

WHAT *EVERY* ENTREPRENEUR NEEDS TO KNOW

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ACKNOWLEDGMENTS

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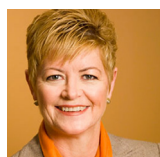
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Bruce Booth,
Partner, Atlas Venture



Ron Cohen,
MD, CEO,
Acorda Therapeutics



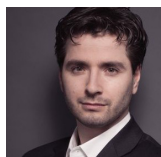
Deborah Dunsire,
MD, CEO, XTuit
Pharmaceuticals



Michael Gilman,
Chairman and CEO,
Arrakis Therapeutics



Kevin Kinsella,
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Avalon Ventures



Peter Kolchinsky,
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Terry McGuire,
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John Carey is a contributing editor at Xconomy and former long-time senior correspondent at BusinessWeek magazine, where his many cover stories covered topics ranging from the biotech revolution and the human genome project to the efficacy of cholesterol-lowering drugs and the science and business impact of climate change.

Carey's stories have won awards from the American Association for the Advancement of Science, the Association of Health Care Journalists, and a number of others, and he was also a National Magazine Award finalist.

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INTRODUCTION

Every year, roughly 100 new biotech companies are formed. Most will fail, because an idea or a research finding, however brilliant, is just the starting point.

Creating and building a biotech company means traveling down a long and challenging road. The startup must get funding, build a team, bring in collaborators, prove the science in the lab and in the clinic, create a compelling business plan, devise a strategy for bringing a product to market, and keep the momentum going through the decade or more it takes before revenues start rolling in. "The thing that's striking about biotech is that you have to build a business where you know the first decade is all about losing money," says venture capitalist Terry McGuire at Polaris Partners.

It's a long and daunting list of steps and requirements. In fact, when Peter Kolchinsky, now Managing Director of RA Capital Management, set out to distill the advice of more than 60 biotech executives, venture capitalists, scientists, and other experts, the manual he wrote, *The Entrepreneur's Guide to a Biotech Startup*, was nearly 100 pages long.

Last updated in 2004, Kolchinsky's guide is still very valuable. It covers everything from the essential elements of a business plan to getting patents and raising money, and has been used in classrooms around the world.

But a general guidebook, no matter how comprehensive, may not prepare a budding entrepreneur for all the challenges that lie ahead, for the simple reason that every startup story is unique. The starting point can be a scientific breakthrough or a new technology platform, or just a passion for finding a solution to an important unmet medical need. Companies have been successfully launched both by experienced biotech hands and by academics with no business background, even by MBA students.

Moreover, the paths of biotech companies are rarely smooth. Most startups experience devastating failures in the lab or the clinic. Others abandon their original business models, for instance switching from marketing genetic information to discovering drugs in-house. Success or failure depends on myriad factors, from the strength of the science and the market opportunity to the network of people that a budding entrepreneur can create.

Of the more than 50 companies that McGuire has nurtured at Polaris, “I can think of maybe one that went in a straight line,” he says. “By definition, biotech companies are on a frontier.”

Most of the time, experience is crucial. When biotech veteran Michael Gilman (now Chairman and CEO of Arrakis Therapeutics) started Stromedix in 2006, he says, “I realized I couldn’t have done it 20 years earlier because it depended on the wealth of experience I had accumulated.”

In fact, the majority of companies started by Avalon Ventures have sprung from ideas that Avalon dug up, not from pitches made by would-be entrepreneurs. “Two-thirds of the deals we do we find from doing ground-level research at academic institutions or reading journals,” explains Kevin Kinsella, the founder of Avalon, and founder of more than 125 early-stage companies. There are times, however, when ignorance is indeed bliss. “When you are just starting out, one advantage is that you don’t realize what you are up against,” says Ron Cohen, MD, CEO of Acorda Therapeutics and Chair of the Biotechnology Innovation Organization (BIO) Board of Directors from 2015 to 2016. “If you realized what lay ahead, you might not do it.”

Biotech also lives in a rapidly changing landscape. With innovative new tools like optogenetics and CRISPR, the science advances dramatically every year. Investors change, markets evolve.

So it is difficult to give specific recommendations in a guide. “Anything anyone writes is likely to become obsolete rather quickly,” cautions Vicki Sato, professor of Management Practice at Harvard Business School, and former President of Vertex Pharmaceuticals. Adds Kolchinsky: “Given how quickly our sector is evolving, entrepreneurs always need the most current advice and case studies to supplement the more timeless principles of company building.”

This guide thus makes no attempt to list all the required steps on the path to biotech success or to provide a comprehensive

manual for creating a business plan and raising money. Such an approach may not even be very helpful anyway. “Any notion there is a bullet point checklist for a business plan that you need in order to get attention from a venture capitalist is absurd,” says Kinsella. “Cutting-edge venture funds are delighted to fund an idea sketched out on a cocktail napkin.” If it’s a great one, of course.

So instead, this report is an effort to distill the insights, wisdom, and inspiration from a carefully selected group of industry pioneers on what it truly takes to start a successful biotech company, with examples from their own experience. In interviews, these biotech leaders highlighted a number of crucial topics:

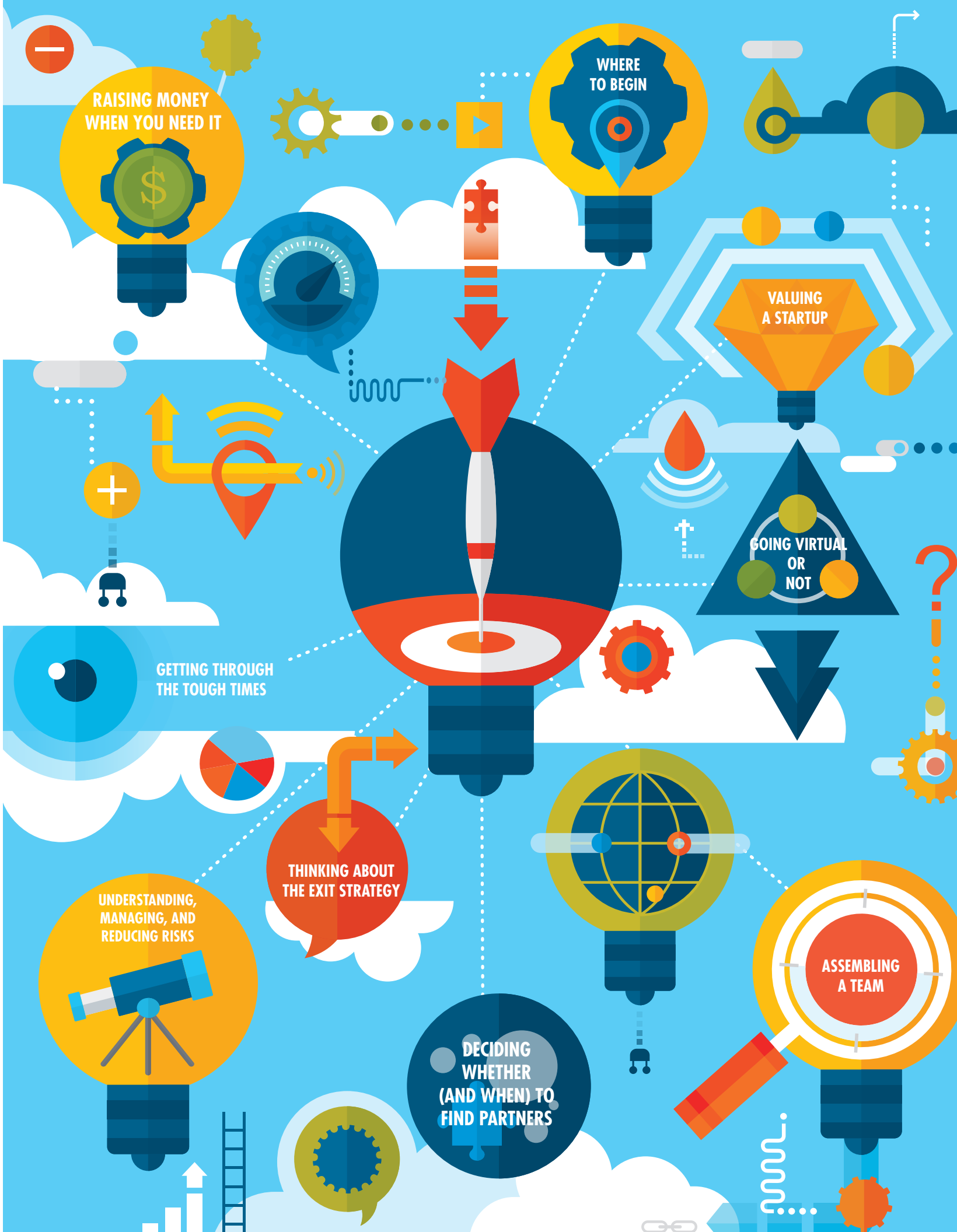
- where to begin
- assembling a team
- going virtual or not?
- understanding, managing, and reducing risks
- raising money when you need it
- valuing a startup
- deciding whether (and when) to find partners
- thinking about the exit strategy
- getting through the tough times

“The best advice is just to dive in,” says Deborah Dunsire, MD, CEO of XTuit Pharmaceuticals and former CEO of Millennium Pharmaceuticals. “Like surgery, you can’t learn it all from a book. You have to do it.”

But with the wisdom and experience of the pioneers interviewed for this guide (see list at end), you can get a crucial leg up.

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MORE THAN HALF
of the top 10 current
blockbuster drugs
ARE BIOLOGICS



ANNUAL SALES RANGING FROM
\$3 BILLION to
\$12 BILLION

WHY START A BIOTECH COMPANY?

Business is usually about making money, but biotech in particular offers immense rewards. More than half of the top 10 current blockbuster drugs are biologics, with annual sales ranging from \$3 billion to \$12 billion. The sector as a whole pulls in more than \$130 billion a year.

For most people in the biotech industry, however, the motivations go far deeper than the potential monetary gain. Sure, being able to buy a Porsche can be nice, but the far greater satisfaction comes from making a difference in the world, veterans say. When a biotech company successfully develops an

important new medicine or treatment “you produce something that for the rest of your life you can say: ‘I did something worthy. I made a contribution to my fellow humans,’” says Cohen. That’s why Cohen hands every visitor to Acorda a copy of the famous quote from Teddy Roosevelt about “daring greatly,” which says, in part:

“The credit belongs to the man who is actually in the arena, whose face is marred by dust and sweat and blood, ...who spends himself in a worthy cause; who at the best knows in the end the triumph of high achievement; and who at the worst, if he fails, at least fails while daring greatly....”

I did something worthy.
I made a contribution
to my fellow humans



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than **\$130 BILLION A YEAR**

WHAT EVERY ENTREPRENEUR NEEDS TO KNOW

1) WHERE TO BEGIN: PASSION AND THE RIGHT IDEAS

If there’s one word that pops up over and over in the stories of successful entrepreneurs and biotech companies, it’s “passion.” For instance, Dunsire writes on XTuit Pharmaceuticals’ webpage: “I am passionate about working every day on treatments that can transform the outcomes for patients.”

Or as Cohen says: “What every biotech entrepreneur needs is a passion for their idea, a passion that broaches no demur and that will not be deterred by naysayers or critics.”

Start with conviction and passion and “everything else you do will pick up as you go along,” he says.

Of course, it helps when that passion is justified by the quality of the idea. “The foundation of the company needs to be on great science that can have an impact on patients’ lives,” says Dunsire.

There also must be a clear path to translating the science into products that offer new treatments or improvements over existing treatments. “Make sure that whatever you are doing is great,

with big markets and big potential,” says Kinsella. “It has to be a therapeutic that is targeting a very large unmet medical need.”

Legendary venture capitalist Don Valentine was famous for asking a simple question: Who cares? “That is really the touchstone,” Kinsella says. “You have to have an answer to that question.”

So what makes a great idea? For Gilman, the starting point for Stromedix was an afternoon brainstorming at Atlas Venture. “We left the meeting with the idea of starting a fibrosis company—that was as deep as the analysis got,” he recalls. Gilman then spent a year learning how the thickening and scarring of connective tissue—i.e., fibrosis—can lead to all types of organ failure, affecting tens of millions of people. More important, he had to figure out how to design a short, inexpensive clinical trial that solved the central problem in the field: showing quickly that a drug works in diseases that take years to develop. In the end, Gilman’s idea for opening up this new frontier of medicine was so good that Biogen bought the company “before we even ran the trial,” he says.

ASK THE RIGHT QUESTIONS

When Ron Cohen first pitched a spinal cord injury company to venture capitalists, his business plan was “vestigial” and his slide show was “half-baked,” he recalls. But when they rejected him, “I asked them: ‘Can you tell me why you are not interested and what would get you interested?’ Those were the two most valuable questions I could have asked,” he says.

Over time, the plan and the pitch got better and better, until Cohen was finally able to get Acorda started. “The trick is to learn from people as you go along,” he says. “No one expects you to be a fully formed CEO. They want to see your passion, and that you are smart, dogged, and eager to learn—and that they can trust you.”

GET A GOOD LAWYER: DECIDE IF C CORP OR LLC

“A good lawyer will become a key advisor in the early stages of your company, so it is crucial to seek out quality legal advice,” advises Adriana Tajonar in her guide to starting a biotech company (see source list). “Yes, it is pricey, but you really get what you pay for, so it is worth spending slightly more to set up the foundation of your company correctly.” As for the right company structure, a C corporation makes more sense if a startup is giving equity to its early advisors and if private capital is needed to bring product to market. The C Corp legal structure makes it easy to both generate capital and to give employees equity compensation.

On the other hand, a Limited Liability Corporation (LLC) might be better if the company is operating as a service and doesn’t depend on raising investor dollars. Most biotechs are C Corps. LLCs “have a certain amount of cachet at the moment, and make sense in certain business scenarios,” says Gillman. “But they are legally complex, and if you make a mistake, it’s complex to go back.”

For Cohen, the big idea was turning the huge progress being made in spinal cord injury research into new therapies, though at first “I didn’t have a clue how I was going to do it,” he says. He spent a year and a half reading papers, going to every scientific meeting, and interviewing more than 60 researchers. It then took years to get the company, Acorda Therapeutics, off the ground (See box, Ask the Right Questions) and then additional years to get into the clinic with a drug candidate. “In retrospect, it was a ‘field of dreams’ business plan—if you build it they will come,” says Cohen. “We had ideas and animal models, and we asked investors to trust us to find something. I would license stuff right and left from universities and test it until something stuck.” Eventually something did.

These stories highlight the vital importance of pursuing ideas that offer a clear path to revenues. “No venture capitalist is interested in a science project,” warns Kinsella. “We have to have at least a trajectory to a product. And it really should be something special—a therapeutic that is targeting a very large unmet medical need or an orphan disease with no treatment at all.”

In one good example, Dunsire tells the story of a company she recently joined as a member of the board of directors—Ultragenyx Pharmaceutical, which started up in 2010. Founder Emil Kakkis had already brought drugs for rare diseases to the

market, and had a molecule in hand with the potential to treat another rare disease. “It was a very believable story,” says Dunsire. “Kakkis had done it before. He could explain why the disease is horrible and what the molecule can do to treat it. That is pretty irresistible to investors.”

Sometimes the idea is so good that a company leaps out of a lunch conversation. Catching up in September 2016 with Broad Institute chemist and cell biologist Stuart L. Schreiber at Legal Sea Foods in Kendall Square by MIT, Kinsella heard about a class of transmembrane proteins called solute carrier (SLC) proteins that hadn’t yet been exploited as drug targets.

The Broad Institute had discovered that half a dozen existing billion dollar drugs, whose mechanisms had previously been unknown, actually target SLCs. Moreover, the Broad Institute’s genomic databases contained complete sequence information on hundreds of SLCs, including human mutations in the proteins that offered valuable clues to potential roles of the proteins in disease. “The fact that a target class had already been validated with extraordinarily successful drugs on the market is huge,” says Kinsella. At the lunch, Schreiber proposed starting the first company aimed at purposefully developing drugs to hit those targets. “I said: ‘I love it. Let’s do it,’” Kinsella recalls. Within months, the new company, Jnana Therapeutics, was up and running.

These examples emphasize the overwhelming importance of being able to prove that ideas can be translated into actual products. A key related point is that making the case for successful translation requires a kind of science that can be foreign to many academics.

“Drug discovery is a discipline that’s quite different in many ways from the science you would conduct in an academic lab,” explains Gilman. “The kind of data you need and the experiments are different.” Discovering a new biological pathway or a potentially druggable target can make a good journal article. But turning that discovery into a business requires many specific experiments: testing possible molecules to obtain detailed dose response curves and changes in blood levels, and testing the molecules in a wide variety of animals. “It is a level of analysis and detail that is uninteresting to most academics,” says Gilman.

Llewellyn Cox, founder of BioBuilt, a biomanufacturing accelerator in Los Angeles, writes on his Lab Launch blog that “moving from university research to R&D in a startup is a culture shock that many are ill-prepared for.”

Fortunately for academic researchers, it’s usually easy to find help navigating this journey from discovery to a concept worth pitching to investors. “Because things have become cheap and because there is a startup culture everywhere, many universities have moved into what they called ‘translational’ areas,” says Kinsella. “In the old days, the best you could get would maybe

be an incomplete molecule hitting the target. Now universities can do combinatorial chemistry [to quickly find new molecules]. They can access genomics databases, and can do inexpensive knock-out and knock-in experiments in mice.”

One example of such a formal university effort is the SPARK Translational Research Program at Stanford, which has spun out dozens of successful companies. Another effort, the Startup in a Box Program at QB3, the California Institute of Quantitative Biosciences, has helped more than 200 teams of scientists start companies, reports Adriana Tajonar in a scientific journal article. In addition, more than 50 medical research institutions in 31 states and the District of Columbia get ‘translational’ funding from the National Institutes of Health in the form of Clinical and Translational Science Awards.

A vast amount can also be learned about translating science into products by simply talking to academics who have founded companies, to entrepreneurs, and even to venture capitalists, says Dunsire. “This could be considered an odd statement, but from the perspective of an academic, the venture capitalist is your friend,” she explains. “A VC can challenge the assumptions the academic is making and question the business model. It can be an uncomfortable conversation for the scientists, but getting that input early is very helpful.” (See boxes: Ask the Right Questions, and Pick up the Phone)

PICK UP THE PHONE

Ron Cohen originally pitched the idea that became Acorda to 70 venture capitalists. Not one was interested. “So someone suggested that I talk to Alan Walton, then one of the most prominent biotech venture capitalists,” he recalls. (Walton, who died in 2015, joined Oxford Partners (now Oxford Bioscience Partners) in 1987, and founded such biotech companies as Human Genome Sciences, Exelixis, and GeneLogic.)

“I got his phone number and called him out of the blue,” says Cohen. “He had no clue who I was. But he spent an hour on the phone talking me through the different steps I would need to finance my company and to pressure test each step. I never forgot what he did, and now I try to pay it forward.”

2) ASSEMBLING THE TEAM

Even the very best ideas can’t be turned into successful biotech companies without having the right people on board. “A lot of founders don’t understand the team dimension,” says McGuire. “Yes, the insight is important, but you have to recruit talent to transform the insight into products.”

That includes not only hiring top performers, but also recruiting highly respected scientific advisers and board members. In fact, McGuire says, “if I had to give anyone advice, I think the people-collecting should come before going out to raise capital, because getting people around the idea gives credibility and insight.”

McGuire points to the example of Ironwood Pharmaceuticals, founded out of MIT’s Whitehead Institute for Biomedical Research in 1998 by Peter Hecht and two colleagues. “When

Peter came in with the idea for Ironwood, he had Barry Bloom [former long-time R&D chief at Pfizer] on board as a scientific advisor and other remarkable board members,” McGuire recalls. “He had shown he could attract the best talent—people who believed that what Peter was doing made sense. I said: ‘if Barry Bloom is prepared to spend time on the idea, it must be pharmaceutical ready.’”

Impressed by the advisory team, McGuire and Polaris invested. Ironwood now is on track for \$1 billion in annual revenue by 2020, and McGuire is Chairman of the company’s Board of Directors.

Bringing in top advisors at the start is just the first step, however. Entrepreneurs then must make good hires for each of the required jobs. That’s not easy, says Gilman. “Finding the right people is probably the hardest part of the job.” There’s little margin for

PATENT STRATEGY

“If you have a great idea, you have to patent it,” says Dunsire. This is a task that’s often outsourced. University technology transfer offices can help, or companies can turn to law firms that specialize in intellectual property. “IP is critically important, but I hate it—and I have accepted that there are things I’m not good at,” says Gilman. “But I know a lot of fantastic IP attorneys I can hire.”

In general, the experts recommend a strategy of applying for broad patents first, then going narrower over time, while making sure that the intellectual property evolves with the science. “Our first approach is to understand the science, identify the legal issues, and ask the strategic questions that a new company might not have had time or resources to ask yet,” explains Kathleen M. Williams, Chair of the Life Sciences Practice Group at Sunstein Kann Murphy & Timbers. “IP is most valuable if it fits the company goals like a well-tailored suit and is constantly adjusted as the company goals change.”

ASSEMBLING THE TEAM

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mistakes, especially in small companies. “You can’t afford to make a hiring error,” Gilman says. If a company has just five employees, “one person is twenty percent of your effort.”

Compounding the difficulty is that discovering new drugs is not as straightforward as designing a bridge or creating a new detergent. “Drug discovery is by definition serendipitous,” Gilman explains. “You can’t manage discovery.” That’s why companies typically need an unusual and special kind of scientist. At one of Gilman’s companies, “the best discovery scientist we had, and this is true almost everywhere, was brilliant and intuitive—and could barely function in any other place,” Gilman says.

Management’s challenge is to marry the chaos of the front end of drug discovery with a relentlessly efficient progress for moving drug candidates through a development pipeline. “There are a bunch of paradoxes you have to resolve in hiring people,” says Gilman. “You want people who are super intelligent, but who also play well with others. You want deep subject matter experts, but who are also supple enough to move to new projects when projects fail. And you need super practical problem solvers who can move the ball downfield.”

In many cases, founders don’t make the best CEOs, so top talent must be brought in. “Talented C-level executives in biotech remain (like always) the critical challenge: great CEOs are hard to find,” writes Atlas Venture partner Bruce Booth on his blog, Life Sci VC. That’s why venture capitalists themselves often step in as the CEOs of startups.

Given the long time frame for bringing new biological ideas to market—an average of 10–12 years—budding entrepreneurs don’t need their full teams in place from the start. “You don’t need all the people right away,” says Dunsire. “You start with getting the people you need to prosecute the chemistry, the biology, and the preclinical models of efficiency. Then you start to look at toxicity, and add people who have that capacity. It is a fairly well-defined path of which people are needed when.

“The important thing is that you have a tightrope to walk,” Dunsire adds. “You don’t want to bring it too many skills too fast, which

burns capital. On the other hand, you don’t want to bring in people too late. It is a very fine balance, which is different in every company.”

In this process of growing the company as needed, though, it really helps to start with the best people, beginning with the advisory board. “It’s a virtuous cycle,” says McGuire. “The more talented people you surround yourself with, the more talented people you can acquire.”

Experienced and well-known biotech veterans like Gilman have a trusted network of people they can count on to bring in to a new company. New entrepreneurs, in contrast, must figure out how to separate the wheat from the chaff. “If there is a skill set, it is learning how to pick the people around you—who is the real deal and who has something to offer,” says Cohen.

That means avoiding two common mistakes in hiring. “One of the classic mistakes is to hire a résumé,” Cohen explains. “You get people with glittering credentials, who went to great schools and had great jobs. Sometimes that clouds your judgment, so that you don’t pay attention to what you might be sensing when you interview them.”

The second mistake: moving too fast. “We tend to hire too quickly, and fire too slowly,” says Cohen. “It is worse to hire the wrong person than to wait to find the right person. I tell people here to take their time in hiring; never be desperate, even when you feel desperate.”

To find the right person, biotech entrepreneurs need to develop a skill required in any type of business—being able to interpret what they hear, and don’t hear, when they evaluate a candidate (see box: Listening to the Subtext).

And for all aspects of the job, from finding people to serve on advisory boards to identifying possible investors and getting advice on pitches, they also need to network relentlessly, advises Llewellyn Cox. “Go out and meet people you don’t know. A lot. Especially when you don’t feel like it,” he writes.



HIRING: LISTEN TO THE SUBTEXT

In addition to looking beyond the résumé and conducting a probing interview, successful hiring requires careful due diligence. The key is learning how to interpret what you don’t hear about a job candidate, says Cohen. “Even if someone is terrible, people will not tell you that,” he explains. “You have to learn to listen to the subtext.”

For the very best candidates, outside reviews tend to be glowingly positive. Things like: “I would hire that person in a second, so grab her if you can.” Or, “his people would walk through fire for him.”

For lesser candidates, the reviews will still sound positive—but something important may be missing. “You might hear that she is very knowledgeable and extremely competent,” says Cohen. “Then you have to probe. What you heard was very positive but in a narrow sphere. So you need to ask about other dimensions. How does she get along with others? How do her managers view her?”

You may hear only guarded responses to those questions, rather than effusive, overwhelmingly positive answers. If so, then the person may not be the right fit.

“You really have to listen for what’s not there,” says Cohen.

3) HOW VIRTUAL?

Should a new biotech company start off outsourcing much of its research and other work? Or should it build up capacities in-house?

The answer: It depends.

When Gilman founded Padlock Therapeutics in 2014, “we started out being completely virtual,” he says. Padlock’s initial work on turning protein-arginine deiminases, or PAD enzymes, into new drugs for autoimmune diseases was farmed out to a contract research organization (CRO), Evotec AG, headquartered in Hamburg, Germany. “We had five or six full-time employees at Padlock and 25 people working for us at Evotec,” says Gilman.

That structure offered a number of advantages. “I’ve been a huge advocate of virtual companies in general,” Gilman explains. “It is

very efficient. You can dial the effort up and down every month as needed. And by outsourcing so much of the wet science, you also outsource your organizational complexity.” There’s no need to invest in a human resources department, for instance.

Moreover, Padlock specifically selected a top CRO in Europe, rather than in, say, China, which might be cheaper, because the researchers were just a few time zones away and spoke English. “We got on a plane and flew there once a quarter to sit with the team for a few days,” says Gilman. “That was really valuable. It built strong relationships and helped them care more about the project than they might have otherwise.”

And for academic researchers starting companies, going virtual at first is often the best choice. “My advice is: don’t give up your

day job until you are certain you are on pretty solid ground,” says Dunsire. “If experiments can be done ethically in your own lab, without conflicts with your employer, that’s ideal. Another approach, if you have seed funding, may be overseeing a CRO and paying to replicate the work. Those types of approaches reduce the risk of ultimately leaving academia and becoming a CEO of a new company.”

In fact, one of the very first virtual biotech companies, Ron Cohen’s Acorda, was born of necessity. Back then in the 1990s, there were no such beasts. But Cohen had learned from his time at Advanced Tissue Sciences that in-house labs had fixed costs that ate up capital. “We had to keep feeding the monster,” he recalls. Reading up on the story of the making of the atom bomb, he realized that the mammoth Manhattan project was “the ultimate virtual company,” he says, spread out over a huge complex of universities, national laboratories, and companies. “I was fascinated by that and decided to form the first virtual biotech,” Cohen says. “I deliberately started out working out of the labs of ten scientists I had convinced to join me, and did that for the first five years.”

Still, being completely virtual has limitations. “The virtual model breaks down in a couple of ways,” Gilman explains. “There’s just no way these hired guns, whose paycheck comes from someone else, would have the same urgency as you would. If the project fails, you are out of business. They just move on.”

The existential threat of project failure “is a major motivator,” Gilman adds. “One of the prime advantages a small company has over a large one is that you eat what you kill. That focuses the attention.”

The second problem with virtual companies appears when projects move from research that is essentially a commodity, such as synthetic chemistry, to more specialized and more specific research, such as developing new biological assays or solving more complicated biological problems. The more complicated and specific research is harder to outsource. “That’s what prompted us at Padlock to hire our own scientists and build our own labs,” says

Gilman. For Padlock, it worked. Its first in-house experiments were so fruitful that in early 2016 the company was snapped up within months for many hundreds of millions of dollars by Bristol-Myers Squibb.

“CROs have responded to the changing industry need by expanding the scope and types of services they offer. Increasingly, customers are saying “we don’t just want you to be our arms and legs, we want you to be our thinking partners,” says Jonathan Koch, Group President, Research and Development Laboratories at Covance, a global CRO. “We’re being asked more and more to be a strategic partner and offer services that typically were being done by our clients.” Despite this growing capacity at CROs, however, the limitations of virtual companies lead some top biotech experts to recommend a middle ground between outsourcing and bringing everything in-house. “Some companies like to go virtual and acquire talent only when needed,” says McGuire. “Others treasure the organization for itself, and want to build a team for the long haul. There is benefit to the virtual model, but the negative is that the talent you just trained leaves you just when you are getting good. My own bias is towards building an organization.”

Being virtual can also slow down a company, which is especially important to venture capitalists, who have a firm timeline in mind. For a fund that’s ten years long, VCs want start figuring out “harvesting” strategies, such as having an IPO or forging a partnership, by year five or six, “or if lucky, year four,” says Kinsella. “We like the idea of a virtual company, but not to the extent that they are dragging out the time so long and not accomplishing their goals in the time frame of venture capital investments. I’d rather spend now, cutting to the chase and buying the services you need to get to the next stage more quickly.”

4) UNDERSTANDING, MANAGING, AND REDUCING RISKS

Biotech offers the potential for huge rewards. The flip side is that the risks are also enormous. It's very tempting to keep funding a compelling idea that could revolutionize medicine, even after the first expensive clinical trials fail. As a result, "biotech companies can be a smoking crater the size of Arizona by the time the plug is pulled," Kinsella warns.

That's why it's so crucial for biotech entrepreneurs to understand, manage—and try to reduce—risks.

For Gilman, "the touchstone I've relied on for 25 years is that every drug project needs to be hypothesis driven," he says. Those hypotheses come in three types:

- **The first hypothesis is biological:** We expect that this particular molecule will push the buttons on a biological pathway, and the pathway will respond.
- **The second is clinical:** Altering the particular pathways should successfully treat or control a disease.
- **The third is commercial:** Patients and doctors will want the drug, and people and insurers will be willing to pay for it. The more they are willing to pay, the more valuable the idea.

FOCUS ON THE LEAD PROGRAM

In many cases, the scientists working on a drug development project will find all sorts of exciting ideas they want to explore. Don't let them. "In the end, the market will value the company based on the lead program," explains Gilman. "It will give you no credit for any other program, so every dollar spent on a side project is dilution."

"The risk of a program can then be allocated among those three hypotheses," Gilman explains. "If any of the hypotheses are wrong, the program will be a failure."

The entrepreneur's challenge, therefore, is not just proving that each hypothesis is correct. Startup companies must also pick or design projects in ways that reduce those risks as quickly and as inexpensively as possible.

To understand this challenge better, Gilman suggests imagining two potential programs. One is developing an oligonucleotide that would be given to babies born with an abnormal gene splicing that causes muscular atrophy.

The second is developing a kinase inhibitor for rheumatoid arthritis.

"Which is more risky?" Gilman asks. "Most people would say the first one." It's certainly true that the biological risk is far higher with the oligonucleotide. No one knows if the approach would work. In contrast, the mechanism of action and the efficacy of kinase inhibitors have been well established. The biological risk is very low.

What's crucial, though, is that the risk in the first project is all at the front end. If the company can show that administering the oligonucleotide actually leads to production of a correctly spliced

protein, then it's highly likely that patients will benefit clinically. Moreover, the commercial risk is very low, since parents will demand the drug for their affected children no matter what it might cost. "Once you've done the first highly technical experiment, you have solved the lion's share of the risk," Gilman explains. The cost to prove the biological hypothesis? Maybe \$30 million.

In contrast, the risk for the kinase inhibitor is almost entirely at the end of the program. Yes, it's very likely to work as a drug. But will it be any better than existing medications? Will anyone actually want to buy it? Even if there is a market, will the drug end up as a commodity with a low price?

"The risk is almost entirely commercial, and is not discharged until very late in the program," says Gilman. The price tag for learning if the program will be successful would therefore be very large—maybe \$300 million.

As a result, companies and investors would be risking ten times more money in the biologically safer program than in the one where the biology is highly risky.

To understand and highlight this vital question about risk, Gilman

suggests a basic exercise. Have the members of every program team write down their three hypotheses in simple terms. Then, ask them to allocate the risks across the three hypotheses, and write a justification for taking those risks.

It's not always a comfortable exercise, since it may challenge cherished assumptions. "But the way to create value in a biotech company is to be clear about what hypotheses you are testing," Gilman says. "And you have to start with a problem that matters." Gilman did that with Stromedix. The short, inexpensive trial he designed would prove the biological hypothesis—that a drug could affect the development of fibrosis. From there, the clinical development and commercial risks would be low.

The same ruthless scrutiny can be applied to all spending. When Gilman was starting Stromedix, he was told that "the question you should ask yourself is whether the money you spend is likely to get a 5X return," he recalls. "That stuck with me. It seems crass, but you have to think about what every dollar is doing. For small companies, money is a precious and limiting resource."

No fancy offices, for instance. No expensive lunches. And no side projects. (See box: Focus on the Lead Program)



5) RAISING MONEY: MATCH MONEY TO PROGRESS

Understanding risks and how to minimize them, in turn, is a vital step towards valuing a company and its ideas. It also enables raising the right amounts of money at the right time—and under the best terms.

“People often believe that the more money you raise, the better,” says Gilman.

Not true, he says.

Yes, a company aiming to develop the kinase inhibitor in the example in the last section would need to raise a cool \$300 million to carry the project to completion. But proving the biologically riskier hypothesis requires raising only a tiny fraction of that—and it doesn’t make sense to raise more until the question about the hypothesis is answered.

Why? Because proving the hypothesis will greatly increase the value of the company. “If you believe you can get answers in the

first \$15 million, then you shouldn’t raise \$30 million at today’s stock price,” Gilman explains. “You should raise \$15 million now, and then \$30 million more at the higher stock price when you have been able to move the program forward.”

A corollary of that advice is not being afraid to create more shares in a company in order to raise money. “People get all hung up about dilution,” says Cohen. “But money is king. Without money you die.”

So go ahead and issue more shares if you really have faith that the idea or project will eventually pay off. “In the short term, dilution looks painful,” says Cohen. “But you have to look to the future. If it works, the stock price will be ten times higher ten years later, so you won’t care about the dilution then.” Just be careful, however, to whom you hand out new shares, warns Cox “Grant equity only to people who substantially increase the value of your company, either through investment or effort.”

SHARES

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6) VALUING A STARTUP, DECIDING WHETHER (AND WHEN) TO PARTNER, AND THINKING ABOUT THE EXIT

So how much money should an entrepreneur try to raise? The general rule is to “ground your valuation expectations in reality,” advises Booth. “Believing that a drug discovery startup is worth as much as a Facebook may not be appropriate.”

And what is realistic? That depends. “Valuation is more art than science,” says Booth. Across the biotech industry, the typical first round of financing—the Series A—is about \$10 million to \$20 million. (There are outliers, however, like Denali Therapeutics, which raised more than \$217 million.) The \$10–\$20 million, in turn, usually buys about 75% of a company. If that seems steep, it is. “The capital you raise early on is incredibly expensive,” Booth warns.

That’s why some startups opt for a different strategy, raising perhaps \$1–\$2 million in seed money—just enough to create compelling data that then make it possible to raise more money at a higher valuation.

Whatever the initial financing strategy, a new company needs to get results from its first round of capital. “In true drug discovery, the first \$20 million should get you well down the line to a new development candidate,” Booth says. That means locking in the molecule that will go into Phase I clinical trials, and doing all the preclinical and toxicology work needed to get an Investigational New Drug Application (INDA) approved by the Food & Drug Administration.

Once a company has an IND-ready candidate, it’s time for another choice: Do a second round of financing or find a partner to develop the drug candidate? “At the end of the day, the decision is between equity dilution (selling more of the company) or asset dilution (giving away future value or the rights to a drug),” Booth explains.

Again, the choice is more art than science—and experience matters. “You can look back on the potholes that created issues in past deals, and learn from those mistakes,” says Booth. (See box: A Tale of Two Companies)

Meanwhile, entrepreneurs and investors should always be thinking about the eventual exit strategy in the back of their minds—though the answer usually becomes clear over time. “We don’t get religious or overzealous about having an explicit exit strategy,” Booth explains. “We’ve done this long enough that we know that if we create value for patients, great things will happen, and there will be a buyer—either the public markets in an IPO or Pharma.”

The actual exit is usually unique to each individual company, but there are general patterns. “Bigger platform companies need to consume more capital, so they are more suited for the public capital markets,” Booth explains. In contrast, “single product companies are less likely to go public, because Pharma loves those,” he says.

A TALE OF TWO COMPANIES

Find a partner or raise more capital? In early 2016, Surface Oncology made the first choice, forging a deal worth up to \$170 million with Novartis to develop a portfolio of antibodies to treat cancer. “We were able to preserve enough value—keeping the U.S. rights to two of the four programs—that the deal made a lot of sense compared to a Series B financing,” Booth explains.

In contrast, Unum Therapeutics took the other path, raising \$65 million in a Series B round in June 2015. It was done “at a very attractive price,” says Booth. As a result, that route made more sense than trying to find a partner.

7) GET THROUGH THE TOUGH TIMES

The paths of even very successful biotech companies are usually bumpy. “In most companies, the first idea is not the one that becomes the ultimate revenue generator,” says Dunsire.

The company that Dunsire led as CEO, Millennium Pharmaceuticals, is a classic case. Mark Levin founded Millennium in 1993 to spot genes that are active and then to sell that knowledge to others who would use it to discover new drugs. The company raised enormous amounts of capital based on that idea. “But it never panned out,” says Dunsire. “So Millennium used that capital to do its own drug discovery.”

Since then, pivoting from offering just a technology platform to running an in-house drug discovery operation has become a common pattern (see box: Keep a Golden Egg), though, ironically, Millennium’s first revenues came not from its own discoveries but from an acquisition.

Whatever the path, success is hard to predict. “The thing I’m always amazed by as an investor is that the ones that shine, that become your stars later on, are like any other average first grader when they start,” says McGuire. “I couldn’t have told you then which would be the winner.”

What eventually sets them apart? In many cases, it’s a trial by fire.

There inevitably comes a moment when “the shit hits the fan, and it was the worst day to wake up,” says McGuire. It may happen more than once. “My wife remembers all the times that I’ve come home, tail between my legs, saying that ‘this is really the worst it’s ever been—it’s hopeless,’” says Cohen. She always reminds him that this isn’t the first time, and the company always has managed to bounce back. “It’s great to have the perspective of having been there before,” says Cohen.

When those moments do come, the successful people “put on their pants, go to work, and find out who they are,” says McGuire. “Almost every company hits a bump in the road.” How they respond can mean ultimate success or failure.

McGuire likes to sum this trial by fire by saying: “A company’s moment of greatness is found in its greatest moment of despair.”

And when the despair hits, the companies that tend to pull through are those with the passion, the right people—and a special kind of discipline. “In the drug business, unlike other types of technology, the ultimate scarce resource is time, not dollars,” Booth explains. “Our entrepreneurs tend to be in their 40s and have earned their stripes in biotech or Pharma, and have learned to be disciplined with their time.”

While a software company might be able to continue working on an initially unsuccessful product for months, biotech doesn’t have that luxury. “Biotech is a truth-seeking culture,” says Booth. An entrepreneur must be able to identify those programs that aren’t panning out—and to quickly and ruthlessly pull the plug. “Being able to weed those out by being disciplined is crucial,” Booth says.

It’s also tough, especially for hard-driving biotech entrepreneurs who passionately believe in their ideas, and are ready to run through walls to prove that they’re right.

“It’s miserable when it doesn’t work; it’s miserable when you have a setback,” says Cohen.

But ultimately, the struggle is worth it, says Cohen: “In the end you want to be able to say: ‘I fought the fight and got it done.’ What else do you want out of your life?”



KEEP HOLD OF A GOLDEN EGG

AnaptysBio was formed on the strength of an innovative technology for rapidly identifying and manufacturing antibodies. But it “just wasn’t taken seriously by the financial powers of the biotech world,” says Kinsella—until it used its own technology to find antibodies that it plans to develop in-house.

The lesson: “If a company has been created around a technology platform, the company will not realize a significant value, even if it has partnered the technology, until it has kept a couple of the golden eggs for itself,” says Kinsella.

Interviewees (in alphabetical order):

- Bruce Booth, Partner, Atlas Venture. Currently chairman of AvroBio, miRagen Therapeutics, Nimbus Therapeutics, Rodin Therapeutics, and Quartet Medicine.
- Ron Cohen, MD, CEO at Acorda. Chair of the Biotechnology Innovation Organization (BIO) Board of Directors from 2015 to 2016. Former principal in the startup and an officer of Advanced Tissue Sciences, Inc., a biotechnology company engaged in the growth of human organ tissues for transplantation.
- Deborah Dunsire, MD, CEO, XTuit Pharmaceuticals. Former CEO of Millennium Pharmaceuticals, senior executive at Novartis, and many others.
- Michael Gilman, Chairman and CEO of Arrakis Therapeutics, former founder and CEO of Padlock Therapeutics and Stromedix, Inc, and former Senior Vice President at Biogen Idec.
- Kevin Kinsella, Founder, Avalon Ventures. Formed, financed, or developed more than 125 early-stage companies, including: Athena Neurosciences, Onyx Pharmaceuticals, Inc., Sequana, Vertex Pharmaceuticals.
- Terry McGuire, Founding Partner, Polaris Partners. Has invested in more than 50 companies and co-founded three companies: Inspire Pharmaceuticals (public and sold to Merck), AIR (sold to Alkermes) and MicroCHIPS (private).

Experts Consulted by Email:

- Peter Kolchinsky, Managing Partner, RA Capital Management, LLC
- Vicki Sato, Professor of Management Practice at Harvard Business School, former President of Vertex Pharmaceuticals and Chief Scientific Officer at Biogen

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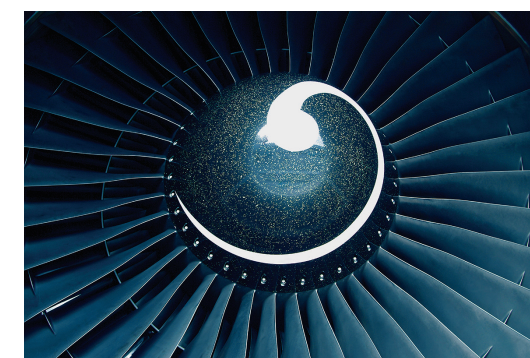
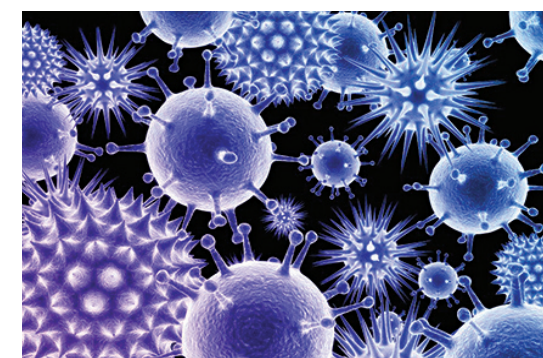
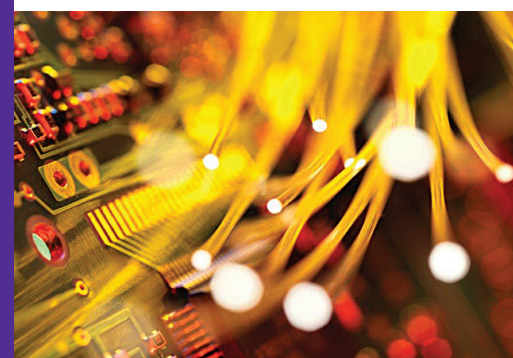
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