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The path to developing a cervical cancer vaccine

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The path that led me to where I am today in my career as a vaccinologist was not a straight one: it was riddled with twists and turns, opportunities and obstacles and full of decisions that could have taken me down very different avenues. Working and interacting with many dedicated and brilliant scientists and taking apprenticeships to become a better and more versatile scientist have been rewarding experiences and more than once luck has come into play.

I was born in Erfurt, East Germany, two years before the Berlin Wall was built. My mother decided in 1960 that enough was enough, she would not tolerate living again under a totalitarian regime. She was the driving force that led my parents to flee East Germany via different routes with simply the clothes on their backs, leaving everything behind. My aunt, who lived in the West, drove me across the border pretending that I was her child, while I happily slept in the back of the car under the influence of some sleeping pills so that there was no chance for me to wake up at the border and tell the border police who I really was. I am still thankful to my mother for her farsighted stance to leave East Germany. Undoubtedly my life would have been very different if not for that decision.

As long as I can remember, biology has always been an interest of mine, which early on manifested itself—much to the dismay of my parents—by a tendency to bring home all kinds of creatures. As I grew older, my interests in biology grew stronger, coupled with an interest in medicine. Instinctively, I knew that both disciplines could eventually come together by studying biology with a goal to obtain a position in the pharmaceutical industry to discover new medicines. I remember that my parents were not thrilled about my choice. My father worked as a chemical engineer in a large chemical company and was concerned that the career prospects for a woman in industry were dismal based on his experiences. Yet, my parents did raise a very determined and independent child who, when convinced of something, would not be easily swayed.

Studying biology in Marburg, Germany was a wonderful experience, exposing me to many different aspects of science and rigorous training in chemistry and biochemistry. I also took classes and internships in pharmacology, which helped widen my interests. My career path became more focused when Professor Rudolph Thauer, a world-class expert on archaebacteria, was appointed to build and chair a new microbiology department at Phillips University in Marburg. Professor Thauer introduced a new style to the biology department, enforcing rigorous and logical thinking, quantitative rather than descriptive science, good work ethics and English language microbiology and biochemistry textbooks. Some biology students were complaining about the style of this new professor, which immediately intrigued me, so I started to attend his lectures. It only took a few lectures and I was hooked. All his lectures started at eight in the morning, for other biology courses starting at that time I would usually sleep right through, but I would not miss a single microbiology lecture. I enrolled in every microbiology class and laboratory course he offered, and I finished my diploma and doctoral thesis in his laboratory. The training under Professor Thauer molded me into a curious and questioning scientist, as he always challenged his students to think

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on their feet and he demanded perfection in experimental design and execution. I learned a very valuable lesson at the end of my PhD work when I realized, during the study of the carbon assimilation of a new isolate of a sulfate-reducing bacterium, that my whole hypothesis of the pathway completely crumbled after the data from my last experiments came in. Checking over and over where I could have made a mistake or may have overlooked something, I finally had to accept my data and the conclusion that I had not discovered a new pathway for this class of bacteria but that the bacteria were using one that was already known. I went to Professor Thauer, who as usual was working late in his office, to discuss the data, feeling awful and like a failure. He had an amused look on his face while I excitedly showed him the data and discussed the conclusions. What he taught me that evening was that science is not predictable, that one should not always expect a positive or unique outcome for success, and that negative data are just as important, provided that they were based on solid experimentation and interpretation. Equipped with that experience, I was ready to strike out on my own.

After my PhD, I received a Humboldt postdoctoral fellowship to work at Cornell University in Ithaca, NY. From biosynthetic pathways of anaerobes, I switched to molecular biology and yeast expression of multi-subunit neuronal receptors for receptor function studies. Little did I know what I was getting into, both from the standpoint of knowing nothing about either discipline and finding myself in a very different and very competitive environment from graduate school. In retrospect, this was probably my toughest time as a scientist and one that was the most character-building. It taught me resilience, self-reliance and most of all, that I could stand truly on my own feet and, following my own instincts and intuitions, could be successful. I cherished the multiple collaborations and friendships (including meeting my husband) that evolved during this time and the interactions with excellent scientists like Professor Toni Claudio, Yale University; Dr. Nathan Nelson, Roche; Dr. Jon Lindstrom, Salk Institute and Professor Tom Fox, Cornell University; to name a few.

About Dr. Kathrin U. Jansen

Dr. Kathrin Jansen studied Biology at the Philpps-University in Marburg (Germany) and earned her PhD in 1984. Over the next years she gained experience in Microbiology and Molecular Biology at different academic institutions, including the Philipps-University, Cornell University (Ithaca, NY) and Massachusetts General Hospital (Boston, MA).

In 1989 Dr. Jansen joined the Glaxo Institute for Molecular Biology (Geneva, Switzerland) as research scientist and studied the structure and function of CD23, a low affinity receptor for IgE. From 1992 to 2004 she was affiliated with Merck Research Laboratories (West Point, PA), where she championed and led the development of the HPV vaccine Gardasil® from pre-clinical studies to clinical trials and product development. At Merck Dr. Jansen's career advanced to becoming Executive Director and Department Head of Microbial Vaccine Research in 2003. From Merck she moved to VaxGen Inc. (San Francisco, CA) as Chief Scientific Officer and Senior Vice President for Research and Development, where she supported VaxGen's anthrax and smallpox vaccine programs.

In 2006 Dr. Jansen joined Wyeth (now Pfizer Inc.) as a Senior Vice President for Vaccine Research and Early Development. At Pfizer's Pearl River, NY site, she manages a group of over 200 scientists and support staff and is responsible for vaccine discovery and early development of prophylactic vaccines against infectious diseases as well as the development/validation and performance of vaccine clinical serology and diagnostic assays.

Dr. Jansen is co-organizer of the ECI Vaccine Technology conference series and regularly invited to present at national and international meetings in the field. She received several awards and honours, including the *PhRMA Discoverers Award* for Gardasil® in 2009. Her research resulted in over 80 publications in peer-reviewed scientific journals and numerous patents on HPV vaccines, novel bacterial vaccines, assays and processes.

After my postdoctoral work, I felt very strongly about returning to Europe, so my husband and I took positions in Geneva, Switzerland. At the Glaxo Institute for Molecular Biology, I built on my molecular biology background and "convinced" immunologists to use molecular biology to produce a receptor of their interest, the low affinity receptor for IgE (CD23) for structure-function studies, rather than purifying the receptor from animal tissue. Even though I had been hired for my knowledge of yeast and yeast expression, I spent a lot of time and effort solving quite different problems. Taking knowledge and experiences gained during my postdoctoral years into account, I sensed that yeast was not the appropriate expression system for this receptor. In contrast, insect cell expression using baculoviruses had been recently developed in Dr. David Bishop's laboratory at Oxford and appeared to be a better system for the purpose. An internship in Dr. Bishop's laboratory allowed me to learn the system in order to bring it back to Geneva, where I established it in the laboratory. Working with my colleagues at Glaxo, we successfully expressed CD23

recombinantly and were able to discover its ligand, CD21. In return for my contributions, the immunologists and protein purification folks taught me their trade, which provided the foundation and more tools—even though I certainly did not appreciate this at the time—to become a vaccinologist.

At some point, both my husband and I were ready to go back to the US. Here luck came into play. A good friend and colleague of mine, Dr. Alan Shaw, had left Glaxo earlier to take a position at Merck Research Laboratories (MRL) in the vaccines group. Unbeknownst to me, Alan had posted a job advertisement in Science magazine that fit my experience perfectly. I had not realized that he was working on vaccines and the advertisement only listed the HR contact. So I called him up to inquire about the position. He laughed heartily and said that he was glad I called. He had sifted through hundreds of resumes but was frustrated to have not found a good candidate and asked if I would like to interview. I accepted the eventual job offer and joined the vaccine R&D group at Merck.

About the time I arrived, Merck had licensed in the intellectual properties from CSL to produce a vaccine against human papillomavirus (HPV) based on the major capsid protein of the virus. Again, I got myself into a situation where I was hired for one program and immediately became interested in something else, in this case the exciting opportunity to work on a cervical cancer vaccine. The idea at the time was to produce the vaccine antigen in insect cells using baculovirus expression. Neither Alan nor I found this approach particularly appealing from a production standpoint, so we decided to use a yeast expression approach. The deal was that my team could either demonstrate that the viral capsid protein could be expressed in yeast successfully, or the program would default to the insect cell approach. Merck had a spectacular yeast expression platform developed under Dr. Loren Schultz, who worked with me, and in a very short period of time we were successful in expressing the capsid protein and demonstrated that the capsid protein folded correctly into virus-like particles (VLPs). We subsequently used an animal papillomavirus model to determine the effectiveness of the VLPs as a vaccine. In collaboration with Dr. Darron Brown at Indiana University, we also worked on the capsid protein for HPV type 11, an HPV that causes genital warts. We demonstrated that anti-HPV11 virus-neutralizing antibodies developed after immunization with purified HPV11 VLPs expressed in yeast. While the initial successes came quickly and an ever-growing team of experts collaboratively and enthusiastically worked with me on advancing the program, the goal to make a quadrivalent vaccine to protect against >70% of cervical cancers and >90% of genital warts became more difficult by the minute. Innovations in the development of yeast strains were needed to prevent degradation of some of the HPV VLP types, new approaches to gene-engineering were required to solve expression hurdles for others, innovations in fermentation and purification approaches had to be implemented by process development groups led by Drs. Wayne Herber, Hugh George, and Ann Lee to solve aggregation and degradation issues of the VLPs, and new formulation approaches had to be developed to get the quadrivalent vaccine ready for phase 2 evaluation. In parallel, Dr. Frank Taddeo in my lab designed and developed new innovative diagnostic tests that had to be highly accurate to measure vaccine efficacy in clinical trials. As so often with new technologies or approaches, the efforts to do the work and to convince scientists both internally and externally that the approach was justified were significant. Luckily, Dr. Emilio Emini, my boss, and Dr. Edward Scolnick, the president of the Merck Research Laboratories at the time, were strong supporters of my program. One of the major hurdles was to convince colleagues to accept the design of a proof-of-concept phase 2 clinical trial using the newly developed diagnostic assays to measure HPV infection in the human genital tract. Many scientists strongly believed that this would be difficult if not impossible to do. Dr. Laura Koutsky, an epidemiologist at the University of Washington, had with her colleagues conducted excellent prospective HPV natural history studies that laid the groundwork for our phase 2 study and she was one of my strongest external supporters to get the green light for the study. Her input in the design and conduct of the trial was critical. And finally, about seven years after we conducted the first HPV expression experiment in the laboratory, the interim analysis for the phase 2 proof-of-concept study was completed: the data showed that a monovalent version of the cervical cancer vaccine had 100% efficacy in the prevention of infection with HPV16. I remember very fondly that day, dancing with my clinical colleague Dr. Eliav Barr through the hallways when we were informed about the positive interim analysis by Dr. Scolnick. One cannot put into words the excitement that the team felt after hearing these results and in one moment all the hard work and long hours were forgotten and the team started pushing for the finish line: licensure of Gardasil™ in 2006. Today, Gardasil™ has shown exquisite efficacy against precancerous lesions and genital warts not just in women, but also in men. My hope and wish is that the vaccine deployment globally progresses fast enough to prevent most of the annual 500,000 cervical cancer cases and 200,000 associated deaths.

The experiences at Merck developing Gardasil™ and working on other vaccine programs have further strengthened my passion for vaccines. The last few years, working at different vaccine companies developing a number of vaccines, have been rewarding, especially most recently with the licensure of a 13-valent pneumococcal conjugate vaccine [Prev(e)nar 13®] for infants and young children at Wyeth/Pfizer. A common theme that I have encountered in all company settings is the incredible passion, personal sacrifice, hard work, absolute dedication and teamwork of people involved in the development of vaccines across all levels and disciplines to create these important medicines. The effort, time and costs associated with successful vaccine development are enormous but worth it as the positive public health impact of vaccines is spectacular, with millions of lives saved every year by these medicines. Personally, I feel gratitude and satisfaction that my career path has led me to contribute to important vaccines and nothing is more inspiring than past success to take on the challenges posed by other vaccine-preventable diseases.