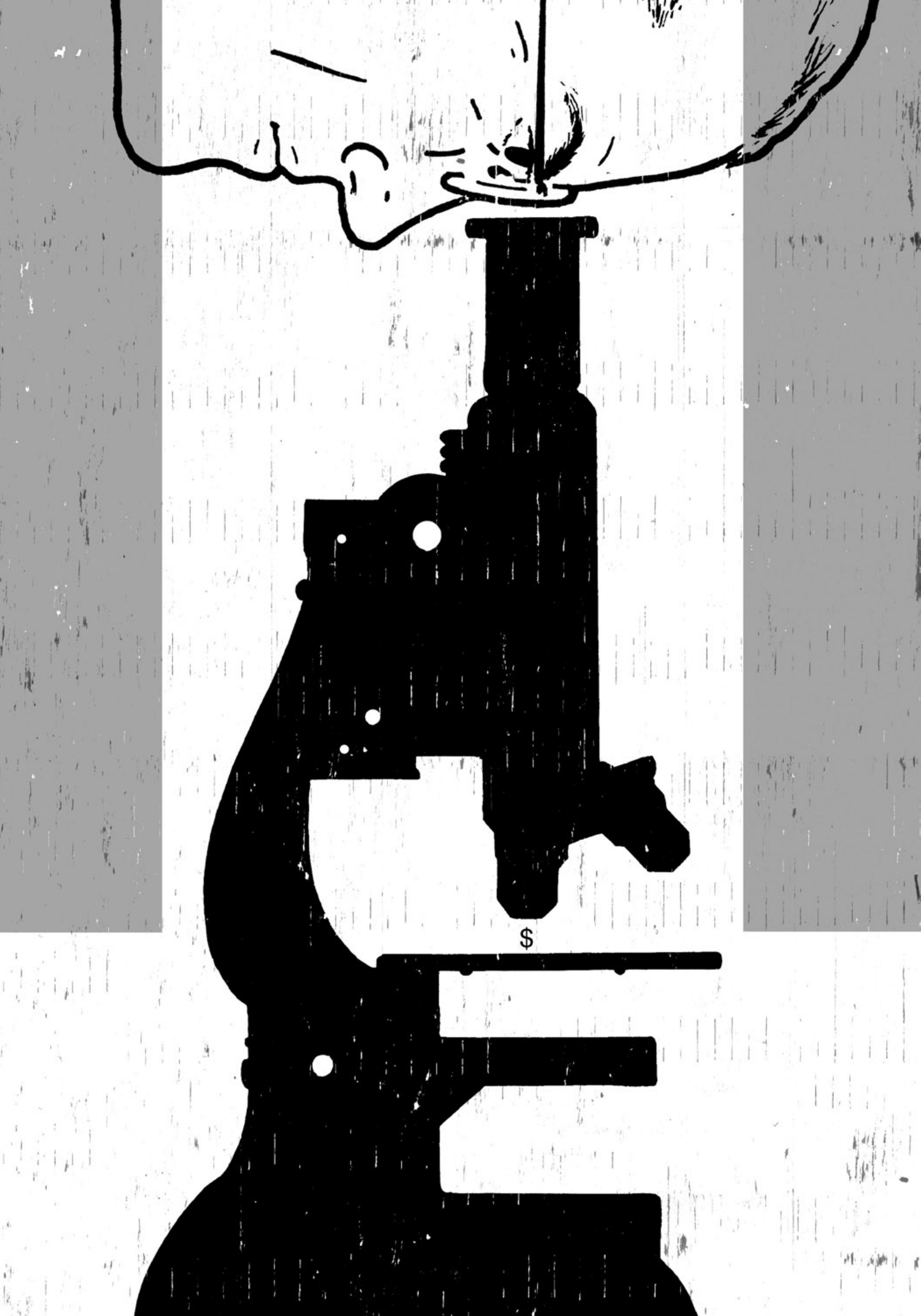

BIO TECH ON THE BRINK

THE PROGNOSIS FOR HIGH-RISK LIFE SCIENCES START-UPS

BY LAWRENCE M. FISHER

Some years ago, when the biotech industry was in one of its buoyant periods, a young reporter for *The New York Times* wrote that senior executives in biotech firms ought to be singing "Back in the High Life," Steve Winwood's big comeback hit. Nowadays, the Doors' apocalyptic classic, "When the Music's Over," might be the more appropriate tune.

The industry was in trouble even before the stock market cratered last September. There was just one initial public offering for a biotech company in 2008, and while mergers and acquisitions activity was high, many of these deals returned little to investors. Indeed, by the end of the year, only one in 10 companies in the industry was profitable, and fully one-third of the 370 publicly traded biotech companies in the United States were operating with less cash than they needed to finance their operations for the next six months. Five companies filed for bankruptcy in November alone.

When the economic recovery begins, investors will surely jump back into the stock market. But it seems safe to assume that for at least the next several years, their appetite for risk will be much diminished and companies with uncertain prospects will not be favored. Adding to biotech's woes, tighter government regulation of financial markets – and gun-shy investment bankers – will make high-risk life sciences ventures that much harder to promote.

Businesses and business sectors ebb and flow – as they must if economies are to adjust efficiently to changing demands and costs. But in the case of biotech, the market test is not the only appropriate one from the perspective of society as a whole. For this, after all, is the industry on which we all depend to translate advances in biology into products that extend life and improve its quality.

Some biotech companies have delivered on that promise, as attested to by the oversized portraits of cancer survivors adorning Genentech's headquarters in South San Francisco. New therapies for previously untreatable diseases, more-accurate diagnostic tests and a vastly safer blood supply are all gifts of the marriage of molecular biology and risk capital.

But, sad to say, the industry's triumphs

DAN PAGE (ALL)

have been few and far between. Subtract the three biotech companies with the largest market caps – Genentech, Amgen and Gilead – and the cumulative return on investment over the life of the sector was negative even before the financial markets' collapse. In aggregate, biotech shares have proved to be a high-risk, no-return investment.

With hindsight, it's easy to see why. On average, it takes about 10 years and $1 billion to bring a new drug to market, and nine out of 10 drugs fail somewhere along the way. A typical venture fund lasts 10 years, but must show returns to investors in half that time if the sponsors are to have any hope of inducing investors to subscribe to the next fund and the next. Yet with no easy path to liquidity – with no go-go investment bankers itching to raise billions to create a payday for pioneers on the route to success – biotech start-ups and their venture backers are lost in the woods.

It's no coincidence that the first public offering of stock in a biotech company (Genentech) occurred in 1980, the beginning of nearly three decades in which heavy-handed government regulation was out of fashion and risk was the elixir that powered Wall Street. Indeed, it's worth remembering just how unprecedented that IPO was at the time: bankers handily managed to raise $35 million for a company with no products or profits, and none on the horizon. Perhaps the industry's very existence was an artifact of an era of optimism.

It's surely time, then, for a new model, one that doesn't depend on investors with 5-year attention spans to finance 10-year projects or on market bubbles to provide "liquidity events." Getting from here to there will require a fundamental rethinking of how emerging biotechnology enterprises are structured, financed and operated.

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WHY M&A WON'T WORK

In most industries, a capital drought would lead to consolidation, with mergers and acquisitions pairing cash-starved but prospect-rich companies with better-financed suitors. But this kind of contraction of the biotech market has never occurred during any previous financial downturn, and it's not likely to now.

Since the early 1980s, biotech has vacillated between periods in which any start-up company with a mass spectrometer and a dream could raise money on decent terms, and times in which the most meritorious firms went begging. Each downturn produced calls for consolidation, but there have been few mergers of any consequence between biotech companies.

One reason is promiscuous partnering. Since no company ever gets to the finish line of an approved drug on equity capital alone, virtually all biotech companies license portions of their intellectual property to others or to large pharmaceutical companies.

For example, a biotech may choose to develop a molecule as a potential cancer therapy while licensing its use to another firm for exploration in autoimmune disease, in return for cash up front and royalty payments later. The downside is that divesting a prospective application of the company's technology is equity dilution by another name. Moreover, the tangle of relationships created by such licensing makes it difficult to value a company and puts potential buyers in the position of inheriting unwanted partners.

When biotech mergers do occur, they often face exceptional integration issues. Disdain for formal business practices, all too common in enterprises managed by scientists, means that post-merger assimilation is particularly challenging for biotech companies.

Historically, bankruptcies (which can sometimes lead to the efficient redeployment of assets) are also rare among biotech companies. "Most biotech companies have an ability to rely on hope longer than is reasonable," says Fred Cohen, a former professor of endocrinology who manages life sciences investments for TPG, the giant private equity firm. "The only thing that meaningfully changes a biotech's behavior is a bankruptcy proceeding, and the only way they get forced into that is when there are debt securities." And most biotech companies actually have little, if any, debt.

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BIG PHARMA TO THE RESCUE?

Biotech has long had a problematic relationship with established pharmaceutical companies, prompted in part by biotech executives' inclination to view the latter as "a source of dumb money," as Daniel Vasella, chairman and chief executive of Novartis, puts it, even though they have manufacturing and distribution capabilities that the biotechs often lack.

Biotechs also bought into the idea that their approach to medical research represented a new paradigm that would eclipse the old chemistry-based pharmaceutical houses as surely as the semiconductor industry replaced vacuum-tube makers. They believed that drugs based on the body's own hormones and proteins would be safer and more effective than the traditional pharmaceuticals companies' host of often-toxic chemicals found by serendipity like aspirin, or by screening thousands of random compounds against disease targets.

But the voracious capital requirements of the new companies thrust them into a Faustian bargain with Big Pharma from the very beginning, when they signed away a portion of their future in return for cash. Genentech licensed its genetically-engineered human insulin to Lilly; Amgen joined with Johnson & Johnson on the anti-anemia drug erythropoietin; Chiron sold its recombinant hepatitis B vaccine to Merck. These deals were often troublesome – Amgen and Johnson & Johnson litigated for years over sales rights to artificial erythropoietin (EPO). But biotech coveted the big companies' bankrolls, and Pharma needed the small firms' intellectual property.

Over the decades, Big Pharma has become more biology-savvy. The opportunistic hookups of the early 1980s have given way to strategic alliances and acquisitions. Nearly all pharmaceutical companies now have in-house biotech programs or bio-venture units to seek out and finance promising start-ups. About 75 percent of liquidity events for privately held biotechs in the past 10 years have been through acquisition by larger drug firms – not through IPOs.

But time is not on the pharmaceutical companies' side. Their internal R&D efforts have largely come to naught in recent years, and the industry faces an imminent revenue cliff as blockbuster drugs like Pfizer's Lipitor and GlaxoSmithKline's Imitrex come off patent and face generic competition. The urgency to replace these blockbusters is reflected in the industry's appetite for big M&A events, like Pfizer's recent $68 billion acquisition of Wyeth (which has a portfolio of biologic drugs) and Roche's $47 billion purchase of the 44 percent of Genentech it didn't already own.

There ought to be a good match between capital-challenged biotechs and cash-rich, product-hungry Pharma, but mutually beneficial marriages are difficult to arrange. Pharma ideally seeks companies with products on the market or close to receiving approval. But most biotechs are still risky years away from that goal, and those that are closest often come with substantial infrastructure and big employee bases that the majors neither need nor want.

In addition, biotech companies have too often pursued niche drugs. And Pharma executives know that it's not practical to try to replace a single $12 billion cholesterol drug with dozens of compounds that can each generate only a few hundred million in sales.

This mismatch of buyers and sellers shows a fundamental flaw in the venture capital paradigm as applied to biotechnology. If the only tool you have is a hammer, all jobs look like nails. So if you are a venture capitalist, all ideas look like start-up companies. Many, perhaps most, of the biotech companies formed since 1976 should never have received tens of millions of dollars in venture money, should never have had hundred-million-dollar IPOs, and should never have built out the infrastructure supported by that capital.

"In a way, it seems that venture investing in biotech always had this element of a confidence game," says Josh Lerner, a professor of investment banking at the Harvard Business School. "If they could get it to a time when there was a market mania and foist it on the public, there could be tremendous success. Now, in the cold light of day, it's hard not to wonder if there isn't a mismatch between the time it takes to get a biotech drug and the time frames of venture capital and public equity."

Some biotech entrepreneurs acknowledge that the old model has run its course, and are exploring new ones. One approach is to keep a new company virtual for as long as possible, relying on academic partners to advance the research phase and outsourcing drug development and clinical trials to the contract organizations that have grown up around the biotech industry. But outsourcing requires its own set of management skills and still demands significant funding.

Companies also fall prey to the need to maintain appearances, often building unneeded sales and manufacturing capacity in advance of regulatory approval so that investors and potential acquirers will take them seriously. Never mind that any capable buyer of biotech property will already have all the sales and manufacturing structure it needs.

A few venture capitalists have embraced a model that recognizes from day-one that they are building organizations to be acquired by Big Pharma, and thus need not invest in the illusion of creating fully integrated drug companies. This kind of enterprise can take a promising molecule or technology platform from the discovery phase to preclinical trials in animals without the capital to take a drug through human trials and then manufacture it. Although substantial risk remains at this stage – countless compounds that cure cancer in mice do nothing for humans – it is the sort of risk that pharmaceutical companies know how to evaluate.

"We're exploring new models with Pharma where we actually build companies together," says Mark Levin, a serial entrepreneur and venture capitalist based in Boston. "It's not just a matter of transferring assets, it's having relationships early on. We say 'we're going to create this discovery vehicle for you, and if we all do well over the next five years, this company becomes part of your company.'"

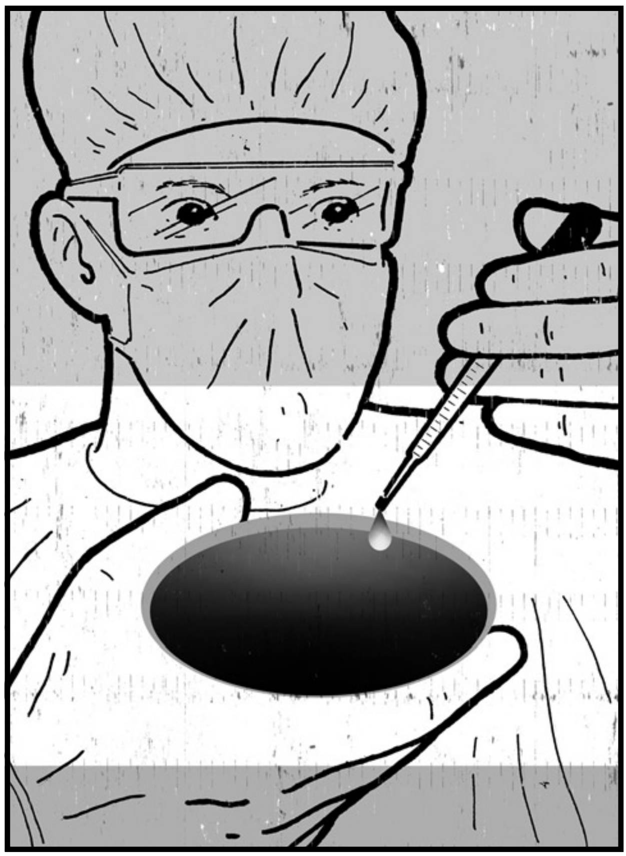
FOUNDERS, FRIENDS AND FAMILY

Some biotech entrepreneurs are saying "no thanks" to venture capital altogether. By running very lean while working with federal research grants and foundation money, they believe they can take their companies to the point where Pharma will be interested without surrendering the founders' equity or control.

AvidBiotics, for example, is six bright guys and a dog. And one might not take the company seriously but for the pedigrees of its co-founders. David Martin has served as senior vice president for R&D at Genentech, president of DuPontMerck Pharmaceuticals and president of Chiron Therapeutics. He was the founder and chief executive of Eos Pharmaceuticals. James Knighton was president of Caliper Technologies and chief financial officer of Sugen and held finance positions at Chiron, DuPontMerck and other drug companies. (The dog, incidentally, is a black standard poodle that comes to work every day with Martin.)

Since creating AvidBiotics four years ago, Martin and Knighton have relied on friends, family and their own not-so-deep pockets. "I have the term sheets on my desk," says Knighton, referring to venture capital firms' proposals. He says that venture capitalists looking for 10-fold returns inevitably undervalue the companies they invest in, and that Martin felt stung by the control he had to give up at Eos when he took venture money.

"We burn $1.3 million a year," says Knighton, noting that some of their South San Francisco neighbors go through several times that much cash in a month, with no drugs to show for it. "There are only six guys here, and Dave and I take a fraction of our market rate" in salary, he said. "You don't have to raise a lot



of money to keep going if you practice a bit of capital efficiency."

AvidBiotics has a technology based on naturally occurring bactericidal proteins that may prove useful both in assuring food safety and in treating antibiotic-resistant infectious diseases. Because food-safety additives are subject to relatively light regulatory review compared to drugs but require significant manufacturing and marketing capacity, the company plans to license that application to a major food products firm. It will then use the license revenue to finance its drug development. In the meantime, AvidBiotics stays afloat on federal research money along with small infusions of capital from the founders and a group of angel investors.

"One thing we can tell these people, with a straight face, is we are only taking the amount of money we need to get to the next step, and if it doesn't work, we're folding the company," Knighton explains. "We're not going to raise 10 million, spend three, and if it doesn't work, find something else to do with the money."

BANKING ON A NEW DAY IN WASHINGTON

Biotech executives span the political spectrum, but Democrats and Republicans alike cheered the Obama administration's arrival in Washington. After eight years of an administration that blocked funds for stem cell research, suppressed scientific publications it did not like and treated the theory of evolution as one wild and crazy idea, the biotech world is thrilled to have a science-friendly executive branch. What's more, the industry is smitten with the science advisers named by the new president.

Since Obama announced that he was nominating Steven Chu, a Nobel-prize-winning physicist, as energy secretary, scientists have placed new faith in the campaign line "change we can believe in." But it was the appointments of Harold Varmus, a former director of the National Institutes of Health, and the biologist Eric Lander of MIT as co-chairmen of the President's Council of Advisors on Science and Technology that put sentiment over the top. Both are closely connected to the biotech community, which is hoping for a reversal of eight years of reduced funds for the National Institutes of Health.

NIH grants are typically small and no substitute for venture capital or equity, but they can serve as lifelines for an early-stage company. Grants support the countless hours of wet work and bench time that precede patent applications or clinical studies. If more companies adopt a lean operating model, and if a new administration directs a lot more money to the NIH, federal money could make a significant difference.

Those are both big ifs, and some biotech executives concede that the global financial crisis presents the Obama administration with more-pressing concerns than the plight of their industry. A plea by the Biotech Industry Organization for a Detroit-style bailout captured little attention. In addition, a climate of increased regulatory scrutiny will mean tougher reviews of new drugs, which will also increase costs for struggling companies.

Nonetheless, Levin, the venture capitalist, argues that the president's stimulus package will give biotech a big boost. "When the government puts this multi-trillion dollar stimulus to work, there's going to be very aggressive science policy. You will see the biotech companies lining up," he predicted.

FOUNDATIONS TURN ENTREPRENEURIAL

Biotech companies are already lining up to tap another source of funds – private nonprofit organizations, including the Cystic Fibrosis Foundation and the Michael J. Fox Foundation, which focuses on Parkinson's disease. These groups have always paid for some research, primarily at the academic level, but their involvement with public or private drug companies faces hurdles.

Because foundations are often created to attack the illness of the founder or the founder's loved ones, they tend to go for home runs. But science progresses in increments, and even most of the approved biotech drugs on the market today are at best singles or doubles – drugs that give cancer patients a few more months or improve the quality of life for sufferers of chronic diseases like rheumatoid arthritis.

In addition, companies need to provide a return on investment to shareholders and many foundations are focused on diseases with tiny patient populations that will not generate substantial sales. In the United States, the Orphan Drug Act of 1983 provides tax incentives and enhanced patent protection for drugs developed for patient groups of less than 200,000, and other countries have similar laws. But these drugs are often extremely expensive. Genzyme's Cerezyme, which treats a rare enzyme deficiency and costs about $300,000 a year per patient, has been a perennial football in the debate about rising health insurance costs.

Another hurdle is tax law that restricts nonprofits from investing endowment funds in ventures that might provide sub-optimal returns. "In a way, the most natural thing you can imagine the foundations doing, they can't do," says Professor Lerner of Harvard. "They can't play the role of venture investor in areas that are close to their mission, where they might get returns but not as good as their typical financial returns."

Nevertheless, collaborations between foundations and biotechnology companies are on the rise, and leaders on both sides are actively seeking more ways to work together. The foundations still tend to shy away from discovery or preclinical studies, but become interested after a drug is ready for human trials.

In January, the Leukemia and Lymphoma Society agreed to give $3.7 million to the privately held Celator Pharmaceuticals to support Phase II development treatment of acute myeloid leukemia. The society also provided research funds for Novartis' Gleevec, used for the treatment of chronic myelogenous leukemia. Another recent example is a $1 million grant from the National Multiple Sclerosis Society to the privately held Belgian biotech Apitope in exchange for stock warrants – a decision vindicated when Apitope signed a development and commercialization agreement with Merck.

Yet another entrepreneurial nonprofit is the Multiple Myeloma Research Foundation, which was founded by a former pharmaceuticals industry executive who has the disease. The foundation has raised over $102 million to help finance 70 laboratories worldwide, which have had four new drugs – Thalomid, Velcade, Revlimid and Doxil – approved in the past four years.

"We don't fit the traditional nonprofit model; we're really a venture philanthropy organization, working to advance the development of promising drugs," Louise Perkins, the foundation's chief scientist, explained.

The foundation finances two to three milestone-driven projects in multiple myeloma annually. It provides $500,000 a year over the three-year life of a project, but also offers help in recruiting patients, designing clinical trials and dealing with the Food and Drug Administration. Separately, the foundation has spent $8 million to sequence the genomes of 100 multiple myeloma patients.

SOMETIMES LESS IS LESS

For many years, the industry's bellwether event was the biotechnology conference organized every January by Hambrecht & Quist, the San Francisco-based boutique investment bank that took so many biotechs public. Part *Revenge of the Nerds*, part *Bonfire of the Vanities*, it was a four-ring circus where suits and scientists partied together and Masters of the Universe matched wits with Nobel laureates in the crowded halls.

Then Hambrecht and Quist merged with Chase, and Chase merged with J.P. Morgan, and biotech took a back seat to a mix of Big Pharma, insurance providers and benefits managers. This year's J.P. Morgan Healthcare Conference was a dour affair, that reached a nadir of sorts when the chief executive of one biotech company pressed Jamie Dimon, Morgan's chief executive, to speak out in support of the biotech bailout before Congress. Dimon politely demurred, admitting this was the first he had heard of the measure. But the anguished entrepreneur pressed on, asking how Dimon could support bailouts for the manufacturers of Hummers though not for desperately needed medical innovations. "Just because we're doing something stupid over there is no reason to do something stupid over here," Dimon replied, dropping the temperature in the room about 10 degrees.

The last big biotech blowout was the genomics bubble of 1999, when investors and pharmaceutical companies threw billions of dollars at companies piggybacking on the Human Genome Project. Despite filing thousands of patents on so-called "disease genes," none of these companies ever produced a drug from its research – although some of the more resourceful ones used their cash hoards to acquire marketable drugs or diagnostic tests.

After the bubble burst, venture capitalists and investment bankers played it safe, financing so-called specialty pharmaceuticals companies – which primarily repurposed and repackaged existing drugs. This wasn't biotechnology, it wasn't innovative, and it wasn't even entrepreneurial. To no one's great surprise, health care insurers balked at premium prices for old wine in new bottles, and none of these companies could now be mistaken for a success.

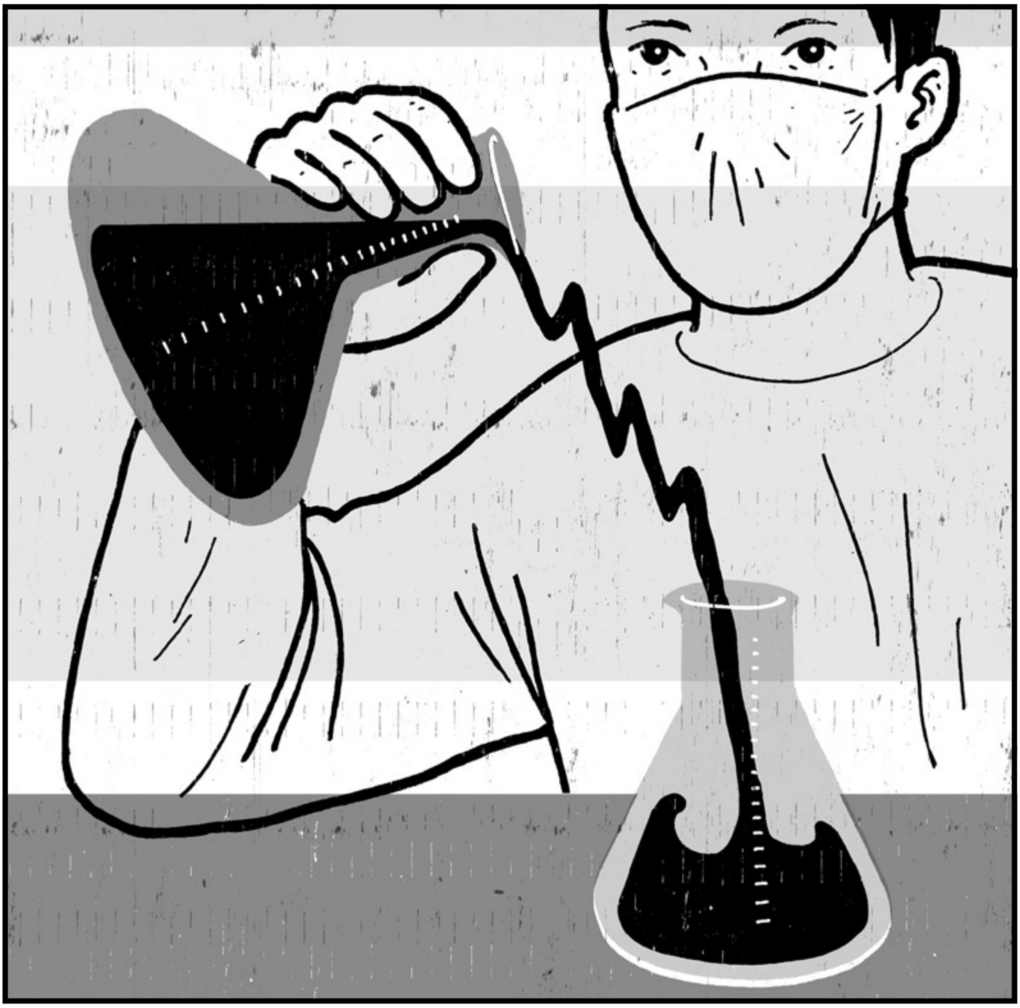
When the finance window does reopen, which even the most optimistic bankers do not expect to happen before late next year, the innovation bar will be higher. Companies with a compelling raison d'être will find ways to pay for R&D. But they will have to be able to demonstrate early and often that they have the scientific and managerial expertise to move biology from the laboratory to the clinic without cash-burning delays. Moreover, they will have to present the case, even before recruiting patients for clinical trials, that there indeed exists a viable market for their molecules.

REQUIEM FOR AN INDUSTRY?

Biotech companies are wonderful places to visit. The concentration of bright minds working on things that really matter is engaging and uplifting in a way that most for-profit enterprises can't match. There is also an air of Never-Never Land, a place where talented biologists and chemists can stay in grad school forever – only, this time, with six-figure salaries, cool T-shirts and Friday afternoon beer busts. But reality now intrudes.

After Roche absorbs the rest of Genentech, rivals will all want a biotech of their own – if only to silence securities analysts asking why they don't have one already. Amgen, Biogen Idec, Gilead, Genzyme and the few other operating biotech companies with real products and revenue streams could thus all disappear into the maw of Big Pharma quite rapidly. And without a surviving entity as a model, the days of the truly independent biotechnology company could truly be over.

The financing alternatives outlined here may well support substantial biomedical in-



novation, but not necessarily at a socially desirable level. Federal grants can finance research; foundations will pay for drugs within their areas of emphasis; Big Pharma may ante up for a discovery program or a new technology platform; the occasional lean and hungry bootstrapped biotech may have a shot at survival on its own. Among the hundreds of cash-starved biotech companies now languishing, some will be acquired, some will form strategic alliances to live another day, and most will simply fade away.

In biotech myth and legend, the industry began the day that Robert Swanson, a young venture capitalist, met for a beer with Herbert Boyer, the co-inventor of recombinant DNA, and roughed out the plans for what became Genentech. While venture capitalists still sit down with scientists and advances in molecular biology continue apace, it's not clear that such an enterprise could be built again today.

Back in 1980, the year of the Genentech IPO, a band called the Talking Heads had an unlikely hit with a song that seemed to presage the decade's stunning wealth creation and cultural discontinuity – and perhaps even the denouement of the biotechnology story. It's name: "Once in a Lifetime."