HIS BEST SHOT

BY CORIE LOK

Can Bruce Walker transform HIV vaccine research?

Bruce Walker didn't want to sit next to Terry Ragon on the 24-hour plane ride from Boston to South Africa. He had only recently met the wealthy, Cambridge, Massachusetts-based software executive and was about to spend two full days touring AIDS-ravaged Durban with him in hope of obtaining a donation. Walker, an immunologist and physician at Massachusetts General Hospital (MGH), wanted to give Ragon some space and get some work done, but Ragon insisted they sit together. During the flight, he peppered Walker with questions about his research in South Africa. He also warned him not to get his hopes up. "I go on a lot of these kinds of trips, and I don't give people very much money," Ragon said.

Walker was disappointed, but he stuck to the plan. He took Ragon to the crumbling, 100-year-old McCord Hospital, where he followed doctors and visited impoverished, young people with HIV. "All three of the patients I sat in with were going to die, and one of them was dying right there in front of me," says Ragon. He had been to Africa before but never had he so intimately seen the pain and suffering caused by AIDS.

As the trip neared its end, Walker knew that it was time to broach the subject of money ▶

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again. He had been trained by MGH fundraisers to give potential donors a range of options. For a modest sum, US$5,000–20,000, Ragon could fund lab equipment or nurses — $1 million might fund a small clinical trial. But on a whim, Walker decided to float a more ambitious idea: creating an institute in which researchers from different fields could focus solely on HIV vaccines under one roof, with the kind of funding that would enable high-risk projects. "I thought the idea was half-baked," says Ragon, "but it intrigued me."

That was in March 2007. Talks continued, and about a year later Ragon and his wife, Susan, agreed to give $100 million over 10 years to create the Ragon Institute of MGH, MIT and Harvard. Established in early 2009, with Walker as its director, the institute was a positive note at a challenging time for HIV vaccine development. In late 2007, the pharmaceutical company Merck announced that a high-profile vaccine candidate in a large phase II clinical trial failed to protect people from infection with HIV, and even increased the risk of infection for some[1]. Then, later in 2009, another surprise came with the results from a huge phase III trial in Thailand, dubbed the RV144 trial, showing that a combination of two previously unsuccessful vaccines had defied expectations and provided modest protection from infection[2]. Although researchers were cautious about the work, the results offered a glimmer of hope that protection was possible.

"Walker provides an environment that inspires innovation."

Researchers say that the trials — two of only three major vaccine efficacy studies undertaken in 25 years of research — have reminded them of just how little they know about harnessing the immune system to block this deadly disease. Researchers have called for a return to basic HIV research (see 'Where the money goes'). But they need stronger interdisciplinary collaboration, innovative trial designs and, perhaps most of all, freedom — through funding — to take chances. Now, many say that the Ragon Institute has the opportunity to put these factors to work. Walker can clearly draw the money, and Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, says that Walker can also gather the right team. "He has a special talent for getting groups of people together from diverse backgrounds in a collaborative, synergistic way," he says. "The challenge," says Herbert Virgin, an immunologist at Washington University in St Louis, Missouri, and head of the institute's external scientific advisory board, "is now putting it all together to generate a vaccine."

HOOKED ON BASICS

Two months ago in his MGH office, Walker was hanging on the words of Krista Dong, a Ragon Institute physician who lives in South Africa. Dong was rifling through detailed, handwritten notes about a clinical study she has been helping to design. The project aims to look at the immunological events during the first few days of HIV infection — most studies haven't been designed to capture this information. The researchers planned to collect blood samples from 200 young, uninfected women twice a week for a year.

The research could provide crucial information about how the virus takes hold in the body — information that cannot be gleaned easily from animal studies — but it requires extraordinary cooperation and trust from the participants. As Dong explained how she and her team would do this through HIV-prevention and job-training programmes, the smile on Walker's face grew. Walker is a listener and, unlike many of his Boston peers, he speaks softly and slowly. Walker asked a few well chosen questions on logistics but was clearly sold. "Let's start!" he said, then began to list possible sources of funding, mostly from foundations and philanthropists. Although he hadn't actually secured the money, he urged Dong and her team to plough ahead. "Bruce is endlessly optimistic in an infectious way," says Dong. "He provides an environment that inspires innovation and personal drive."

Walker's education as a fundraiser began in the mid 1990s, when he was head of the Partners AIDS Research Center at the MGH. He learned from a development officer there how to ask for a million dollars, something Walker found difficult at first. "How could I ask that?", he recalls thinking. "But then I realized — how could I, in good conscience, not ask for help?"

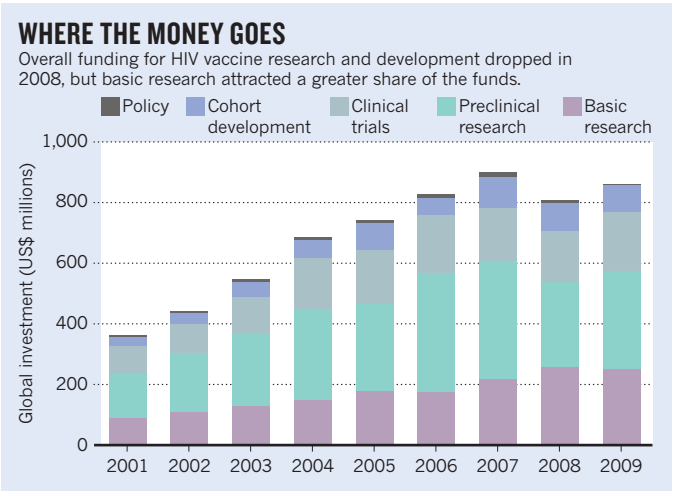
He soon learned the power of showing, rather than telling, people what their money can do. In 2000, a postdoctoral fellow working out of a closet-sized lab in Durban encouraged Walker to visit what was becoming the epicentre of the African AIDS epidemic. South Africa had come to lead sub-Saharan Africa in both the number of people living with HIV (5.6 million in 2009) and the number dying from AIDS (310,000 in 2009). Durban is the largest city in the most highly affected province, KwaZulu-Natal. Here, six in ten women are HIV-positive by the age of 23.

Walker was moved by what he saw. And when he met with other local HIV researchers looking for a bigger, better lab space in which they could work together, they hatched an idea to build a new research institute. Walker sent a proposal to the Doris Duke Charitable Foundation in New York, which was already funding some of his work. As he would do for Ragon several years later, he invited the head of the science programme to Durban. Shortly afterwards, the foundation committed $1.8 million to the construction of a new building, and another $2.25 million to support research and training for four years. The Doris Duke Medical Research Institute opened in 2003 on the campus of the Nelson R. Mandela School of Medicine at the University of KwaZulu-Natal. It was the foundation's first major international grant for HIV. Walker maintains close ties with the researchers at the institute through frequent phone calls and videoconferences. He also makes the long flight over there every other month, and co-supervises two PhD students and a postdoc.

Walker's laid-back, affable style helps him connect with people, and his connections have greatly helped his work. With his collaborators, he developed a cohort of around 1,200 people with HIV in South Africa. Studies on these individuals have provided many insights over the past decade, demonstrating, for example, how the virus evolves as the disease progresses. "It's not easy establishing all those links and collaborations and trust," says Andrew McMichael, an HIV immunologist at the University of Oxford, UK.

Walker has also taken an interest in the roughly 1 in 300 people with HIV who are able to keep the virus in check without any drugs and don't progress to AIDS. Walker and his colleagues painstakingly tracked down some of these rare patients, known in some circles as 'elite controllers', by connecting with HIV patient groups and physicians. They built up a cohort of about 1,500 controller patients, along with a bank of their blood samples, which they have shared with other research groups. They want to discover how these people suppress the virus, in the hope that the mechanism can be mimicked using a therapeutic vaccine.

The clues are mounting. A type of immune-system cell called a $CD8^+$



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Bruce Walker takes potential funders to meet patients and staff such as Nurse Kesia Ngwenya at McCord Hospital in Durban, South Africa.

or 'killer' T cell may exert selective pressure that allows only weaker versions of the virus to survive in controllers[3]. "Our direction right now is to try to understand how exactly these cells are driving these viruses to be less fit," says Walker. But some researchers think that the controllers' killer T cells are able to reproduce more and produce larger amounts of perforin — a protein that can poke holes in infected cells to help kill them[4]. Whatever mechanisms are at work, exploiting them will be a challenge, says Larry Corey, the principal investigator for the HIV Vaccine Trials Network (HVTN) and the head of the Fred Hutchinson Cancer Research Centre in Seattle, Washington. Studying the controllers "is important conceptual work", he says. "How to translate that into making an effective vaccine is easier said than done."

BRANCHING OUT

Meanwhile, Walker has been trying to pull researchers from other fields into the fold. From the start, he wanted to build an interdisciplinary team to oversee the Ragon Institute, one that could bring fresh perspectives to bear on issues that have dogged HIV researchers for 25 years. Walker recruited a steering committee to help him oversee the institute, including a materials scientist and a computational biologist, both from the Massachusetts Institute of Technology (MIT) in Cambridge. A group of 14 labs at the MGH form the core of institute, which funds collaborative research projects headed up by at least two principal investigators. One key area Walker has built up in his institute is basic HIV research, which has been held back by inadequate animal models. The HIV field, he says, has grown insular, with little interaction with immunologists doing basic research. He brought in a leading immunologist, Laurie Glimcher at the Harvard School of Public Health in Boston, Massachusetts. Glimcher had a history of branching out into different disciplines but had never worked on HIV. She now heads the institute's basic immunology programme and is overseeing the development of a humanized mouse core — a bank of mouse models that have key components of a human immune system. Walker hopes that these mice will allow researchers to test preliminary vaccines *in vivo* sooner than they can now.

Walker also pushed to have physical scientists join the team, something that resonated with Ragon, who has a physics degree from MIT. Three years ago, Walker approached Arup Chakraborty, a computational immunologist at MIT who had not studied HIV. Chakraborty was sceptical that he could contribute much to the field. But, as for others, an emotional trip to South Africa changed his mind. Now he heads the computational biology programme at the institute and more than one-third of his lab's work is devoted to HIV. Chakraborty's modelling expertise has helped to reveal important information in the wealth of immunological data already available. His preliminary work has shown, for example, that some variations in the HIV genome are linked. This means that if some mutations happen without others, the virus might become vulnerable to immune attack, says Walker.

Walker's overarching goal for the institute is to contribute to the development of an HIV vaccine and, while doing so, create a team culture rather than one that emphasizes individual credit. "It is going to take all of us making a contribution," says Walker.

Walker says that better modelling of data and broader collaborations could feed into a new breed of clinical trial. Typical phase II and III vaccine trials are geared towards showing efficacy. That means that they need to recruit enough patients to be able to statistically show an effect. For a single trial, that can take years and cost many millions of dollars. (The RV144 trial enrolled more than 16,000 participants at a cost of $103 million, which is typical of vaccine phase III trials.)

Walker aims to do a different type of vaccine trial: one that enrols 10–20 people, half of whom would receive a placebo. Researchers would then do a detailed analysis of the patients' immune responses, from T-cell activities to antibody generation. He hopes that the analyses, when done alongside or even before larger efficacy trials, would provide more clues about whether and how a vaccine candidate is stimulating the immune system — a crucial missing piece of the HIV vaccine puzzle. Such smaller, faster trials would allow candidates to be tested in parallel and hopefully give quicker indications of success or failure for less cost. This approach has been tried before, but until recently few HIV vaccine candidates elicited a strong enough response to study in this way.

Two vaccine candidates inherited by the institute are now in phase I trials; one of them is being tested in collaboration with HVTN and the International AIDS Vaccine Initiative (IAVI), headquartered in New York. The institute is also developing other candidates and is collaborating with the IAVI to build clinical laboratory infrastructure in Durban, where testing can be done more cheaply than in Western countries. The facility should be operating by early 2013.

Getting vaccine candidates into clinical trials, and testing them in innovative ways at a lower cost, will be key to the success of the Ragon Institute. And to encourage more interactions between the groups, Walker's lab, along with several other Ragon labs at the MGH and MIT plan to move in about a year into a new building near MIT. Ragon researchers based at other institutions will have space there as well.

But future trials will depend on whether Walker can continue to raise funds. Even $100 million, the largest donation in the MGH's history, is not enough to tackle the sheer complexity of the virus and the large number of unknowns about how to stimulate the immune system to fight off the disease, Walker says. He is still searching for funding from donors and chasing grants. He will undoubtedly be bringing more people to Durban. And he remains optimistic. "This is a solvable problem," he says. "There's no time to waste." ■

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