QnAs with Philippe J. Sansonetti

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As a young resident doctor at France's Hôpitaux de Paris in the 1970s, Philippe Sansonetti saw a lot of patients with infectious diseases, such as typhoid, whooping cough, and leprosy. Sansonetti and his colleagues treated those patients with antibiotics. By that point, however, the first signs of antibiotic resistance were beginning to emerge. Sansonetti realized that treating infectious diseases might require alternative therapies, the development of which requires knowledge of how infectious microbes make people sick. Therefore, after completing his residency and training in molecular genetics at the Institut Pasteur, Sansonetti accepted a postdoctoral fellowship with Samuel B. Forman at the Walter Reed Army Institute of Research, then located in Washington, DC, to isolate the genes that let microbes invade host cells. Sansonetti's model pathogen was *Shigella*, which causes febrile bloody diarrhea and can be lethal in infants. The disease Shigellosis primarily afflicts individuals in developing countries who lack access to basic hygiene. Over the years, Sansonetti, now the Chair of Microbiology and Infectious Disease at the Collège de France and Professor at Institut Pasteur, has used *Shigella* to ask questions about microbial mechanics: What genes allow a microbe to penetrate a cell? How does it move once inside the host? How does it kill the cell? Elected as a foreign member to the National Academy of Sciences in 2012, Sansonetti is seen as a founding member of the field of cellular microbiology. For his work, Sansonetti has received numerous awards, including the Prix Jacques Monod for excellence in molecular biology in 1983, the Louis-Jeantet Prize of Medicine in 1994, and the Robert Koch Prize in 1997. He has been a Howard Hughes Medical Institute foreign scholar since 2000. In his Inaugural Article, Sansonetti provides an explanation for why individuals must go through several painful bouts of Shigellosis before developing immunity to the disease (1). His findings could help efforts to develop a Shigellosis vaccine.

PNAS: What prompted your shift in focus from medicine to research?

Sansonetti: One person who was key to my decision was a man by the name of Stanley Falkow. He was a pioneer in the field of molecular genetics. He published a book in 1975 that I still have on my shelf. It's in pretty bad shape. The name of the book is *Infectious Multiple Drug Resistance*. Falkow reviewed and collected most of the recent data on the genes and

systems that supported antibiotic resistance. However, there were two or three chapters at the end of the book that dealt with the genetics of pathogenesis. For me it was really a revelation that the idea I had in mind could be done.

PNAS: What was your first major discovery in the field?

Sansonetti: Just before I left Paris to go to my postdoc at Walter Reed, I found that the invasive capacity of *Shigella* was due to the presence of an extracellular element, known as a plasmid. I was playing with a particular subgroup of *Shigella* called *Shigella sonnei*. When I streaked *Shigella sonnei* on a Petri dish, I could see colonies with different morphologies. Normally, *Shigella sonnei* has polysaccharides, or sugars, on its cell surface and looks small and spherical. However, some colonies had lost expression of their polysaccharides and looked large, flat, and sort of dry on the surface. The loss of the polysaccharides was irreversible. Curious, I extracted DNA from the two colony types and found that the larger, flatter colonies had lost a high molecular weight extrachromosomal DNA element: a plasmid. The day I saw that the plasmid was not there was probably one of my most exciting moments in science. It's like your first love. You never forget it.

PNAS: How does your Inaugural Article advance your research into *Shigella*?

Sansonetti: It's well known that getting infected with *Shigella* once does not protect people well from subsequent infections. You need to accumulate several infections to be protected. This situation also exists for other infections, like malaria. The reasons for this poor immune response to *Shigella* were not known. By using in vivo approaches and a new technology, two-photon microscopy, we discovered that the *Shigella* bacterium actually blocks T cells from mounting an immune response. Specifically, T cells tell antigen-presenting cells like dendritic cells and macrophages to fight off invaders. However, the *Shigella* bacterium injects T cells with effector molecules, or toxins, using a sort of molecular syringe. Those toxic molecules paralyze the T cells so they cannot move in the lymph nodes, where the antigen-presenting cells are located. That provides one explanation for why immune resistance to *Shigella* is rather poor. It's also clear that if you want to improve the performance of a live-attenuated *Shigella* vaccine, you have to eliminate the expression of these immunosuppressive molecules.

Philippe J. Sansonetti.

PNAS: Speaking of vaccines, how close are you to developing a vaccine for *Shigella*?

Sansonetti: We have been developing vaccine candidates in the laboratory. Now two candidates have passed phase 2 trials, which typically involve testing the vaccine in about 100 volunteers. Our hope is that these candidates will soon be ready for large field trials.

PNAS: Can you discuss your work with the healthy gut?

Sansonetti: That's our new adventure. I got an advance grant from the European Research Council two years ago to find out how nonpathogenic microbes in the gut affect homeostasis. We are starting to get some interesting results. In one study, we identified a set of microbes that are located in the intestinal gland, or crypt, in the colon that seem to help with homeostasis. The crypt is an important area of the epithelium because this is where the stem cells are located. These stem cells account for epithelial regeneration. Once we have established the conditions of homeostasis, we can go back to pathogens and ask questions. For instance, do pathogens attack stem cells to destroy the epithelium?

1 Salgado-Pabón W, et al. (2013) *Shigella* impairs T lymphocyte dynamics in vivo. *Proc Natl Acad Sci USA* 110:4458–4463.

This is a QnAs with a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 4458.