Patience for patients

Researchers find that perseverance and an altruistic streak keep them going along the long road to drug discovery.

BY NEIL SAVAGE

When Ripley Ballou — Rip to his friends — started to feel sick at a party in 1987, he thought it was because of his friend's home-brewed beer.

Ballou was taking a break from his work on developing a malaria vaccine at the Walter Reed Army Institute of Research in Silver Spring, Maryland, which he was doing in collaboration with the pharmaceutical giant GlaxoSmithKline (GSK). Back then, researchers could be a principal investigator as well as volunteer in their own projects. "We had a great tradition at Walter Reed where it was normal if you were developing a vaccine you had to take it yourself and you got your friends to take it with you," Ballou says. "So you'd walk down the hall and you'd get pulled in and they'd say, 'Would you be in my vaccine trial?' 'Sure, if you'll be in mine.'"

He and his colleagues injected themselves with a candidate, then allowed themselves to be bitten by infected mosquitoes. If the vaccine worked, it would mean they were well on their way to conquering a disease that may have killed half of all the people who have ever lived.

He realized he was wrong about the beer when he got home from the party. He developed a fever of 39 °C and the worst headache of his life. He had shaking chills, followed by a soaking sweat, in a cycle that was repeated half a dozen times over 48 hours. The experience had a profound impact. "I had no appreciation of what malaria was until I had it," Ballou says. "You're working on it, you read about it, you see people with it, but having it yourself was another experience and it made me want to beat that disease."

Seeing people endure malaria during field trials of vaccine candidates in southeast Asia and sub-Saharan Africa, where the disease is endemic, drove the point home. He ▶

Left to right: Quarraisha Abdool Karim, Una Ryan, Bahija Jallal, Ripley Ballou.

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especially remembers a young girl in a Burmese refugee camp bringing a sick baby to him. He ran across the camp with the baby in his arms to get to the hospital, where the child was treated and survived. "This is a disease that really does touch people and families, and having had this disease myself and knowing how sick I was it's just hard to believe that people can survive in an environment where this is part of their daily life," he says. "It kept me going."

Personal experience, a love of science and a desire to make the world a better place are all factors that fortify researchers as they move through the long process of drug discovery. Shepherding a drug from the preclinical stage to regulatory approval can take a decade or more, and the journey from fundamental research to practical application can last even longer. For scientists facing that long slog — sometimes with hypotheses that don't pan out, drug candidates that fail to meet their promise and funding that gets slashed — a certain amount of emotional fortitude is necessary.

COMMITMENT TO THE CAUSE

It helps to have passion for your work, says Bahija Jallal, who is executive vice-president of the biotechnology company MedImmune in Gaithersburg, Maryland, a subsidiary of the UK-based pharmaceutical giant AstraZeneca. "It requires a very personal investment, and you're also working on a much bigger goal, which is helping patients," she says. "But it's also not for the faint of heart. Drug development is tedious, it's long, it's hard, and so you really have to be passionate about doing what you're doing."

She also feels lucky. Her team currently has 50 compounds at some stage of clinical development. But even with the best efforts, research does not always turn out so well, she says. "There are some great scientists who will work their whole lives and will not be associated with one single medicine."

For Ballou, persistence paid off. He remembers the day in 1997 when he got word that a vaccine candidate was actually working. He and his team had created a vaccine by adding an adjuvant to boost the immune response, and were testing it on volunteers. One weekend morning, he called the lab from his kitchen to get the day's test results. Whereas everyone in the control group was infected, six out of seven people on the vaccine were showing complete protection. He called his colleagues at GSK in Belgium with the good news. "I can clearly remember just being euphoric about that success after so many years," he says. "I mean it was literally ten years of failure, over and over again not really getting any significant protection."

There were still years of work ahead, supported by the Bill & Melinda Gates Foundation and the international non-profit organization PATH, both in Seattle, Washington. But GSK now has a malaria vaccine, and Ballou is vice-president and head of the GSK Global Vaccines US R&D Center in Rockville, Maryland. The vaccine will be distributed in a pilot programme in Ghana, Kenya and Malawi beginning next year.

Another GSK malaria researcher, Yannick Vanloubbeeck, admits that stumbling blocks sometimes get to him. Vanloubbeeck is head of preclinical research and development in Rixensart, Belgium, where he's working on ten other potential vaccines, some or all of which may never make it out of the lab. "Obviously there is frustration," he says. Instead of getting discouraged, he tries to find out which candidates won't work as early as possible. "The sooner you stop a programme it means the sooner that you start another one," he says. And if researchers understand the weaknesses of a drug candidate, it can help them to refine their research.

Quarraisha Abdool Karim is philosophical about dud experiments. "If we knew something would work we wouldn't need to do any research," says the epidemiologist at Columbia University Medical Center in New York City and associate scientific director of CAPRISA (Centre for the AIDS Programme of Research in South Africa) in Durban, South Africa. "Even when something that you thought was going to work doesn't work, we learn a lot from that process."

One of the challenges that Abdool Karim has had to face as a researcher is the social customs of rural South Africa. She is working on tackling the HIV epidemic there, where women often lack the standing to refuse sex or demand that men wear condoms, and has spent years on the hunt for methods that women could use to prevent infection. In 2010, she showed that women can halve their chance of contracting HIV if they use a gel containing the antiretroviral drug tenofovir at least 80% of the times they have sex (Q. Abdool Karim *et al. Science* **329,** 1168–1174; 2010).

YOU REALLY HAVE TO BE PASSIONATE ABOUT DOING WHAT YOU'RE DOING.

That was the first demonstration that a woman-initiated approach could work. "To be able to make some contribution to that is quite an incredible feeling," Abdool Karim says. "But it also is a really sobering moment" knowing that the work needs to continue. Her clinical trials put her in direct contact with the women she's trying to help, and knowing them motivates her. "They are a constant reminder of the urgency for women-initiated technologies," she says.

Quarraisha Abdool Karim discusses the importance of HIV prevention with young women in South Africa.

L'ORÉAL FOUNDATION

CHILDHOOD DREAM

For Una Ryan, the desire to help people through science came early. When she was five, her aunt took her to see her first film; a story by some missionaries about a little boy with leprosy who was taken away from his family. "I just decided there and then that was heartbreaking and when I grew up I was going to be a missionary doctor, cure all the dread diseases in the world," she says. "You know these great noble thoughts you have as an impractical child."

Not that impractical, it turns out. She wound up as a researcher at the University of Miami School of Medicine in Florida. "My career at the beginning was very much driven by innate curiosity, but also personal tragedies that made me want to discover how things work," she says. At the time, her father was dying from complications from high blood pressure, and she'd had a premature son who died from respiratory distress. She wanted to explore what lay behind those conditions, so she looked at where breathing and blood pressure intersected. Her studies of capillaries, where gases pass between the bloodstream and the lungs, led to her discover that these small vessels contain angiotensin-converting enzymes (ACEs), which help to regulate the volume of fluids.

Based in part on her findings, scientists went on to develop ACE inhibitors, which are widely used to treat high blood pressure and congestive heart failure. Ryan even takes one herself, which she calls a positive kind of poetic justice.

She's had other successes, too. She was president and chief executive of Avant Immunotherapeutics in Needham, Massachusetts, which in partnership with GSK developed Rotarix, an

oral vaccine against rotavirus in infants, which she estimates saves about 400,000 lives a year. She does not want to measure her success with hard numbers, though. "I did not want to have on my gravestone, 'She saved X million lives' with a sort of tally of things," Ryan says. "I wanted to leave behind something that people wouldn't have had if I hadn't been here."

THE DIFFERENCE BETWEEN LIFE AND DEATH

Mark O'Connor knows the ups and downs that drug development can take. He joined a biotech start-up — KuDOS Pharmaceuticals in Cambridge, UK — in 1999 to work on the DNA damage response. A number of biological pathways check for and correct errors as cells replicate, but some of them are disabled in cancer cells. Steve Jackson, a molecular biologist at the University of Cambridge and founder of KuDOS, thought that if an inhibitor could be discovered to block the ones that persist in tumour cells, it would make an efficient cancer-specific therapy.

The team eventually identified olaparib. The drug showed promise in cancers with mutations in *BRCA1* and *BRCA2* — two genes that are normally involved in repairing DNA damage and, when mutated, are linked to some breast and other tumours. As with most small companies, there were struggles with money. O'Connor remembers the uncertainty when early funding was running out and new sources had not been secured, but he learned to set that worry aside. "If you spend all your time worrying about things you can't control then that's not good for you, so we just focused on delivering the science," he says.

By 2005, the company had made enough progress to be acquired by AstraZeneca, which helped to ramp up the research. But progress stalled. It had decided to test olaparib on a broader sample of ovarian cancers, not just those with *BRCA* mutations. The results seemed promising, but regulatory agencies wanted more data on long-term survival, and in 2011, the company decided not to go into phase III trials.

Rather than give up, the researchers refocused their efforts on just the cancers with *BRCA* mutations. They collected enough data that in 2012 they convinced the new AstraZeneca chief executive, Pascal Soriot, to move to phase III testing. Olaparib was ultimately approved in 2014 by both the US Food and Drug Administration and the European Medicines Agency.

Not long ago, O'Connor, now a chief scientist at AstraZeneca, was reminded of the real impact of the drug's success. A patient who had been taking olaparib wanted to meet the scientists who developed it. The 5-year survival rate for people with end-stage ovarian cancer is just 17%, but this woman had responded well to chemotherapy and had been taking olaparib for more than six years to stop the tumour from growing again. She told O'Connor and his colleagues that the treatment had kept her alive to see two new grandchildren.

"It was just brilliant," O'Connor says. "She just was really thankful, and she encouraged myself and other people who had been working on this 'you just need to keep going', because it had made such a difference to their lives."

He finds such experiences to be a good motivator. "It just reinforces why we do what we do," he says. "And if you've had a bad day and you've had meetings that you are unhappy about or experiments haven't worked the way you thought they would, you just have to keep focused on the patient." ■

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