THE BILLION-DOLLAR BIOTECH

Moderna Therapeutics has big ambitions and a bankroll to match. How a fledgling start-up became one of the most highly valued private drug firms ever.

BY ELIE DOLGIN

At a breakfast meeting two-and-a-half years ago, Pascal Soriot, the newly minted chief executive of pharmaceutical giant AstraZeneca, shook hands on the first major drug-development deal of his tenure. It was a research partnership with little-known biotechnology company Moderna Therapeutics of Cambridge, Massachusetts. Worth up to US$420 million, the deal was unusually large for a start-up that offered only a fledgling drug technology, especially one that had not yet even been tested in humans.

That was the first of many huge cheques for Moderna. This January alone, the company announced a record $500 million in financing from a handful of investors, pushing it over the $1-billion fund-raising mark and making it the most highly valued venture-backed private company in drug development today.

"Everybody is talking about this," says Johannes Fruehauf, who runs LabCentral, an incubator and shared laboratory facility in the bustling Cambridge biotechnology hub known as Kendall Square. "It's inevitable with these large, eye-popping numbers."

Investors are clearly attracted to Moderna's technology, which aims to use chemically modified messenger RNA (mRNA) molecules to produce any protein that the body might need. Backers have also bought into the reputation of the company's high-profile co-founders and its charismatic chief executive, whose bold ambition is to move 100 drugs into clinical testing within the next decade, treating everything from cancer to rare genetic diseases.

But Moderna is also something of a mystery. As a private firm, it has revealed very little of its research. Its academic founders have published only one study[1] using Moderna's mRNA therapeutics technology in rodents. And the company itself has disclosed scientific details (including some about early work in non-human primates) only through patent filings. Add in questions about the strength of Moderna's patent position and the troubled history of other RNA-based drugs, and some analysts are wondering whether the company will be able to deliver on its promises.

"I don't think they've really overcome the critical issues," says Dirk Haussecker, an RNA-therapeutics consultant in Rastatt, Germany. Based on the publicly available records, he says, "I haven't seen anything from Moderna that makes me say, 'Oh, they really have a competitive edge or they're very different — in a league of their own.' From a science point of view, it doesn't seem to make sense." But as a business it is surging ahead.

A SIMPLE APPROACH

On paper, the idea of mRNA therapy seems simple. If someone cannot produce enough of a certain protein, or produces a broken version, doctors could inject their cells with mRNA that codes for a replacement protein. This would avoid the risks of tinkering with the genome permanently, as is done in some forms of gene therapy. And whereas growth factors, antibodies and other complex 'biological' drugs can be produced in vats by bioengineered cells, these are mostly limited to secreted molecules. An mRNA-based therapy would be able to make proteins that operate inside the cell as well. "mRNA delivery would reinvent how we as an industry tackle many diseases," says Peter Kolchinsky, managing partner of RA Capital Management in Boston, Massachusetts, which is one of the latest investors in Moderna.

But delivery is tricky. In the early 1990s, scientists first demonstrated that injected mRNA could generate proteins in mice[2] and rats[3]. But protein production was low and transient, and the mRNA seemed too unstable to make a suitable drug. Years later, researchers also realized that lab-synthesized mRNA tends to spur an immune attack after it is injected, triggering potentially dangerous inflammatory responses. So a handful of researchers started working their way around the body's defences by modifying the RNA.

Moderna traces its origins to one such effort, in the laboratory of Derrick Rossi. A stem-cell biologist at Boston Children's Hospital, Rossi and his postdoc Luigi Warren were trying to use mRNA to coax cells into a 'pluripotent' state, capable of giving rise to many cell types. To avoid triggering inflammation, the researchers replaced some of the RNA's molecular building blocks — the nucleosides uridine and cytidine — with pseudouridine and 5-methylcytidine. This makes the RNA look more like something that the cell would produce itself, because invaders such as bacteria cannot usually make these modifications to their own mRNA.

It worked. In 2010, Rossi and Warren filed to

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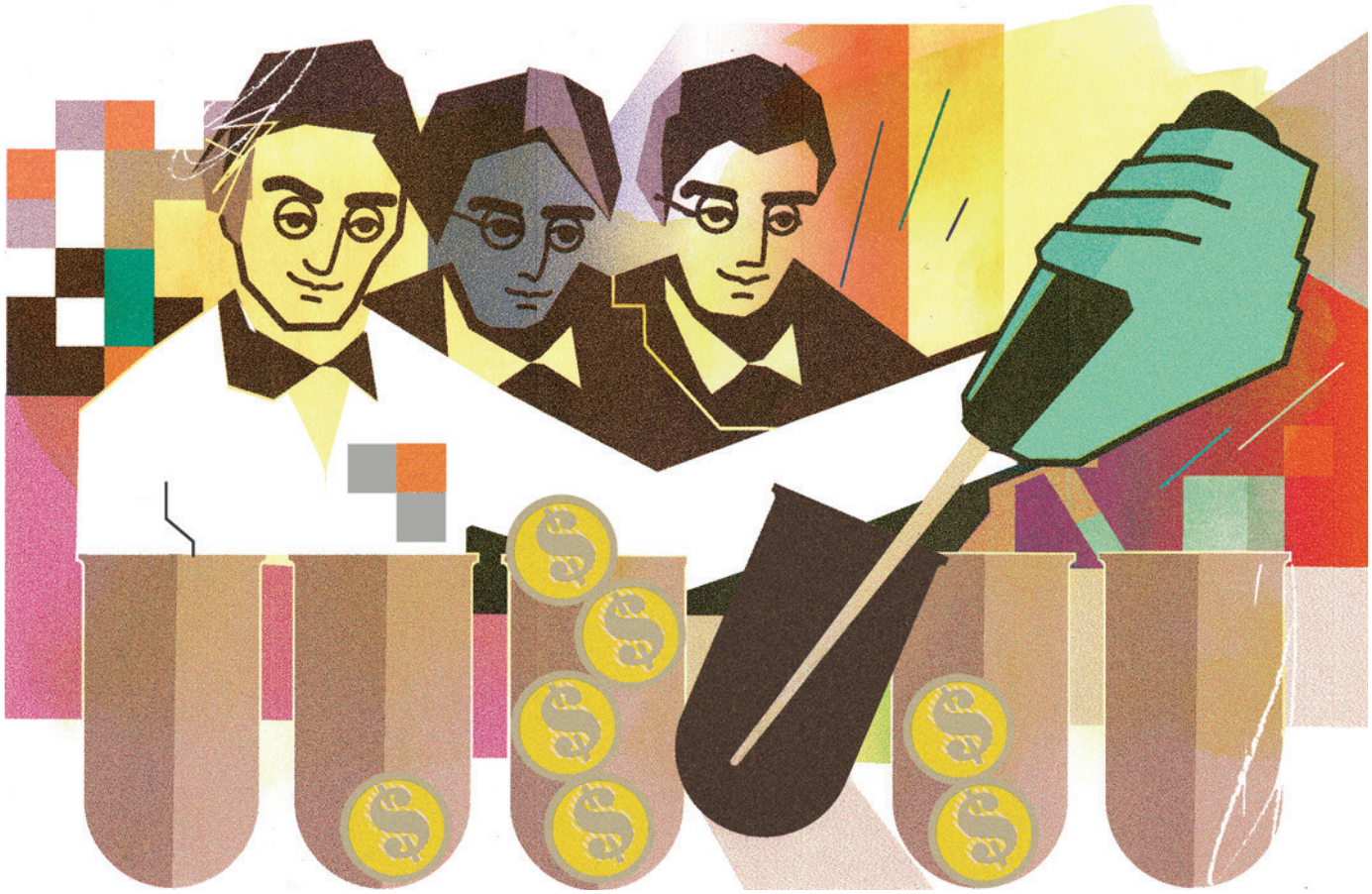

PADDY MILLS

patent their method for making stem cells and later published the results of their research[4].

The work caught the attention of Robert Langer, a respected bioengineer and serial entrepreneur from the Massachusetts Institute of Technology in Cambridge, and Noubar Afeyan, chief executive of Cambridge biotech investment firm Flagship Ventures. Both men immediately saw the sweeping potential of the modified mRNA. The idea of side-stepping the cell's defences "was intriguing instantaneously", says Afeyan, who now chairs Moderna's board of directors.

Rossi and Langer brought in a third academic co-founder — cardiovascular biologist Kenneth Chien, formerly at Harvard Medical School in Boston and now at the Karolinska Institute in Stockholm — and together they launched Moderna in September 2010. The name was Rossi's invention, a portmanteau of modified and RNA.

There was just one problem. "Our paper really put the whole thing on the map but, ironically, our paper didn't have anything really to do with mRNA therapeutics," says Warren, who now runs Stemiotics, a company in San Diego, California, that makes custom-order stem cells using modified mRNA. The modified RNAs were not even their innovation.

They got the idea from Katalin Karikó and Drew Weissman at the University of Pennsylvania in Philadelphia (UPenn). In two papers that largely fell under the radar at the time, these scientists showed that using pseudouridine and 5-methylcytidine made mRNA nearly invisible to cellular defences, both *in vitro*[5] and in mice[6]. In 2005, the pair started filing to patent the technology for therapeutic purposes.

DIFFICULT DEALINGS

Karikó and Weissman created a company called RNARx, which received close to $900,000 in small-business grants from the US government. In mice and monkeys they showed[7] that regular mRNA injections could boost production of erythropoietin, a hormone that is prescribed to treat some forms of anaemia.

The company's research efforts ended there, however, in part because of disagreements between the researchers and the University of Pennsylvania over the licensing of their intellectual property (IP). The university eventually sold the licence to Cellscript, a firm in Madison, Wisconsin, for an undisclosed sum. Cellscript has mostly used the rights to market kits for making mRNAs with modified nucleosides, but chief executive Gary Dahl says that the company also has "an interest in therapeutics". He declined to discuss specifics.

Karikó and Weissman's patent posed a challenge for Moderna. A 2010 internal report from Flagship Ventures, which was nurturing Moderna into existence at the time, states that if scientists could not identify alternatives to pseudouridine and 5-methylcytidine, "our company technology may be limited to licensing IP from UPenn".

Moderna needed to find a way around the patent, and the task fell to its first employee, Jason Schrum. A nucleic-acid biochemist by training, Schrum set to work testing different types of modified nucleoside. He bought RNA-expression kits from Cellscript and assembled an array of nucleoside analogues, some of which he designed.

Most of the modified nucleosides were not up to the job. But Schrum found one, a variant of pseudouridine called 1-methylpseudouridine, that seemed to do the trick. According to Schrum, mRNA with this nucleoside produced even higher levels of protein expression with less inflammation than did the mRNA in Karikó and Weissman's papers. Last year, the US Patent and Trademark Office granted Moderna patents covering the use of 1-methylpseudouridine, among other nucleosides — but the University of Pennsylvania also received a patent that covers many of the same nucleosides.

Several other mRNA-therapeutics companies say that they have proprietary formulations of modified RNA molecules as well, although few are willing to discuss details. "In mRNAs, everything is deathly quiet," says Ali Mortazavi, chief executive of Silence Therapeutics, an RNA biotech in London. "There's really no understanding of who owns what, so nobody wants to disclose anything — and we're included in that."

Karikó, who now works at the German mRNA-therapeutics firm BioNTech in Mainz, points to early "signs that there will be a fierce battle for licensing" — and not just in the United States. Last year, the European Patent Office received two anonymous letters challenging the validity of Karikó and Weissman's patent application covering modified mRNA;

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US authorities granted the patent in 2012, but a decision is still pending in the European Union.

The uncertainties over intellectual property have clearly not dissuaded Moderna's investors. Kolchinsky says that patent disputes may be painful and expensive, but they eventually resolve. "Companies that enable such breakthroughs typically have the resources to fend off baseless claims, and settle, on reasonable terms, the ones that turn out to be legitimate," he says.

Moderna also has time on its side. Flush with cash — the company has an estimated $900 million in the bank — it can continue to sign on pharmaceutical partners and outspend its rivals on science. This year alone, Moderna plans to spend between $150 million and $180 million on research and development — more than any other mRNA drug-maker.

"They've created this air of inevitability," says Fruehauf. "It's a good strategy."

FUND-RAISER-IN-CHIEF

Much of that momentum boils down to one man: chief executive Stéphane Bancel. "He's a damn good salesman," says Justin Quinn, a staff scientist who worked at Moderna until 2012.

Bancel joined the company in July 2011 after leading the diagnostics firm bioMérieux of Marcy-l'Étoile, France, for five years. Afeyan had repeatedly tried to recruit Bancel to run Flagship-launched companies, but Bancel was not interested in most of the projects — start-ups that tended to focus on one lead product in one disease area.

Moderna was different: it promised to reinvent the drug industry. And for Bancel, a smooth-talking businessman with a penchant for stylish, slim-fitting clothing, "it was worth taking a career risk and a massive pay cut to go to a start-up if it had the potential to be something really big", he says.

Bancel quickly set to work on raising capital — with great success — but some question his tactics. In the opinion of a former staff scientist (who requested anonymity) Bancel used his charisma and connections, as well as the clout of the company's co-founders, to convince investors and partners of the uniqueness of the Moderna platform, while glossing over any possible holes in its intellectual property. "He did a tremendous job of persuading people to give the company money for technology that was not 100% theirs," the ex-employee says.

In response, Bancel says that of course investors in Moderna did their due diligence before writing cheques: "Companies are a bit more sophisticated than that."

He and other Moderna executives also acknowledge the seminal contributions made by Karikó, Weissman and others. But Tony de Fougerolles, who was Moderna's first chief scientific officer and now leads research efforts at Ablynx in Ghent, Belgium, argues that such early work was largely academic, and that Moderna approached the research "from a pharmaceutical perspective". Moreover,

> "THEY'VE CREATED THIS AIR OF INEVITABILITY. IT'S A GOOD STRATEGY."

Bancel says that Moderna's technology has now advanced to the point that the company's initial patent filings are "irrelevant". "This is Moderna generation 1.0, and we're at 6.0 now," he says. Moderna no longer relies on 1-methylpseudouridine in its mRNAs, for example.

And modified nucleoside chemistry is just one part of what goes into building an mRNA drug. Another crucial aspect involves working out how to get the mRNA into specific cells and tissues in the body — a challenge that continues to vex the related field of RNA-interference therapeutics, which emerged more than a decade ago but has had few clinical successes. "The key for messenger RNA is going to be delivery," says Joseph Payne, president and chief executive of Arcturus Therapeutics in San Diego, one of many drug developers working on nanoparticle-based delivery of mRNA therapeutics. "That's really the rate-limiting step," adds Haussecker.

Bancel says that Moderna is exploring several delivery technologies through its in-house team and partnerships with others — although he would not divulge details of the company's approach. "People will figure out in 18 months where we are now when they see the patents," he says. Although at that point, he adds, even those methods will probably be out of date.

THE BEAST

At its sleek Cambridge headquarters, Moderna is equipping itself with the best laboratories that money can buy. In the middle of a third-floor lab sits "the beast", as Bancel calls it: a suite of robots that can make up to 50 lots of therapeutic mRNA per day for testing in non-human primates. Moderna also plans to open a facility for making human-grade mRNA later this year.

Its resources have allowed the company to launch more than 50 drug-development programmes, mostly through external pharmaceutical partners, but also at three wholly-owned spin-offs: Onkaido, Valera and Elpidera, which focus on oncology, infectious diseases and rare diseases, respectively. Bancel says that Valera will be first to the clinic, with an mRNA drug that targets an undisclosed infectious disease. "By the end of 2016, we will have trials for all the therapeutic areas we are in today," he says.

But clinical success is by no means guaranteed. "It will probably be like the technologies before it," says James McSwiggen, an independent biotechnology consultant who has worked with Moderna in the past. Other RNA-based drugs, such as antisense therapies, RNA interference and, most recently, microRNA, have all gone through periods of industry exuberance. These are generally followed by years wrestling with scientific realities before the technologies begin to show their true clinical promise. "I suspect that the same will happen" with mRNA, says McSwiggen. "If any company can weather that boom–bust bit, I would imagine that, given the amount of money that they've raised, Moderna should."

Other mRNA-therapeutics companies are persevering, and are getting promising data from studies in large animals. CureVac, a German company that spun off from the University of Tübingen in 2000, has found that it can get injected mRNA past the immune defences of pigs and monkeys by picking molecules with optimal sequences rather than by modifying their nucleosides[8]. So far, CureVac has struck deals with several big pharmaceutical companies and raised around $220 million in equity, including $52 million secured from the Bill & Melinda Gates Foundation in March this year.

Dublin-based rare-disease specialist Shire, in collaboration with Ethris of Planegg, Germany, has achieved targeted lung delivery of mRNA in a pig model for cystic fibrosis. "For a huge idea" like mRNA, says Michael Heartlein, head of MRNA therapeutics at Shire, "I think there's a lot of room for different technologies and different players".

But Bancel's ambition is for Moderna to grow so fast and so big that the competition simply has no chance. "We want to be the company that, if you want to make an mRNA drug five years from now, you pick up the phone and you call Moderna," he says. "Think about it: if you're going to put $50 or $100 million into mRNA, do you want to put it into your own team, starting four years behind, and with all the IP issues? Or do you want to pile it on $900 million of someone else's money?"

As for the naysayers and critics, Bancel says, "I understand people are not happy. I understand people are jealous. I understand all that. It's life." ■

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