Profile of Stephen Beverley

Paul Gabrielsen, *Science Writer*

During high school, Stephen M. Beverley attended a Science Day event at the California Institute of Technology. As he explored research laboratories, he felt that the entire world of science was open to him. "It just seemed like a candy shop," he says. Beverley's inquisitive pursuit of scientific truth has led him to study the factors that make the parasite *Leishmania* a devastating human scourge. Now, as Chair of the Department of Molecular Microbiology and Director of the Center for Infectious Disease Research at Washington University School of Medicine in St. Louis, Beverley, a member of the National Academy of Sciences, investigates how viruses influence *Leishmania* and how those viruses may be brought under control.

Supportive Parents

Beverley was born in southern California, but his family's roots reach into eastern Kentucky. His father earned a degree in engineering from Virginia Polytechnic Institute, was the first in his family to graduate from college, and moved the family to California to pursue a career in aerospace. Beverley recalls that his father was unafraid to try risky approaches to a problem before arriving at a solution. "The 'plan A, plan B, and so on until you got it right' mentality served me well in science, where my mentors were similarly minded," Beverley says.

Beverley's parents and teachers allowed him to explore and pursue his own interests. Beverley felt that his imagination had no bounds. "Looking back at things," he says, "I didn't realize how special that really was."

Caltech and Berkeley

Inspired by his Science Day visit, Beverley entered the California Institute of Technology (Caltech) in 1969. He worked in several biology laboratories, including the laboratory of future DNA sequencing pioneer Leroy Hood. Beverley's laboratory work was so substantive that his biochemistry professor waived his laboratory requirement, because he had already demonstrated the requisite skills.

Beverley began graduate school at the University of California, Berkeley in 1973. He worked with evolutionary biochemist Allan Wilson, studying the evolutionary differences between *Drosophila* fruit flies on the Hawaiian Islands and their counterparts on the mainland. Genetics suggested that fruit flies arrived in Hawaii more than 40 million years ago (1), although the oldest Hawaiian island known at the time was around 5 million years old (2). "It seemed unlikely the flies were spending 30 million years treading water in the middle of the Pacific," Beverley says. With data and advice from the US Geological Survey, however, Beverley concluded that the flies had first colonized earlier islands and had emigrated down the chain as old volcanic islands disappeared into the ocean and new islands arose (3). "That became the prevailing paradigm for introduction of other colonizing species early in Hawaiian evolution," Beverley explains.

Stephen Beverley. Image courtesy of E. Holland Durando (Washington University, St. Louis).

Discovering *Leishmania*

Beverley received his doctorate in 1979 and began looking for postdoctoral fellowships in the San Francisco Bay Area to stay close to fellow Berkeley graduate student Deborah Dobson, whom he would later marry.

Beverley attended a seminar given by Robert Schimke of Stanford University, who described how tumor cells offset drug activity by overproducing proteins through gene amplification. Beverley was intrigued and approached Schimke about the possibility of joining his laboratory. "He seemed moderately interested, but when he heard I'd been through Leroy Hood's lab at Caltech he said 'Okay, you're in!'"

Beverley worked for more than a year trying to apply gene amplification to insecticide resistance, but with little success. Looking for a new direction, he worked on side projects, but struggled to find a project that captured his interest.

From time to time, Schimke would walk down the hall of his laboratory, looking for people to work on various projects or problems that his colleagues had brought to him. "One day he went walking down the hall saying 'Does anybody want to work on *Leishmania*?'" Beverley says. "Nobody bit, and he stuck his

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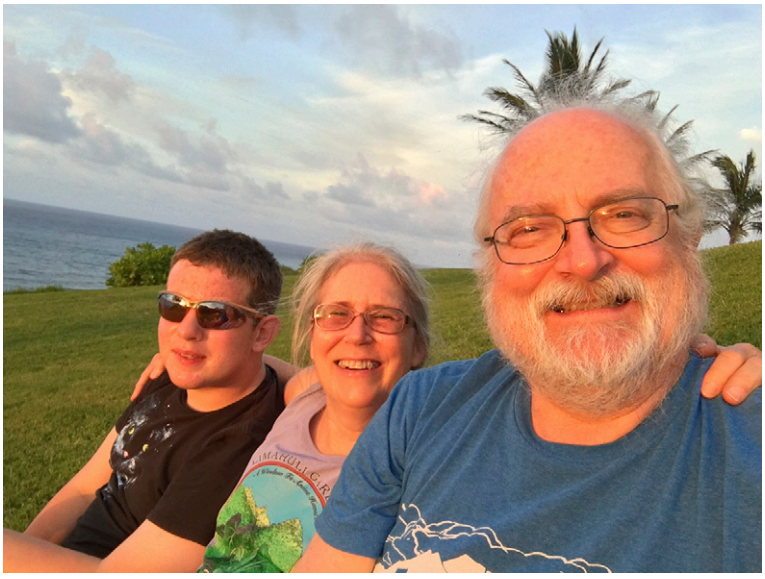

Beverley and family. Image courtesy of Stephen Beverley.

head in my bay." Schimke explained that Beverley's gene-amplification skills could come in handy in a colleague's study of a chemotherapy target enzyme produced by a *Leishmania* mutant. Beverley was intrigued by the evolutionary aspect of the project and asked "'By the way, what's *Leishmania*?' Schimke says, 'Oh, it's a parasite,' gives me a little smile, and walks out the door."

Beverley read everything he could on *Leishmania*. "They were very interesting creatures, causing devastating disease outside of the US" he says. "No one was working on them. I had the perfect set of tools and a whole set of interesting new questions. I was hooked."

Leishmania is a single-celled parasite transmitted through biting insects, like sand flies. The parasite can cause the disease Leishmaniasis, which has several forms, ranging from skin sores and ulcers to internal organ damage.

Beverley found that the amplified DNA molecules in *Leishmania* were circular (4), a finding that offered insight into their origin and function. He explored similarities between the origin of the amplified DNA in *Leishmania* and tumor genes frequently amplified in human tumors, work he would continue at Harvard University.

Genetics and Glycobiology at Harvard

When Harvard invited Beverley to apply for a position, the California native had reservations about the Northeast. "The night I flew in was a giant blizzard. I thought 'No way is this going to work out,'" he says. But when Harvard offered, Beverley accepted. "A key factor was the emergence of a strong molecular parasitology community," he says. In addition, Boston's many universities and laboratories afforded his wife abundant career opportunities. "Science was the major determinant, but boy, right behind it was the opportunities for my wife's career to develop," Beverley says.

Arriving at Harvard in 1983, Beverley got to work on developing a set of genetic tools that would enable researchers to parse the genetic pathways responsible for *Leishmania*'s biological functions. "It took longer than we had hoped, but once we did, it changed the way we looked at science," he says.

Now he could put genetic tools (5) to work. Because a pathogen's first contact with a host is its surface, Beverley connected with a glycobiologist, Salvatore Turco, at the University of Kentucky. Together, they explored the genetic pathways and structures behind the sugary coating on the surface of *Leishmania* (6). In the course of their investigation, the two found pathways (7) that could serve as drug targets (8) and mutant lines that could be useful in a future Leishmaniasis vaccine. Turco and Beverley are still close collaborators. "I'm a card-carrying glycobiologist now," Beverley says.

In articles published in 1995 (9) and 2003 (10), Beverley described engineered and mutant parasites that did not cause disease and hence could survive in a host for a long time, with the potential for live-vaccination strategies. If parasites could be engineered to produce a useful protein, hormone, or other bioactive molecule, they could also serve as long-term therapeutics for people deficient in that molecule.

The articles caught the attention of entrepreneur Dennis Vaccaro, who approached Beverley with a proposition for a start-up company to pursue this possibility further. "We called it 'Symbiontics' because we were trying to engineer a symbiosis between the parasite providing something to the host and the host providing a safe haven," Beverley says.

New Opportunities in St. Louis

Launch of the business was put on hold, however, as Beverley pondered an invitation from Washington University in St. Louis to chair its molecular microbiology department. Although he was content at Harvard and was serving as acting chair of his department at the time, at St. Louis Beverley found a department emerging with tremendous strengths in studying host–pathogen interactions.

"Lots of microbiology departments are focused on bacteria, viruses, but rarely on protozoan or fungal pathogens," he says. "For me this was an opportunity, as a protozoan researcher, to be in charge of a major microbiology department, with an opportunity to integrate molecular parasitology back into microbiology." Beverley moved to St. Louis in 1997.

Symbiontics launched soon after. The company focused on lysosomal storage diseases, which arise through lack of critical enzymes required to break down cellular components. "*Leishmania* lives inside lysosomes, so it was a perfect target," Beverley says. With former postdoctoral fellow Jon LeBowtiz on board, the team focused on targeting adjacent cells, and found a peptide tag that would guide proteins to the lysosome much more efficiently than before (11). It worked so well, Beverley says, that the parasite-delivery route was no longer necessary. He left Symbiontics in 2003 and the company was acquired by San Francisco-based BioMarin in 2010.

Beverley's move to St. Louis was accompanied by personal as well as professional milestones. In 2001, he and Dobson welcomed a son into their family. "Better late than never," he says. "My son's 15 now and he's a joy."

Leishmaniavirus

Beverley's work in St. Louis investigated the factors contributing to *Leishmania* virulence, and while he studied the parasite he worked with immunologists to also understand responses in the host. His scientific journey, which had so far led him through fields of genetics and glycobiology, now took a turn into virology.

Most organisms harbor pathways for producing short snippets of RNA that can block expression of specific genes, a process called RNA interference (RNAi). In *Leishmania*, Beverley found that although some strains had retained RNAi pathways, many had lost theirs through evolutionary processes (12). Surprised, he investigated further and found that the strains that retained RNAi often carried virus-like elements.

The *Leishmania* RNA virus LRV1, a relative of totiviruses, had been described nearly 20 years earlier (13), but its role in parasite biology was unknown. Beverley and Nicolas Fasel of the University of Lausanne showed that strains containing the virus greatly increased the severity of the disease (14). To study the effects of the virus, they would need tools to compare infected and virus-free strains.

Defanging the Parasite

In many organisms, RNAi effectively controls viruses, suppressing the viral load. But although *Leishmania* strains displayed an active RNAi pathway, the virus persisted at a high level. The team hypothesized that the virus existed in a balance with RNAi, and that tipping the balance in favor of RNAi could eliminate the virus. This was far from guaranteed to work. "We tried anyway," Beverley says. "We have bold students."

In his Inaugural Article (15), Beverley and his colleagues report the generation of a long-hairpin double-stranded RNA generated by genetic elements engineered into the parasite's ribosomal RNA. The engineered hairpin triggers the RNAi cascade, stimulating overproduction of the short-interfering RNAs specific for *Leishmaniavirus*. The team observed that the virus-specific interfering RNAs in natural parasites comprised around 2% of the total short RNAs. In engineered parasites, however, the virus-specific total was as much as 87%. "We could kill any virus we tried," Beverley says.

The team turned to *Leishmania braziliensis*, which causes severe mucocutaneous leishmaniasis. Virus elimination in *L. braziliensis* reduced the host's inflammatory response to the parasite, concomitantly reducing virulence. Beverley is now extending these studies to viruses in other protozoans and their roles in pathogenicity. "A lot of protozoans and fungi have been reported to contain viral elements, but were largely overlooked as molecular curiosities," he says. "Once you have an idea in science, you start trying to apply it to everything." The next step, he says, may be to translate discoveries about viruses in protozoans into treatments for tropical diseases (16).

"One of the nice things about being a scientist is you never run out of questions," he says. "My grad[uate] advisor complained that he wasn't going to know everything before he died. I'm finding myself saying the same thing." Science is his favorite form of recreation, Beverley says. "Science will never run out of opportunities for folks like me."

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