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Neglected No More
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Neglected No More

Nudging biotech startups to tackle diseases of the developing world.

BY DENNIS PRICE

It was a game of cat and mouse—a very special mouse. The *mus musculus* in question was a transgenic laboratory mouse that researchers coveted for its human-like immune-system response. The cat was the Bill & Melinda Gates Foundation, which after several unsuccessful attempts was determined to secure a supply of the mice to advance research into vaccines for HIV, malaria, and other diseases that disproportionately affect the developing world. When the foundation spotted a company with a promising mouse technology that was in need of capital, it pounced.

In May 2014, the Gates Foundation made a \$20 million equity investment in Kymab Ltd., based in Cambridge, England. Kymab's promising technology and strong team were ideal for early-stage venture capital. The company was also being sued for patent infringement. Other investors balked at the increased risk and the prospect of spending millions on legal fees.

The Gates Foundation did its own due diligence and found the risk manageable—and balanced by the opportunity to secure reliable access to the mouse and to future drugs and vaccines that could be delivered for affordable prices in developing countries. Along with the equity investment, by the end of 2014 the foundation committed \$3.65 million in targeted research grants.

Such financial packages, along with the Gates Foundation's willingness to take on risks that many others investors would avoid, are critical components of the foundation's strategy to “nudge” private biotechnology startups to turn their techniques toward neglected diseases that wreak havoc in the developing world. Like many things,

the Gates Foundation's \$1.5 billion set-aside for program-related investments (PRIs) is the nation's largest. And the foundation has been among the most active in the ways it has used PRIs to leverage private technology for the public good.

The foundation has committed \$167 million to 14 biotech investments, many of which were accompanied by grants to fund specific projects. With many of the most promising approaches being pursued by private companies, the PRIs are intended to increase the chances of a hit on vaccines and drugs for diseases such as malaria, HIV, and typhoid.

In each case, the Gates Foundation insists on a legally binding commitment in a side letter that outlines the deal's charitable commitments, including a “global access agreement” that guarantees low prices for less-developed countries. Such commitments can raise concerns for executives and venture capitalists, who are reluctant to see young biotech companies divert resources from potential blockbusters toward diseases for which no developed-world markets exist.

Equity investments can help align the interests of the companies and the foundation in ways that grants cannot, says James Rosen, deputy director of PRIs at the Gates Foundation, who joined in 2015 after a decade as a biotech venture capitalist at Intersouth Partners.

“If, say, there's a vaccine platform technology for heart disease and cancer that is also applicable to HIV, we say, ‘Let us help you with the development of the platform,’” says Rosen. “There are incredible technologies that are housed within biotech companies.”

A \$5 million investment in 2012 by the Gates Foundation in Genocoe Biosciences, Inc., for example, nudged the Cambridge,

Mass., company to focus its groundbreaking T-cell target discovery technology on malaria. Eventually the foundation's investment and grant for malaria research paid off with the identification of components that may be useful for a malaria vaccine.

“The notion of going after big, big ideas is something that in today's environment investors really like,” says Chip Clark, CEO of Genocoe, which became a publicly held company in 2014. “To do so with support like the Gates Foundation's is a positive.”

The arrival of a new investor like the Gates Foundation on the startup biotech scene can have a huge impact, not only on the unmet needs of populations exposed to a high burden of infectious diseases, but on the companies themselves and their investors.

“I think a huge amount about aligning incentives,” says Julie Sunderland, the founding director of the Gates Foundation's PRI team. Sunderland says that the key is the amount of overlap between the objectives of the foundation and the company. “If there's not enough overlap, then we shouldn't do the deal. If there is a lot of overlap and we can de-risk or we can provide capital in creative ways to enable them to do the things that they want to do, those are our best deals.”

MOUSE TRAP

The Gates Foundation's investment in Kymab repeated its “nudge” approach. Historically, as much as 90 percent of the research and development investments in medical technology globally has been spent on health issues that affect only 10 percent of global morbidity and mortality. One way to overcome that disparity is to increase access to leading technologies with the potential to improve human health—technologies like a humanized mouse model.

The Gates Foundation investment team knew from their scientific colleagues that mice that make human antibodies (in scientific terms: transgenic mice with a human B-cell repertoire) would be valuable for vaccine research, in addition to their potential use in the discovery of potential drugs for asthma, rheumatoid arthritis, cholesterol, and even cancer.

“We had a clear need for mice able to generate human antibodies both as potential products and as a means for testing vaccine responses,” says Chris Karp, a director in the Gates Foundation's Global Health

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Program and its former lead on vaccine discovery. Most pressing was the need for a vaccine for malaria, which still kills roughly half a million people each year and debilitates many more.

The Gates Foundation had previously tried to gain access to these types of technologies. Not surprisingly, potential partners had not quickly embraced the research the foundation was proposing. There's a huge need for vaccines for diseases that mostly affect poor countries, but revenues from those markets are unlikely to cover the costs of the drug's research and development. In other words, there is little business incentive to take on diseases like dengue fever or typhoid.

and did ultimately commit \$3.65 million in grants to Kymab for the research on malaria and other projects.

The foundation was looking beyond the malaria project. At some point it would need access to the mice to advance research on its other priority diseases, notably HIV and typhoid. Kymab might well decide that such projects were not worth pursuing, even with additional grants or contracts.

If the Gates Foundation could get Kymab to accept an equity investment in its core platform as well, the foundation could not only secure a reliable supply of lab mice, but also lower the price of neglected-disease drugs and vaccines developed with the technology via the Global Access agreement.

the foundation's largest direct equity PRI to date. The Wellcome Trust, the founding investor in Kymab, agreed to match the Gates Foundation's investment dollar-for-dollar.

The Gates Foundation used a side letter to the equity agreement, a standard approach for clarifying investor-specific legal terms, to document the company's commitment. The agreement obligated Kymab to make any vaccines discovered with the foundation's funding available at affordable rates in developing countries. It also included a requirement that if Kymab deviated from the charitable commitment, it was obligated to buy back the foundation's shares.

That still left the company free to apply its technology to tackle diseases such

as cancer and sell its products in developed markets at whatever price it chooses. "It's essentially a cross-subsidization structure," says Jenny Yip, a program investment officer at the Gates Foundation. With that agreement, the foundation granted Kymab the funds to implement the malaria research.

In May 2015, Kymab completed the Series B financing that the foundation and Wellcome Trust had launched earlier with matching \$20 million investments. Kymab raised an additional \$50 million from Woodford Patient Capital Trust and Malin Corporation.

With access to the Kymouse, the foundation and Kymab have completed the first phase of the malaria project. And, earlier than expected, the Gates Foundation and Kymab have embarked on additional grant-funded projects

to seek drugs and vaccines for typhoid, HIV, pertussis, and other infectious diseases.

Each of these global health projects provides low-cost, rapid information about the human immune response to the building blocks of future vaccines—data that previously were not available until clinical trials were performed in people. Data that used to require years to obtain are now produced within months.

The Kymab malaria project has generated data pointing to vaccine components that could be used in humans to provoke antimalarial responses. The project has gone



Lab technicians at the Ikafara Health Institute in Tanzania prepare mosquito samples for DNA extraction.

"We didn't have the opportunity to start these types of vaccine programs, because they're not as commercially viable as our therapeutic antibody projects," says Glenn Friedrich, Kymab's chief operating officer. "We need to spend our equity on programs with a clear commercial benefit."

Kymab's "Kymouse platform" could be fine-tuned for multiple immune responses that mimic a natural human response—just what the Gates Foundation's product development partners needed. The Gates Foundation team considered using a traditional grant, or even a fee-for-service contract,

In addition to money, the Gates Foundation brought an imprimatur of social purpose. With a malaria vaccine mission, Kymab could demonstrate the efficacy of its platform and invigorate its staff. Even without a commercial market, a successful vaccine project could propel the company to the forefront of vaccine innovation.

The timing was good. Kymab was in the market to raise an additional round of funds. The company wanted an equity investment to ensure broad access to the Kymouse platform. The Gates Foundation's \$20 million Series B equity investment in Kymab was

as far as identifying individual antibodies that on their own block parasite infection in preclinical test models. Using this type of data, the foundation and its global health partners are able to focus precious resources on the vaccines and immunotherapies with the highest potential. Getting it right may save millions of lives.

"We're investing with a goal," says David Rossow, a senior program investment officer on the Gates Foundation PRI team. "Small pushes can have big changes."

TEST DRIVE

Meanwhile, in that other Cambridge, in Massachusetts, Genocoea had pioneered a T-cell target discovery technology to develop

from malaria than from bullets.

"When the parasite is injected through the bite of an infected mosquito, it rapidly travels to the liver, where it replicates in large numbers and is released into the bloodstream, causing sickness," Genocoea says on its website. "T-cells in the liver could potentially kill the cells in which the parasite is hiding before the parasite is able to break out into the bloodstream."

Identifying an effective T-cell antigen for malaria, however, "is like finding a needle in a haystack. You need a massive number of samples from people who are protected from malaria," says Rossow.

The Gates Foundation had been working with other pharmaceutical companies

you take the customer for a test drive, right? It's easier to prove it runs if it starts," he says. "The Gates investment made it easier for Genocoea to invest and do other products."

In October 2012, Genocoea closed a \$30 million round, including \$5 million from the Gates Foundation. In addition to adding the capital, the foundation introduced Genocoea to other research partners that would ensure the availability of additional T-cell samples.

In its charitable-intent side-letter agreement with the Gates Foundation, Genocoea agreed to make the T-cell platform available for its other priority diseases and to make any drugs produced through the partnership available in developing countries at an affordable price. The side letter also protected the global-access rights in case of an acquisition. As required, it gave the foundation a right to withdraw its capital if the company willfully neglected the agreed programmatic goals.

The malaria research sputtered from the start. "It was challenging working with collaborators from other countries and getting everyone working on the same timelines," says Clark. "The other collaborations weren't so urgent." Getting public and private partners to work together on the research, he says, "was a herding-cats problem for the Gates Foundation." One problem was getting access to enough T-cell samples. Says Rossow, "The timeline kept getting pushed back."

In September 2014, the foundation put up another \$1.2 million, in the form of a grant, to extend the malaria project. Then another obstacle arose over control of the intellectual property associated with the T-cell samples from other researchers. In the end, Genocoea did gain access to the samples and was able to identify a cluster of antigens that may be useful in a future vaccine.

In February 2014 Genocoea became a publicly held company. After a dip in the company's stock price, the foundation subsequently exited its position in 2015 for \$4.7 million, a small loss relative to the initial \$5 million investment. Because of the side-letter agreement, the research project and Global-Access commitments survive. If the restrictions came up in discussions with investors at all, they came up in a positive way, Clark says. "The foundation is at the forefront of stimulating investment in underserved diseases," says Clark. "I'd partner with them again in a heartbeat if it meant we can go after other diseases." ♦

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vaccines and immunotherapies for infectious diseases. Most vaccines have stimulated B-cells, another part of the immune system, to generate antibody responses against pathogens. But T-cells are increasingly recognized as critical to the immune response to a wide range of infectious diseases.

Such breakthroughs are still many years and dollars from commercialization. But the Gates Foundation believes that developing critical components and ensuring global access are critical steps in creating effective, low-cost products for the developing world.

Founded in 2006, Genocoea is a leader in working with such T-cell technology, having started vaccine programs against three pathogens that appeared to work in animals. No T-cell vaccines, however, had achieved human proof-of-concept. At the time of the Gates Foundation investment, Genocoea's lead product was a herpes vaccine.

"A treatment for herpes was not the objective," says Rossow, who has helped put together many of the foundation's biotech investments. "We wanted to work on malaria. A successful application of this technology to malaria would be huge."

Genocoea, in fact, had been working with the US Navy on the early stages of a malaria vaccine discovery program. Malaria is very much a threat for the US military. In tropical zones, the military faces more morbidity

and research partners to collect such samples. Besides capital, the foundation team could bring to a partnership with Genocoea access to its world-class scientists. It could also introduce the company to other entities that could provide an array of T-cells for the malaria research the foundation funded.

Genocoea was preparing to raise its Series C financing after raising more than \$46 million in previous rounds. Many of its previous investors, including Johnson & Johnson Development Corporation, Polaris Partners, Skyline Ventures, Lux Capital, and SROne, the venture arm of GlaxoSmithKline, were preparing to double down on Genocoea.

With a \$5 million equity investment on the table, earmarked specifically for the development of the platform technology and its application to malaria research, the Gates Foundation was expecting pushback from Genocoea's other investors. Instead, "The other investors got comfortable with the project," says Genocoea CEO Chip Clark. "For one, the foundation's capital would be additive to the round financially. And we weren't proposing to hose out cash at just any idea. And two, the foundation is building a reputation as smart money, so we saw it as an opportunity to get validation."

Clark says taking the Gates Foundation's investment to work on a malaria vaccine was like selling a car. "When you're selling a car,