Is it virtuous to be virtual? The VC viewpoint

To the Editor:

A Commentary in the August issue by Bruce Booth[1] highlights the importance of the virtual business model as an increasingly important facet of strategies for making biotech companies more capital efficient. In a previous study examining the portfolio companies of his venture capital (VC) firm, Booth also provided evidence that companies with fewer full-time employees are markedly more productive than peer companies with more employees[2]. Other venture industry insiders have also commented on the fact that investors are favoring companies that keep a "laser sharp focus," and that "employ virtual and semi-virtual models to maximize cash efficiency"[3]. To characterize the present state and future potential of virtual biotech, we conducted semi-structured interviews with representatives from 25 leading life sciences VC firms and four leading contract research organizations (CROs).

Twenty-five of the 30 VC firms (83%) we contacted agreed to be interviewed (**Supplementary Data**). The firms were all located in North America, with fund sizes ranging from $200 million to >$2 billion. We supplemented interview data with quantitative and qualitative data from Scale Venture Partners (Foster City, CA, USA), a leading investor in virtual biotech companies, and New Enterprise Associates (Chevy Chase, MD, USA), one of the largest venture capital funds worldwide.

On the basis of the feedback in our survey, outsourcing—once limited to big pharma developing small molecules—is now widely exploited in the biotech sector. Indeed, Covance (Princeton, NJ, USA) reports that currently >60% of the business at most CROs comes from small to medium-sized biotechs rather than large biotechs or big pharma. Outsourcing is also not limited to work with small molecules. One of our survey respondents, Canaan Partners (Menlo Park, CA, USA), for example, sees an important role for outsourcing in the strategy of its biologics companies, noting that manufacturing firms in India are creating greater capacity for the outsourced manufacture of biologics. Atlas Ventures (Waltham, MA, USA) also employs the virtual model for enterprises in its biotech portfolio, developing monoclonal antibodies and peptide therapeutics.

Respondents to our survey cited several advantages of the virtual model over the traditional biotech business model (**Table 1** and **Supplementary Data**). Capital efficiency is clearly one benefit. David Collier at CMEA Capital (San Francisco) goes as far as to state that the traditional biotech model with 30 employees running 1–2 trials is a waste of resources because a good clinical team should be able to run 5–6 clinical trials. "The only reason [biotech companies are] running 1 to 2 instead of 5 to 6 programs is because they just don't have the money for it. There's inherent inefficiency built into the traditional drug development model. The outsourced system allows you do the same development with much smaller teams and many more products simultaneously."

Although capital efficiency is often cited as the primary reason for promoting a virtual structure, another advantage is the speed with which virtual companies can reach commercial milestones. According to Brent Ahrens, partner at Canaan Partners, "in a defined time period, either through a return or determining viability, the primary consideration may be that a virtual model is quicker." Other advantages relate to easier governance and management of resources within a virtual company (**Table 1**).

Despite these potential advantages, virtual biotech companies can also be challenging enterprises to lead (**Supplementary Data**). The venture investors we interviewed emphasized the importance of staffing virtual companies with execution-oriented CEOs and with experienced senior operating executives. Investors often seek CEOs or COOs who have had extensive clinical trial experience in large pharmaceutical companies or CROs. In the words of one survey respondent, "If given an A team with a B plan or a B team with an A plan, we'd take the A team with a B plan every time."

Compared with traditional ventures, leadership, organizational and communication skills are even more critical in virtual biotechs, where outsourced resources may be in disparate locations and motivated by slightly different incentives. Tim Walbert, a successful serial CEO and now CEO of Horizon Therapeutics (Northbrook, IL, USA), observes: "You can't be in a situation where you just hand off the work. Company leadership should drive the strategy and bring in consultants to execute under strong guidance." And one early-stage life sciences investor, Kevin Harter, who is senior vice president of business development at Life Sciences Greenhouse (Harrisburg, PA, USA), told us: "The day-to-day entrepreneurial focus that comes with a team being in the same room together allows you to drive business day in and out, to determine what the urgent things are that day and on a real-time basis. Without a cohesive internal staff, things can move very slowly. You need a business developer who can work independently, who is a self-starter that can tackle logistical issues of being maybe a time zone or half a world away."

Investors also often face challenges in identifying and recruiting individuals for virtual ventures who are proficient at project leadership—at navigating the CRO ecosystem and integrating external resources—and who have relevant domain-specific knowledge. Most venture capitalists interviewed indicated that their management teams approach large CROs very selectively and that prior experience and relationships with a given CRO influence which organization is chosen to run a virtual biotech's clinical trials. Doug Given at Bay

Table 1 Pros and cons of the virtual model

Pros	Cons
Reduced fixed costs and expenses	Loss of direct control via contractors (especially those working with larger organizations)
Increased capital efficiency and lower burn rate	Potential delays and lack of urgency
Increased speed and flexibility	Geographical and temporal delays
Lack of employee turnover	Need for highly skilled project managers
Simpler governance and lack of bureaucracy	Lack of drug portfolio diversification

City Capital (San Francisco) distinguishes between working with expert advisors prospectively, and working with these same individuals as operational managers with accountability. "There's a big difference between providing expert advice and actually operating. We see different behaviors in terms of the depth of diligence, and attention to the implications of plans and decisions." A business plan supported with high-quality people in an advisory capacity is much different from one with high-quality people in operational positions. He states that "it's quite surprising when they're accountable to the program how their recommendations change. If you rely too heavily on outside experts, you can find yourself with highly unrealistic operational goals and not realize it. It happens to very good VC firms, and it happens to very good virtual models."

Some of our survey respondents also pointed out that the virtual model is suboptimal for certain types of R&D. Polaris Ventures (Waltham, MA, USA), for example, noted that it is more difficult to outsource assets related to cutting-edge discovery (**Supplementary Data**). As Terry McGuire, a cofounding partner of Polaris, put it: "You want to keep proprietary position to yourself, and outsource the non-unique aspects." What's more, the human element of working face to face, "thinking about a project 24 hours a day," and the need for "creative, passionate input and dedication" is challenging to replicate in a fully virtual model.

What's more, companies involved in innovative drug discovery may need more infrastructure and employee continuity to make sure that valuable institutional knowledge continues to reside in-house. Virtual models lend themselves better to companies exploring disease areas with gold-standard disease models available through CROs and academic and research institutes. That is not to say, however, that a virtual structure cannot be applied to innovative drug discovery. One of the companies in Polaris's portfolio, for example, is an early-discovery biotech firm that employs only one full-time employee, in-licensing intellectual property (IP) from an academic lab while continuing to leverage discovery work done in that lab and supplementing it with proof-of-concept preclinical testing done by an international CRO. According to the venture capitalists we contacted, it is possible to develop in-house assays with minimal corporate infrastructure, even in developing complex drugs and exploring novel pathways. Costs may also be reduced for niche elements of drug development. Another example of a firm that has been able to use the virtual model to keep fixed overheads to a minimum is Cita Neuropharmaceuticals (Cambridge, UK), a portfolio company of the Canadian VC firm VG Partners (Toronto). Cita was able to take a compound discovered in-house together with two in-licensed assets all the way through phase 1 and into phase 2 trials without hiring more than ten full-time employees. Indeed, several venture capitalists commented that the ideal number of product candidates within a virtual model may be two or three to maximize the leverage of the management team.

Our survey also revealed that virtual biotechs have not been embraced by all corners of the venture community (**Supplementary Data**). This may be because the virtual biotechs founded in recent years have not yet provided returns that are healthier than the more traditional platform companies of the past. Public investors have traditionally been skeptical of companies with few employees, though companies with strong data, like Orexigen Therapeutics (La Jolla, CA, USA), have been able to complete successful initial public offerings (IPOs) with under ten employees. Several VC firms believe that the trend towards more virtual models is a fundamental shift in the industry (**Supplementary Data**). Booth at Atlas Venture argues that "it creates a highly networked, connected ecosystem of people doing highly innovative work. For example, if you want an obesity model, you can go to the handful of CEOs who really do obesity models, and [you can] seek out capabilities that are world class." Kevin Starr, founding partner at Third Rock Ventures (Boston), believes, "even for deep thinking intellectual property, in every aspect of exploratory biology, you can outsource tasks."

James Neidel of New Leaf Venture Partners (New York) notes that in many cases, the top university laboratories are becoming sources of viable preclinical molecules and, as such, can function as vendors for biotechs, both virtual and traditional. At Flagship Ventures (Boston), David Berry points out that virtualized structures could increase R&D productivity if companies like Pfizer (New York) could use the biotech industry as an efficient mechanism of getting proof-points before providing the end-stage investment. But the success of the virtual model in resolving industry-wide concerns over R&D productivity may ultimately depend on larger issues at play.

For example, several venture capitalists, including Ali Behbahani from New Enterprise Associates, believe that even though virtualization may help companies become more capital efficient, it may have little impact on overall industry returns if R&D productivity is not improved. They argue that although standard of care has improved over the past decade, our understanding of biology has not yielded more potent targets for a given disease process. Additionally, our ability to determine early on which drugs will work in the clinic has not improved. As a result, for a new drug to show a statistical difference over current therapies requires larger and more expensive clinical trials than a decade ago, which translates into companies needing to raise more capital than before. Thus, although increasing industry-wide virtualization may help decrease a portion of the additional capital required, it has not resulted in improved R&D productivity, which requires a greater leap in our biological understanding of diseases. According to these venture capitalists, for certain indications, such as diabetes or atherosclerosis, even capital-efficient or virtual models cannot be funded anymore due to the high costs required to get a drug approved.

Another group of VCs, including those at Oxford BioSciences (Boston), believe that even if R&D productivity increases, the potential beneficiaries of new compounds in traditional markets have insufficient interest in acquiring them. "The pharmaceutical industry spends most of their money internally, which doesn't produce anything. They're not buying the little companies. It's not a question of the virtual model or not—it's really who cares?" According to this viewpoint, pharmaceutical companies are

increasingly shifting their focus to generics and biogenerics, focusing on partnering, acquiring or setting up distribution companies outside of the United States, with the recognition that 750 million people in other parts of the world will be entering the middle class. "The old strategy of developing for the US and having those profits subsidize the rest of the world is dead. The answer is not capital-efficient discovery companies. The demand for innovation is no longer what it once was. We won't see as many new productive companies, but more of the same and cheaper."

Yet another view is that this is a time of particular opportunity to achieve outstanding long-term returns. Some venture funds, such as Scale Venture Partners and New Enterprise Associates, see innovation in the life sciences as continuing, with big pharmas having an increasing need to bolster their pipelines. At the same time, valuations of existing private and public life science companies have markedly decreased, creating many buying opportunities for those venture funds with adequate capital to invest.

One recent indicator of the venture community's willingness to invest in a proven management employing a virtual model is the creation of Clovis Oncology (Boulder, CO, USA). Funded with up to $145 million in new venture equity from top-tier VCs like New Enterprise Associates and Frazier Healthcare Ventures (Seattle), Clovis will be led by Patrick Mahaffy, former CEO of Pharmion, and key members of the Pharmion team, which in-licensed and developed a repurposed oncology drug before being acquired by Celgene (Summit, NJ, USA) for $2.9 billion. Clovis will use a virtual organization to identify promising oncology therapeutic candidates, in-license them and develop them through to approval.

Another sign of the continuing strength of the virtual biotech model is the robust business, even in the midst of this economic slowdown, of the companies that supply outsourcing services. According to Peter Sausen of Covance, a leading CRO, "Business has not slowed down for us…. We anticipate coming out of [the economic slump] in a very good position." International CROs, such as WuXi PharmaTec (Shanghai, China), a CRO that focuses on preclinical development and manufacturing, have shown sharp growth in demand for their services, despite the financial crisis.

Virtual models imply capital efficiency and intelligent use of capital. The notion that the virtual biotech model is here to stay is clearly the majority view in the venture industry. Indeed, the biotech sector cannot afford to continue with capital-inefficient, vertically integrated structures—as virtualization accelerates, more players will be forced to adapt or die. This may prove to be a double-edged sword. In his recent book on healthcare, innovation theorist Clayton Christensen draws a parallel between the reorganization of the PC industry and the focus of big pharma on improving their profitability in short-term by getting out of the least profitable of their activities, while focusing investments on their most profitable[4]. He ominously notes that by outsourcing "such companies will find that they have inadvertently leveled the playing field in their industry, so that entrants can overcome what have historically been high barriers."

Companies that receive these outsourcing contracts have the opposite motivations in taking on progressively higher value-adding activities their customers are eager to shed. Some major pharmaceutical companies built on blockbuster drugs are now shifting their focus towards generics and biogenerics, placing less and less emphasis on innovative R&D. At the same time, by logically outsourcing more and more activities to India and China, Western pharma and biotech companies also risk creating a new breed of disruptive competitors—companies that may also represent investment vehicles for savvy VCs.

Note: Supplementary information is available on the Nature Biotechnology website.

AUTHOR CONTRIBUTIONS
J.C. conceived, designed, collected data, analyzed and wrote the paper. J.L.C. and A.B. collected and analyzed data and helped write the manuscript. S.M. edited the manuscript, provided a virtual biotech case study and gave conceptual advice.

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The authors declare competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturebiotechnology/.

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The power of social networking in medicine

To the Editor:

Your editorial in last year's September issue[1] outlines some of the ways in which PatientsLikeMe (http://www.patientslikeme.com), an Internet-based social networking site launched in March 2006 to capture patient-reported data for people with life-changing diseases, is opening up new ways of testing treatments and speeding patient recruitment into clinical trials. We would like to provide readers with more detail concerning the utility of the system in alerting patients to new off-label uses of existing approved drugs as well as identifying potential new safety issues.

Currently, PatientsLikeMe has 16 disease communities, which in turn represent information from over 40,000 patients, who can participate 24 hours a day. The US Health Insurance Portability and Accountability Act (HIPAA) regulations do not apply as the information is directly entered by users. These users can anonymously share treatment, symptom, progression and outcome data with the entire