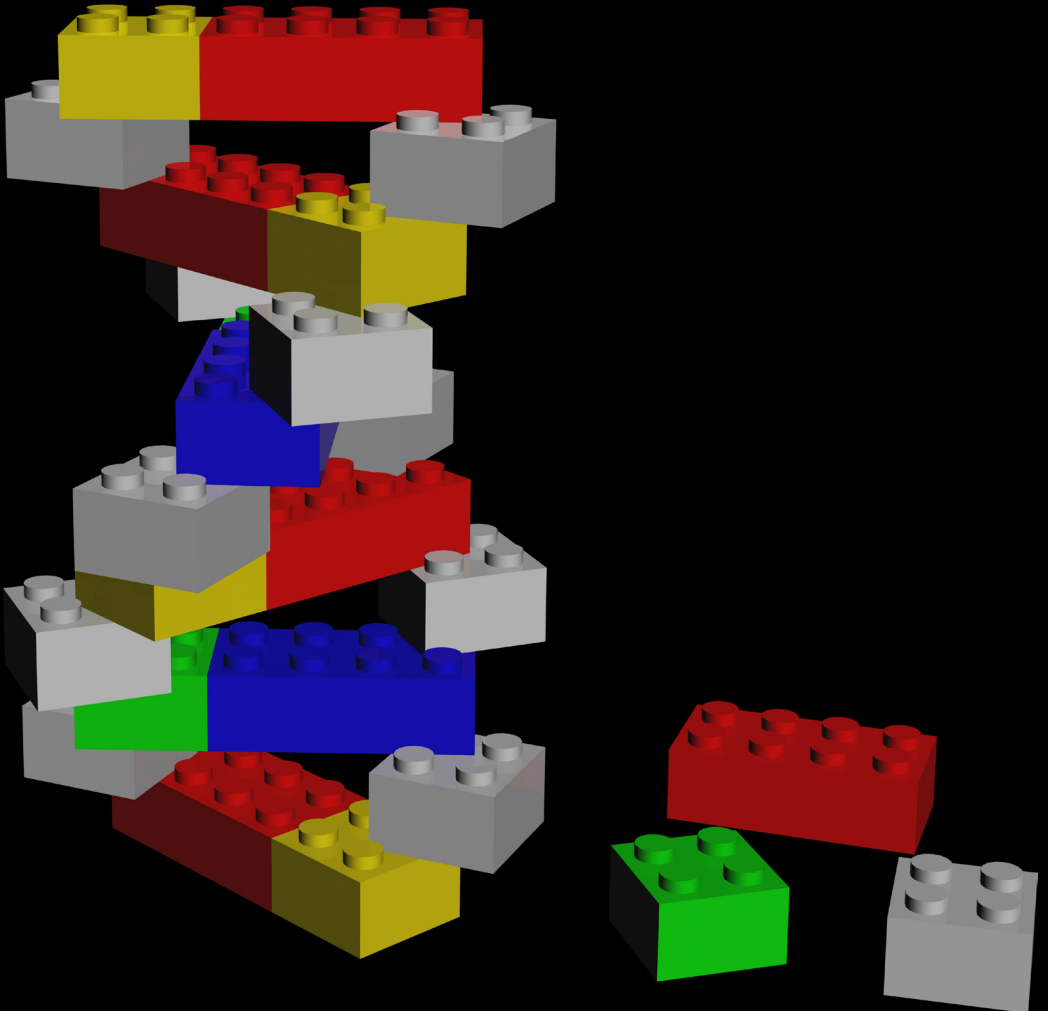


Third Edition

BUILDING BIOTECHNOLOGY

Business • Regulations • Patents • Law • Politics • Science

Yali Friedman



B U I L D I N G BIOTECHNOLOGY

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Third Edition

Yali Friedman, Ph.D.



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To my family, who have inspired, motivated, and supported me.

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Building Biotechnology

Doriot's Rules of Investing

Seek companies demonstrating:

- New technology, new marketing concepts, and new application possibilities
- A significant participation by investors in management
- Staff of outstanding competence and integrity
- Products or processes that have been prototyped and have intellectual property protection
- Promise to enable an initial public offering or sale of company within a few years
- Opportunity for a venture capitalist to add value beyond dollars invested

General Georges Doriot of American Research & Development, the first dedicated venture capital firm

Successful biotechnology business development relies on three elements: technology, management, and capital. The basic value proposition of biotechnology companies is to develop applications based on proprietary technologies, granting them monopolies on the products of their R&D investments. Research and development are supported by management and capital. Management is responsible for identifying commercial possibilities for the markets a company wishes to target, and for positioning the company to realize them; capital is required to fund research and development and ultimately enable commercialization.

An examination of the qualities sought by offices experienced in launching biotechnology companies provides practical examples of factors important for long-term success. According to MIT's Tech-

nology Licensing Office, “[p]ositive indicators include very early-stage research, a technology that has several potential applications, no existing companies dominating the field, and an inventor who wants to participate actively in his or her invention’s commercialization.” They observe that emerging technologies with multiple new markets are often best exploited by focused and dedicated entrepreneurs who are funded by venture capitalists with an understanding of technical and business risk and reward.

Manchester Innovation Ltd., a technology transfer arm and incubator attached to the University of Manchester in England, requires that prospective clients complete the following objectives:

- Define the company’s patent strategy and likely market potential for its products
- Write a robust business proposal
- Obtain at least seed finance
- Set up a board of directors and core team

They identify the most common blind spot for founders as a failure to realistically evaluate the market value of future products and acknowledge competitors.

Fundamental questions that should be asked in evaluating a venture are whether a sufficiently large market exists and if it can be profitably served. Unsubstantiated estimates such as “we expect to serve x percent of the \$ y billion market” indicate a fundamental lack of understanding of business development needs. It is not sufficient to simply assume acquisition of a proportion of an existing market. As illustrated in Figure 13.2 in Chapter 13, an in-depth analysis is required to measure the size of the reachable market. A bottom-up analysis is also essential to account for the key actions and costs involved in acquiring market-share and serving a market.

Many entrepreneurs also fail to account for all existing and potential competitors, or their responses to new market entry. Some competitors may already serve the target market, but potential customers may also be using alternative solutions. These alternatives may not be immediately apparent. Even products addressing unmet

needs may face competition; horse-drawn wagons were competitors to the first cars. Additionally, products for previously untractable or unidentified problems may face challenges in convincing potential customers that the unmet need exists and the solution being offered will work.

Potential competitors, represented by future technologies, must also be considered. Even with a complete inventory of competitors, a common mistake is to assume that competitors will act rationally.

BUSINESS MODEL

Biotechnology business models (described in greater detail in Chapter 10) can be segmented into a few discrete types, each with characteristics that suit them for specific contexts. Factors such as technical challenges, barriers to entry, and the level of competition in a sector (see *Porter's Five Forces* in Chapter 13) may dictate the best model for a new entrant or incumbent firm.

In an environment where barriers to entry are relatively low—no “gatekeepers” controlling markets through broad patents or domination of marketing channels—and the financing climate is amenable, dedicated product development may be a good strategy. As markets mature, control of markets through patents and ownership of key infrastructure or sales and distribution channels limits the ability of new entrants to reach customers, making tool or platform approaches preferable. Other situations, such as a glut of viable drug leads favor “no research, development only” (NRDO) models (see *Specialty Pharmaceutical / NRDO Models* in Chapter 10).

There are often several modes by which an invention can be commercialized. The processes of selecting a business model and attracting funding are linked. Some of these may be more lucrative than others, but attracting funding may ultimately require crafting an opportunity that suits market trends and the interests of investors.

When technological uncertainty is high, or when funding is particularly challenging to obtain, hybrid approaches may be favorable. A company developing a new drug screening method, for example, may prefer to initially focus on refining that technology and licensing it to industry partners. These licensees can offset R&D expenses

Table 17.1 *Biotechnology business models*

General models	Characteristics
Product development	High risk, high reward. Requires supportive financing environment.
No research, development only (NRDO)	Reduced risk, high reward. Dependent upon ability to acquire drug leads; lack of internal R&D challenges decision-making and long-term growth.
Reagents and tools	Low risk, low reward. Subject to commoditization and obsolescence; success is predicated on dominating markets and niches.
Service provider	May deliver value by aggregating technologies from multiple companies, or offer economies-of-scale by ensuring full-utilization of expensive equipment.
Special models	Characteristics
Hybrid product / platform	Reduces risk of product development, allowing a company to prove technologies and generate revenues. Potentially distracting to management and R&D efforts. May be used to distract investors to failing core activities.
Virtual company	Effective for bootstrapping start-ups, difficult and expensive to manage at later stages.
Non-profit	Requires charitable donations and ability to license viable abandoned leads from incumbents.
Repurposing	Similar to NRDO. Requires ability to license and patent existing drugs for new uses.

See Chapter 15 for more detail on business models

while vetting the technology. Once the technology has been proven by external partners, the licensor will be able to cite these cases to financiers, reducing risk and facilitating funding.

FIRST STEPS

With an understanding of the fundamentals of biotechnology business development and a commercial idea, the biotechnology entrepreneur is faced with the challenge of how to proceed. What

should one do first: Write a business plan? File patents? Assemble a management team? Raise money? Perform critical proof-of-principle research? Completing these critical steps in an appropriate order is essential for success. Bad timing can lead to false starts or loss of commercial opportunity.

Technology is first and foremost in biotechnology. Biotechnology is innovative by nature, so the goal of most biotechnology companies is to produce products and services that satisfy market needs and generate profits. But technology is expensive to initially develop, and tends to be less expensive to copy, so it is necessary to protect new technologies through patents, trade secrets, employee confidentiality agreements, or other means.

Because a competitive advantage is central to commercializing biotechnology, this must be secured first. Without possession of a competitive advantage, it will be difficult to attract talent and funding. It is important to validate a competitive advantage. What may seem at first to be a patentable invention may have been previously published or patented by another party. Likewise, an invention developed during or even outside of working hours at a previous employer may still be property of that employer.

While patents are commonly used to secure a competitive advantage, there are other possibilities. Trade secrets are an alternative means to protect inventions; invention assignment, non-disclosure, non-competition, and non-solicitation clauses in employee and consulting contracts can prevent leakage of this information. A company can also obtain an exclusive or limited license for an unexploited technology, a common method in

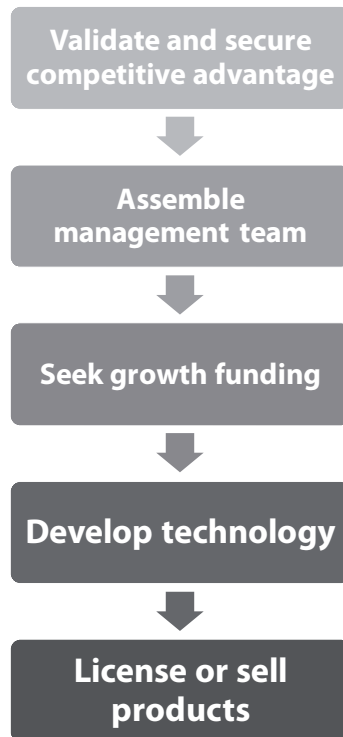


Figure 17.1 *Building a biotechnology company*

university and corporate spin-offs.

With a protected idea, the next objective is to assemble a management team. Investors, seeking a return on their investment, will demand evidence that a company can succeed. While technological abilities and market opportunities can predict how successful a company may be, skilled management is essential to realizing commercial goals. Therefore, investors will either demand evidence of capable management, or will use their own resources to locate and install necessary talent.

Because of the central importance of funding, a balance must be maintained between supporting long-term commercial goals and meeting the relatively shorter-term needs of investors. The primary causes of biotechnology company failure are mismanagement and undercapitalization. Accordingly, biotechnology companies should secure able investors and ensure that performance and economic-based milestones are consistently met.

SELECTING OPPORTUNITIES AND BUSINESS PLANNING

It is not the planning that is important; it is the planning that makes you able to change it.

Dwight D. Eisenhower

To attract investors and build a biotechnology company, a commercial idea must exist with the potential to generate revenues. Innovative technologies and ambitious goals may attract press attention and early investors, but continued success requires profitable commercial execution.

Consider the case of Genentech. The company quickly completed proof-of-principle research to demonstrate the power of their revolutionary bacterial protein-expression system and signed a development contract with the insulin market leader to produce human insulin. After developing a method to produce human insulin in bacteria, Genentech applied the same basic techniques and secured external funding under more favorable terms to produce human growth hormone. While Genentech has since diversified into additional research areas, their initial plan focused on a single,

patent-protected, new technology with multiple defined commercial possibilities (see Box *Genentech: Commercializing a new technology* in Chapter 2).

The primary objective of a biotechnology start-up is to secure a competitive advantage, followed by assembling a management team and obtaining funding. At some stage in this process, a business plan will have to be formulated.

Business plans often change as a company develops. One of the objectives of formulating a business plan is to determine the best course for implementation. While the initial business plan may be a rudimentary outline of a commercial idea, investigations into the feasibility, applications, and market potential of the idea can lead to modifications, resulting in a relatively stable concept that justifies the formation of a company. If an idea has a small market, requires an extremely large investment, or can only be used as part of a third party's patented process, it may be better to sell or license the idea to appropriately positioned firms.

Commercializing biotechnology is a long and challenging process. It is essential to formulate at least a rough plan for commercialization before committing too many resources. In evaluating a core technology, look for intellectual property protection and the ability to generate multiple products or services. Applications should be judged by the criteria presented in Chapter 12: freedom to operate, availability of technological factors, and ability to generate a profit. Before investing too many resources in research and development, it is vital to develop an understanding of who the customers are and how they can be reached. In developing a company, look to Doriot's rules presented at the beginning of this chapter and the criteria sought by university incubators. These are the elements that investors will look for. Why wait until you meet investors to justify whether an idea is marketable?

REDUCING RISK AND MAKING MONEY

The risk-tolerance of investors and their desire for either low-risk or high-return investments (these are not necessarily mutually exclusive) change with market sentiments and ultimately influence

Box**Want biotechnology funding? Use a shotgun!**

One of the challenges in attracting funding is finding an investor aligned with your company's future directions. Venture capitalists and angels may be interested only in large companies, in small companies, in diagnostics, in drug development, etc. One of the challenges, and opportunities, for small firms, is that their future is very uncertain. This makes it difficult for founders to decide how to pitch their company to potential investors, but it also makes it possible to pitch more than one version of the company. Not all these versions may align with the founder's visions, but if they facilitate funding they may be a worthwhile digression.

Rather than limiting the set of potential investors to those whose investment criteria are compatible with the founders' visions, it may be preferable to leverage a company's core elements to appeal to a wider variety of investors. Using a shotgun approach, it is possible to craft several business plans based on a common set of resources, each aimed at a different kind of investor, and to simultaneously pitch these different plans to appropriate VCs.

For example, a firm developing drugs based on a proprietary technology can be pitched as a drug development firm, a platform-licensing firm, or both. It can even be split into two entities—one focused on licensing the platform technology and the other as a licensor of the platform for specific applications. A firm focusing on drug development will have a very different structure than one focusing on licensing. The former will need extensive partnerships and resources to complete development, whereas the latter can be far leaner and focus on using partners to vet the technology to promote further licensing or to facilitate future funding for drug development.¹ Therefore, even if the founder's desire is to focus on drug development, a near-term platform focus can attract funding for later drug development.

The key element is to be creative in seeking funding and avoid unnecessary elimination of options. Most investors will realize that there is a great deal of flexibility in a start-up's business model and business plan, because there are so many unknown elements in a young company, and pitching to more investors increases the likelihood of attracting an investment.

¹ A similar strategy has been used successfully by Domain Associates' Eckard Weber: <http://invivoblog.blogspot.com/2007/08/one-two-punch-in-venture-capital.html>

how much equity an investor will seek in exchange for a given investment: the cost of capital.

Risk is inexorably tied to revenues and profits. Investors in biotechnology companies seek assurances that they will receive a return on their investment. Investors will seek greater portions of equity commensurate with the perceived level of risk, which influences their expected return on investment (see *Valuation* in Chapter 11).

In risk-averse markets an effective way to reduce risk is to demonstrate the ability to generate revenues, and preferably net income, as soon as possible. This may require favoring near-term outcomes at the expense of long-term objectives by reducing R&D expenditures, seeking approval for smaller and/or safer markets, or selling lead compounds. In risk-tolerant markets, where investors may expect greater returns, a focus on short-term revenues can jeopardize long-term profitability by distracting management and R&D efforts from long-term value creation activities. The best way to attract financing in risk-tolerant markets may be to eschew organic growth in favor of large markets, synergistic acquisitions, and bold goals, in an effort to meet the high rate of return expected by investors.

A desire to avoid equity dilution motivates the pursuit of equity-free financing options (described in the section *Other Funding Sources* in Chapter 11), although in many cases equity financing can provide substantial benefits in terms of speed and flexibility. Founders may also seek to reduce the size of investments they are looking for in an attempt to control dilution. This strategy may backfire, as it

Table 17.2 *Raising funds to reach developmental milestones*

Milestone	Funding stage	Funding amount / burn rate
Proof-of-principle	Seed	\$300-600k 3-6 months burn
Prototype	First-round	\$1-5 million 1 year burn
Early product development	Early mezzanine	\$5-15 million 1-1.5 years burn
Commercial launch	Late mezzanine / IPO	\$20-50 million 2-3 years burn

Source: Birndorf, H.C. Rational financing. *Nature Biotechnology*, 1999. 17:BE33-BE34

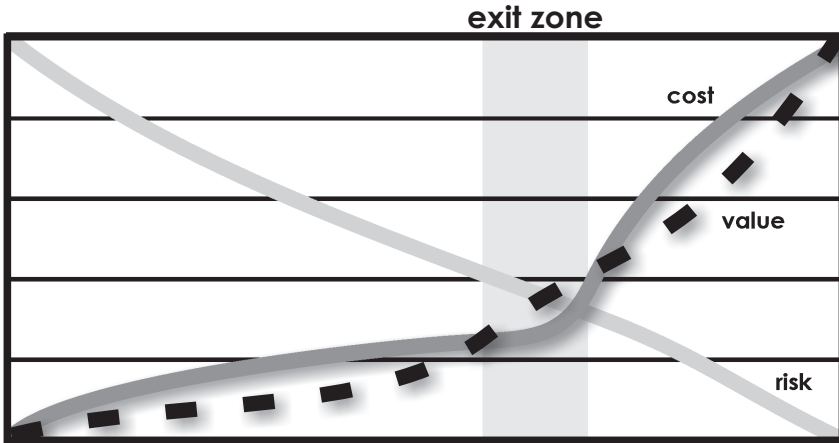
can leave a company with insufficient cash to reach the next funding stage. In a famous example, Hybritech, one of the first biotechnology companies, asked for \$178,000 in seed funding to fund research in preparation for first-round funding. The investors, sensing that more money was needed, gave Hybritech \$300,000. Asking for too little money can also discourage investors. As described in the *Box Venture capital: The poker analogy* in Chapter 11, investors are seldom shy about funding strong companies and often seek to invest as much as possible at the most attractive entry points as a means to maximize their returns. Asking for too little money may indicate modest goals (and, by extension, modest outcomes), encouraging potential investors to seek other opportunities.

MAXIMIZING MULTIPLES

The ultimate goal of biotechnology companies is to use molecular biology techniques to produce novel products worthy of a price greater than the investment in developing those products. While it was once possible for nascent biotechnology companies (e.g. Amgen and Genentech) to develop into fully integrated research, development, and commercialization enterprises, market dynamics have made it much more cost-effective for companies to specialize in discrete elements of this pathway. To be profitable, it is essential for R&D firms to focus on maximizing multiples: developing products and selling them when the cost of further development exceeds the value created by additional R&D, and when further development can be more efficiently and effectively performed by another entity.

In developing a biotechnology product it is vitally important to be cognizant of the actions necessary to reduce risk and increase the value of products in development, and the cost of those actions. Cost, in this case, is not directly measured in dollars, but rather by time and loss of equity.

While equity-free funding is available for biotechnology development, it tends to be restricted to early-stage activities. Development-stage activities generally require exchange of company equity for funding (see *Development Stages and Funding* in Chapter 11). Figure 17.2 shows a general scheme of biotechnology value creation



concept > patent > pre-clinical > clinical trials > approval

Figure 17.2 *Value creation in biotechnology*

in concert with risk reduction and cost for a nascent biotechnology firm, in a hypothetical environment where the returns on investment are optimal for exit in early clinical trials.

As a commercial idea matures from concept to tangible product, the risk of the opportunity decreases. The development cost naturally increases during development, as does the value of the product in development. The factors determining cost, value, and risk are independent of each other (a decrease in risk does not necessarily produce a commensurate increase in value), but are dependent upon the product being developed, a company's business model and resource base, and market conditions determining cost of capital and the value of products in development.

In this very simple example, the cost of proceeding beyond early clinical trials exceeds the value creation of these investments, making early-clinical trials the optimal point to sell a product (e.g., selling Phase I or Phase II leads). Selling prior to the "exit zone" (prior to early clinical trials in this example) is an unfavorable option, because the value of the hypothetical products is less than the cost incurred to proceed to that point of development—not enough risk has been removed from the investment. Selling after the exit zone (after early clinical trials in this example) is also unfavorable, because the

costs of proceeding past the exit zone exceed the increase in value—while the risk has been sufficiently reduced, the capital expenditures are too great. The company in this example would therefore be best served by licensing or selling drug leads that have passed early clinical trials to parties who can perform late-stage development at lower costs.

INTEGRATE MARKETING EARLY

A common cause of product failure is poor integration of marketing with R&D decisions. Biotechnology is innovative by nature, so many products get developed based on availability of new technologies. This is termed a “technology push,” and can lead to development of products with no market. So it is important to start from the endpoint—sales—and consider market needs and demands in directing product development. Many investors and entrepreneurs fail to consider marketing and reimbursement issues, focusing on actions required to sell drug leads or entire companies well in advance of commercialization. This myopic view can lead to problems when the time to sell comes, as downstream partners or investors may be unwilling to consider technologies with poor market potential.

Some of the questions which should be asked early in development are:

- Is there a market willing and able to pay for potential products? What is the path to the market?
 - See Box *Biotechnology myth: Build it and they will come* in Chapter 13
- What regulatory incentives can you leverage?
 - See Box *Genzyme: Building an enterprise on orphans* in Chapter 8
- What resources and partnerships will be required to complete development and reach the target market?
 - See Box *Exubera: When your partner doesn't sell* in Chapter 14

In some cases it is not possible or relevant to answer all these

questions at the outset. For novel products, certain marketing issues may not be known until the product is launched. For early-stage products or those serving dynamic markets, it may not be appropriate to dedicate too much time to measuring markets, as the target markets and products themselves may change over the course of development. However, in these cases it is still important to track marketing issues and to continually reassess them as products mature. Failure to do so may result in development of products for markets that don't exist, or for markets that don't need them.

EXITS AND OPTIONS

It is vital, at a very early point in a company's development, to formulate a path to maturity or exit, and to start planning for unforeseen obstacles. Just as excessive focus on developing technology, to the exclusion of marketing, can lead to failure, it is also important to consider the path a company will take. Some of the questions which should be asked while planning for growth, exits, and contingencies are:

- What if your lead project fails?
 - See Box *Dangers of not having a pipeline* in Chapter 12
- What if your product doesn't have the properties you hoped it would?
 - See Box *Flavr Savr tomatoes: Operating in unfamiliar markets* in Chapter 15
- What if the demand for your product exceeds your capacity?
 - See Box *Enbrel: Underestimating market demand* in Chapter 13
- What if you lack freedom to operate?
 - See Box *Amgen v. Transkaryotic Therapies: Strategic patenting* in Chapter 7
- How do you resolve a valuation disagreement
 - See Box *Remicade: Resolving valuation disagreements* in Chapter 14

- How would you prevent or manage a product recall?
 - See the section *Off-Label Use* in Chapter 8 and Box *Preventing a product recall from bankrupting a company* in Chapter 15
- Do you have a plan for succession?
 - See Box *Replacing founders* in Chapter 10
- What if the IPO window closes?
 - See Box *Alternative route to going public* in Chapter 11

These plans do not need to be rigid or exclude other options, but they are essential to help set future goals and measures of progress. A company seeking to be acquired, for example, should develop in a different manner than one seeking an IPO. The former should focus on developing products which could demonstrate near-term value to acquirers, while the latter should place more emphasis on demonstrating the capacity for long-term growth. Failure to plan for growth and commercialization (or exit) can result in disorientation and lead to failure. Operating without a set of goals and plans to achieve those goals can leave a company unable to make important decisions, and may also motivate investors, partners, and employees to seek better-defined opportunities.