TURNING POINT Engineer takes career risk in moving to biology **p.129**

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BIOTECHNOLOGY

Virtual reality

A growing number of biotechnology companies employ a skeleton crew of managers and outsource hands-on science.

BY HEIDI LEDFORD

If Rosana Kapeller has her way, her company will develop treatments for scourges such as cancer, cardiovascular disease and diabetes. And it will do so with only 12 full-time employees and no wet labs.

Kapeller shares a quiet office with eight colleagues at the headquarters of Nimbus Discovery in Cambridge, Massachusetts. The rest work from their homes in Missouri, Connecticut, Rhode Island and New York. This skeleton crew manages the company's operations and computer analyses; all hands-on experiments are outsourced to an international assembly of contract-research organizations (CROs). "It's a lot like managing a lab down the hall," says Kapeller, the company's chief scientific officer. "But instead of down the hall, the lab's in China and we're using Skype."

Such is life at a 'virtual' biotechnology company, a lean, nimble model that is gaining popularity among cash-hungry start-ups. These companies consist of as few as one full-time employee who oversees a drug from pre-clinical development to tests in patients, all in the hands of outside contractors.

To take advantage of this niche, scientists must have the management experience to run a remote team of researchers, and may need the financial backing to launch a company on their own. Aspirants should also be prepared for quick turnover with regard to projects and jobs: virtual start-ups are often designed to sell off individual projects — or the full company — to larger firms.

MODEL ON THE RISE

Biotechnology leaders — and their financial backers — have embraced the virtual model as a way to save money on workers and lab facilities. Nearly every biotechnology and pharmaceutical company conducts aspects of product development through contractors. But a virtual company outsources almost every step of its research and development chain.

A virtual company can be agile, shifting from drug formulation to toxicity testing without having to build facilities or hire staff. And a slimmed-down business can entice pharmaceutical companies shopping for smaller firms to restock drug pipelines.

These attributes are all the more appealing in the wake of the financial crisis, as the high risk involved in backing young biotechnology companies over the long timelines of product development makes investors wary of the ▶

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sector. That pressure has already forced firms to become more efficient. "This movement is really born of necessity," says Hal Broderson, managing director of the consulting firm Rock Hill Ventures in Wynnewood, Pennsylvania. "It's like a nuclear winter out there for early-stage medical-technology companies."

But scientists interested in working for — or starting — a virtual company should also be aware of the model's limitations. Virtual companies work best when they are developing drugs for an established molecular target, using familiar techniques, cautions Kapeller. The structure is ill-suited for discovering new molecular targets, or for developing a class of drugs with a novel mode of action.

"The heart of a virtual biotech beats with the rhythm of continuous travel."
Leonide Saad

Kapeller's first company, Aileron Therapeutics in Cambridge, is developing drugs based on short helical peptides that can interact with proteins inside cells to treat diseases including cancer and endocrine disorders. Unfortunately, the approach was a little too new for the virtual model, says Kapeller, because CROs are set up to perform well-defined assays and protocols, not tackle innovative biology. Aileron survived for two years as a virtual company but eventually had to build its own wet labs and hire bench scientists. "Cutting-edge new-assay development still resides in academia, biotech and pharma," says Nancy Gillett, chief scientific officer of Charles River Laboratories, a CRO based in Wilmington, Massachusetts.

By contrast, Nimbus's structure has proved resilient thus far. The company, which has partnered with Schrödinger, a computational chemistry company based in Portland, Oregon, uses physics-driven molecular modelling to design molecules to hit cellular targets that modulate disease. CROs do the chemistry and biology studies needed to turn such molecules into viable drug candidates. Among Nimbus's 12 employees are scientists with backgrounds in biology and medicinal chemistry, who coordinate modelling efforts at Schrödinger with the hands-on work at CROs.

COMPLETE OVERVIEW

Working at a virtual biotechnology company requires a special skill set, notes David Cavalla, founder of Numedicus, a virtual pharmaceutical firm in Cambridge, UK. "You need to have somebody who has a 30,000-foot view of the whole process of drug development," he says. "They need to be able to look at the next step and say, 'This is what I'm going to need in 18 months'."

That experience is increasingly hard to come by as pharmaceutical companies and big biotechnology firms shrink their internal research and development departments, laying off scientists and outsourcing their efforts. Increasingly, drug-development jobs are to be found at CROs rather than at classical, integrated biotechnology firms. Gillett says that when she left Genentech, a large biotechnology company based in South San Francisco, California, to join a small CRO, people told her she was committing career suicide.

That was nearly 20 years ago, when CROs were seen as employers of last resort for scientists, paying less and offering less autonomy than jobs at pharmaceutical companies. Since then, things have changed dramatically, says Gillett. "Now the big companies are coming to us for advice."

Scientists at a CRO may gain experience from working on many different projects, and can advise clients on specific areas of drug development. But they rarely get to participate in strategic decision-making about the direction of a project, or develop the overarching view of the process that Cavalla advocates. Senior scientists who have left big pharma, or have been laid off, remain a key source of management experience, he says. "The reason you're able to make this virtual model work is because you can hire all of these experienced grey-hairs from pharma companies."

David Collier, managing director for life sciences at CMEA Capital in San Francisco, argues that some young scientists will still be able to find training at the remaining big firms. While there, he notes, they can seek out the experience most needed in a virtual company: managing outside contractors. "The key part is to understand how a CRO works and how to negotiate a reasonable price," he says. Such a level of experience includes everything from designing contracts to ensure that contractors stick with the company timeline, to making sure that basic lab protocols are up to standard.

Ilyas Washington invented a treatment for blindness that launched a virtual company.

That does not mean that being in charge is all management and no science. The people best positioned for success in a virtual biotech combine management experience with scientific acumen, says Leonide Saad, founder, president and sole full-time employee of Alkeus Pharmaceuticals in Boston, Massachusetts. Saad, a tissue engineer by training, says that running a virtual company frees him from internal bureaucracy so that he can spend more time considering the bigger scientific picture. "It's a blast when you're on your own," he says. "When everything is in-house, you spend much more time managing people rather than thinking about your core drug and your core development."

The virtual model made it possible for Saad to strike out on his own by reducing the cost of launching a company, but investors will still want firm evidence of success before they will risk their cash. Saad had been a venture capitalist for two years when he decided to launch his own company with start-up funding borrowed from family members and his own savings.

His plan was to seek further investment once he had something to show. "If you're an entrepreneur you need to have cash to survive and build value for a full year," he says. "You cannot survive on ramen noodles and then go to venture capitalists and say 'I haven't made progress because I don't have your money'."

THE RIGHT CHOICE

Saad knew that he needed a project that could prove its worth on a limited budget in about two years — before his money ran out. He trawled through more than 150 university patents in search of a technology that he could build his company around, evaluating each with the eye of a venture capitalist. For a situation like his, he says, it was important to seek out projects that were focused, with a clear and preferably short path to therapeutic application.

Saad narrowed the list down to 20 technologies, then researched the intellectual property to determine whether the patents were strong enough to hold up if challenged in court. He also read up on the literature to see whether a scientific consensus was building in support of the proposed invention. Finally, he settled on a possible therapy for macular degeneration — a common cause of blindness — created by Ilyas Washington, an ophthalmology researcher at Columbia University in New York. Saad now spends his days visiting Washington and the five CROs that are working on the project. "The heart of a virtual biotech beats with the rhythm of continuous travel," he says. "I carry the entire office with me on a laptop."

Not everyone is so enamoured with the virtual lifestyle. Stewart Lyman, owner of Lyman BioPharma Consulting in Seattle, Washington, worries that the trend leaves few satisfying research jobs in drug discovery.

Although CROs are booming, he says, jobs

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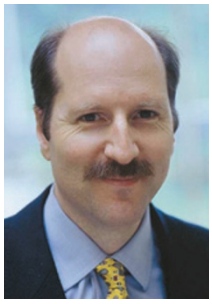
with them will not fulfil many of the best researchers, who prefer to have scientific control over their work rather than doing the bidding of a client. Scientists seeking a career in CROs should look for jobs that will give them autonomy, agrees Jonathan Montagu, vice-president for business at Nimbus. "You have to be selective."

DIVIDE AND CONQUER

Scientists who find jobs at virtual companies should recognize that they may soon be back on the job market. Virtual firms are often designed to be bought by pharmaceutical companies, giving investors a chance to recoup their funds without waiting for the decade or more that it can take to bring a drug to market. "If I were a young scientist, a virtual biotech is not the kind of place I would aspire to work," says Lyman. "Even if you're successful, you're going to get liquidated in a couple of years and then you're out of a job again."



"You need to have somebody who has a 30,000-foot view of the whole process of drug development."
David Cavalla

Nevertheless, job seekers looking for stability may find options in a new breed of virtual biotechnology company. Some companies are structured to enable the sale of individual projects, leaving the rest of the firm intact and allowing employees and infrastructure to remain in place. Nimbus, for example, has set up each of its projects as a separate subsidiary with intellectual property and assets that a pharmaceutical company can acquire without buying the full firm.

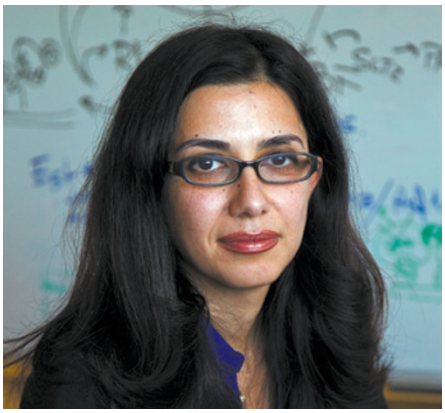
Similarly, when Collier and his colleagues launched Velocity Pharmaceutical Development, based in La Jolla, California, they configured each project as its own corporation. "There is a lot of experimentation now with new models," says Collier.

Ultimately, industry scientists need to adapt to the new normal, says Justin Chakma, an analyst at venture-capital firm Thomas, McNerney & Partners in La Jolla, California. That may mean jumping from job to job. "Scientists need to be comfortable working almost as consultants," he says. "It's not a steady stream of income like it was years ago." ■

Heidi Ledford *reports for* Nature *from Cambridge, Massachusetts.*

TURNING POINT
Hana El-Samad

Trained as an engineer, Hana El-Samad honed her skills to study complex systems, but ended up researching gene expression in real time. This year, she won a US$1.4-million grant from the Paul G. Allen Family Foundation in Seattle, Washington. Unbound by conventional biology instruction, El-Samad feels free to take risks.



Who influenced you to pursue science?
I grew up in Lebanon, where my mother, a maths teacher, instilled in me a love of maths and engineering. At the American University of Beirut, I wanted to study mathematical theories of how things work. I focused on control theory, which looks at automated systems.

How did you shift into biology?
In 1999, I earned a master's degree in electrical engineering with a focus on controlled dynamic systems from Iowa State University in Ames. In 2002, halfway through my PhD, my adviser, Mustafa Khammash, moved to the University of California, Santa Barbara, and I went with him. People were starting to talk about systems biology, and I realized that the theories I had been studying on machines would be relevant to systems created by nature. I completely switched gears.

Did your adviser support that?
He is smart and open-minded, and thought that tackling biology could be really interesting. We divided up chapters of a biology book and taught each other. My thesis was on heat-shock responses that bacteria use to adapt to temperature increases. We tried to model them to understand how they operate in real time.

Was it a difficult to move into biology?
In 2004, I earned my PhD in mechanical engineering. I faced a choice — accept an engineering position or throw myself into biology. It was not a trivial decision. I had offers for several engineering posts, but a collaborator had nominated me for the Sandler Fellows Program at the University of California, San Francisco (UCSF), which funds one person each year to start a small, independent group focused on risky research. I chose that. People thought I was crazy, but it was the best thing for my career. I'm now an experimental scientist, a hybrid of an engineer and a biologist.

How did you expand your lab?
I didn't want a gigantic lab: I wanted six to eight people who do thorough, in-depth science, to try to understand how a small number of systems work in predictive ways. I chose people with backgrounds in maths, physics, molecular biology and computational science.

Did that set-up have challenges?
Yes — piecing together a mosaic of disciplines left us with no common language. At early lab meetings, I wanted to pull my hair out. People were talking about the same thing using different terminology, and getting frustrated. There was also a reluctance to ask what might be considered stupid questions.

How did you get past those barriers?
I wrote a lab constitution that acknowledges that we are all from different backgrounds, that we shouldn't all be expected to understand everything — and that we should ask questions. It is written playfully and we update it as necessary.

Is it hard to get federal grants for your multidisciplinary research?
It can be. I believe that agencies want to fund this kind of science, but they have to funnel grants through review groups that can have conservative reviewers. Still, we did get a US National Institutes of Health grant in 2010 to fund the UCSF Center for Systems and Synthetic Biology.

You have two grants from private foundations. Why do you think your work appeals to them?
The David and Lucile Packard Foundation in Los Altos, California, liked our approach to cell-to-cell variability, and the Allen Foundation liked how we decided to decipher the genetic encoding and decoding that allow cells to survive in complex environments. I think both like to fund high-risk, potentially transformative things that are not necessarily attractive to agencies, and we don't do run-of-the-mill stuff. ■

INTERVIEW BY VIRGINIA GEWIN

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