THE KAVLI PRIZE

An Autobiography by:
Emmanuelle Charpentier
Kavli Prize Laureate in Nanoscience 2018

I was born in December 1968, at the height of the student and civil protest movements and grew up in a small and relatively quiet town about 25 kilometers south of Paris. I have always been encouraged by my parents to explore my own academic interests. In school, I was an enthusiastic and aspiring student, always eager to acquire knowledge and to achieve excellence and therefore, I took my studies seriously. During my time at primary school, the oldest of my two sisters entered university and I understood already early on that academia was a place where one could continue to study, do research, teach and transfer knowledge. I therefore wanted to follow her path and was even more motivated to continue my studies.

Although it was not clear at the time that I would eventually study biology, I showed an interest in science very early on. In fact, I was interested not only in pure sciences and mathematics, but also in the human sciences — psychology, sociology and philosophy. My father liked to explain to me the Latin names of many plants. Maybe this motivated me to pursue natural sciences with later a direction towards medically-oriented questions, influenced by my mother's interests. I also remember that when I had to decide on a host laboratory for my Master's degree, I told my mother that I had selected the Pasteur Institute. She then recalled that I had come back home from school at the age of twelve and said that I would work at the Pasteur Institute one day. I myself do not remember our conversation in detail, but I suppose that my biology teacher at the time must have discussed a topic in school that triggered my interest in microbiology at a young age already.

After I finished my secondary education, I moved to Paris in 1986 to study biochemistry, microbiology and genetics – first at the University Pierre and Marie Curie. Later, my curiosity about micro-organisms and infectious diseases brought me to the Pasteur Institute where I obtained my Ph.D. in Microbiology in 1995. My projects during my Master and PhD theses with Patrice Courvalin as my mentor combined medical microbiology and the genetics of traits of bacteria such as of antibiotic resistance and mobile genetic elements. Here, it became clear to me that understanding fundamental science is the basis of innovation.

I felt a strong attraction to the field of microbiology, not only because of its importance given the rapid emergence of antibiotic resistance at the time, but also because I simply enjoyed the process of experimentation, from planning to execution and analysis. I felt at home in the laboratory. I was given a lot of independence and responsibility for my projects already at an early stage of my student life. Looking back, I think this had a very positive influence on my career,

because I identified myself very early on as a scientist rather than as a student – as someone creating knowledge rather than simply absorbing it. It seems small, but this change of mind-set made me more curious and perceptive of the qualities and career paths of the established scientists at the Pasteur Institute. I was inspired by their enthusiasm of and advocacy for basic research in microbiology. I realized that being a research scientist would fit the many aspects of my personality — my curiosity, intellectual drive for knowledge, enjoyment of communicating knowledge to others and working as a team, and my desire to turn complex scientific discoveries into practical applications that would help society. I was excited about being a scientist.

The education I received in France, my mentors and the wonderful scientists that have been accompanying me, have made me the scientist I am today: curious, persistent and always trusting my instinct that I have to concentrate on the basic science, and the rest will follow eventually. I also never questioned whether women were entitled to a career in a same way as men. At home, my parents were always very supportive with all the choices I made in the course of my career. The same applies for my academic life: I had both male and female mentors. I learned a lot from all of them, and their gender was never an issue. On the other hand, they all realized very early that I would continue with a scientific career and therefore strongly encouraged me to follow my path.

Looking back today at 25 years as a scientist – or, more precisely, as a microbiologist, I have come to understand that my private and professional lives are deeply shaped by interdisciplinarity, mobility and international exchange. Much like microbiology itself, which encompasses the fields of molecular biology, genetics, immunology and biochemistry, interdisciplinary research draws knowledge from various scientific fields – sometimes close, sometimes very far from one's own – to create new concepts by thinking across borders.

Crossing borders, in a literal sense, has been a highlight of my career. I have worked as an independent principal investigator in Austria and Sweden, and I am now based in Germany. I never thought that my career path would take me to these countries when I first started my postdoctoral studies in the US.

But after my time as a PhD student, I understood very fast that I also needed to go abroad. I knew that staying in France – as comfortable as that may have been – was not an option if I wanted to expand my personal and academic horizons. So, after sending out dozens of letters to different microbiology laboratories in the US, I decided to join the group of Elaine Tuomanen at the Rockefeller University in New York.

This was in 1996, when I was 27 years old. I moved into a shoe box of an apartment in New York. It was, in fact, a very exciting and happy time of my life and career. In many ways, New

York is a melting pot, and it gives you the the feeling that you are free to re-invent yourself. This was perhaps part of the reason why I let my curiosity and intuition lead me through several other academic institutions, again with inspiring mentors: Pamela Cowin at the New York University Medical Center, Richard Novick at the Skirball Institute and Elaine Tuomanen at St. Jude Children's Research Hospital in Memphis, Tennessee. The academic spirit in the United States certainly allowed me to explore different fields of research, ranging from bacterial pathogenicity to the genetic analysis of skin development in mice – and I greatly enjoyed this freedom. As new molecular and cellular technologies became available in the early 1990s, I turned my focus to the study of how bacterial pathogens infect and interact with their hosts and environment. I studied molecular mechanisms of regulation involved in gene and protein expression during infection. My aim was to find new pathways that could be further harnessed for the benefit of medicine and biotechnology. It was during my stays in Elaine Tuomanen's and Richard Novick's laboratories that I understood the need for more precise genetic tools, which I developed in order to facilitate the genetics in bacterial pathogens. The choice for a second postdoc with Pamela Cowin was mainly motivated by my wish to gain experience in the genetics and study of higher organisms. I chose to work on skin as I wanted to focus on bacterial pathogens that infect skin such as the human pathogen Streptococcus pyogenes. This bacterium has become a model organism for the past fifteen years of my laboratory's research. It was through the generation of transgenic mouse models and the study of proteins involved in skin cell-cell adhesion and signal transduction that I came to realise the lack of easy-to-use and precise genetic tools for eukaryotic systems. Especially in the late 1990's, there was no possibility to directly modify the DNA of human cells, which are critical to study in the context of human infectious diseases caused by bacterial pathogens.

Following this experience, I came back to focus on the more molecular aspects of regulation in bacteria but always kept in mind that I would take any opportunity in my future path to develop genetic tools for human cells if I had the chance to do so. CRISPR-Cas9 revealed to be the mechanism that led me indeed achieve this goal, and I expect more models to study infectious diseases based on the CRISPR-Cas9 technology to continue to develop.

One crucial aspect of my experiences in New York and Memphis was the chance to be surrounded by people that shared my level of ambition and my enthusiasm for basic science, and this was very enjoyable. I met so many researchers there who loved what they were doing and wanted to achieve major breakthroughs for themselves and for science. These were people that saw science as their vocation. Research was a fundamental part of their lives.

Moreover, as a medical microbiologist coming from a more conservative European research tradition, it was incredibly inspiring for me to witness how the research environment in the United States builds bridges between the academic world and the biotech sphere and pharma-

ceutical industry. I learned a lot from the American way of doing science, and the country's enterprising spirit. Although I had a very clear motivation for each move – there was either a specific topic that I wanted to study or a method that I wanted to learn – you also have to approach the unexpected when you move to a new country, which is part of why mobility can be such an enriching experience.

Nevertheless, I returned to Europe in 2002 to establish my own research group as an Assistant and Associate Professor at the Max F. Perutz Laboratories of the University of Vienna in Austria where I also habilitated in the field of Microbiology. I found myself in an historically rich and beautiful city. I was pleasantly surprised by the international spirit that was blowing through the academic institutions at the Vienna BioCenter. Science was managed in a way that nobody felt excluded regardless of which country she or he was from. In Vienna, I developed several projects aiming to identify and decipher RNA- and protein-mediated regulatory mechanisms mainly in the bacterial pathogen S. pyogenes. One of these projects consisted of identifying more RNAs with regulatory functions, others than the few we were already focusing on at the time. And this is how my research on bacterial CRISPR-Cas systems started. In 2006, Maria Eckert and Karine Gonzales from my laboratory performed a bioinformatics screen to search for new molecules of small RNA nature in S. pyogenes and identified CRISPR RNAs of the CRISPR-Cas9 system as well as tracrRNA among other RNAs. At that time, CRISPR ("clustered regularly interspaced short palindromic repeats") was hypothesized to act as an adaptive immune system in bacteria and archaea that would involve RNA-guided proteins to target the genomes of invaders such as viruses or plasmids. The hypothesis still needed to be tested and nothing was known about the mechanisms that would then be involved in such immunity. I saw this fundamental topic of microbiology as an opportunity to discover new types of RNA interference mechanisms that could be exploited to silence and recombine genomes of cells and organisms. One type of RNA, tracrRNA, retained the attention of my laboratory. Our focus on this RNA led us to demonstrate that it could have a regulatory function on the expression of a critical virulence factor, CAMP, but experiments failed to demonstrate such a function.

After six years in Vienna, I was appointed Associate Professor at the Laboratory for Molecular Infection Medicine Sweden (MIMS, part of the Nordic European Molecular Biology Laboratory (EMBL) Partnership for Molecular Medicine) at Umeå University where I habilitated in the field of Medical Microbiology and was active as a Visiting Professor until 2017. Being very far north in Umeå was a completely different experience. I was in a very remote environment and living through extreme winters. But I found state-of-the-art facilities and excellent working conditions with a great sense of respect for junior scientists. This framework enabled me to do some of my best research there. With my move to Umeå, I decided to focus more on the CRISPR-Cas9 system known at the time as the Csn1 system. My group had identified tracrRNA (trans-acting CRISPR RNA) (mentioned above) as an RNA encoded in the vicinity of the

type II CRISPR-Cas9 system, and I was interested in investigating whether tracrRNA was an integrative part of or would have a regulatory function on the system. No one knew the details of how CRISPR-Cas9 was working as a genome targeting machinery. But it was very clear for us at early stages that if a CRISPR-Cas system would be attractive to be exploited for genetic purposes, then the minimal CRISPR-Cas9 system with an enzyme guided by a duplex of RNA would offer a simple way to cleave DNA and harness it as a genetic tool. The other CRISPR-Cas systems described at the time were too complex.

In 2011, my group published a breakthrough paper in Nature that laid the foundation of our entire work on CRISPR-Cas9, whereby we identified the critical role that tracrRNA performs in the development of the CRISPR-mediated viral defense mechanism. I am grateful to have worked with highly enthusiastic and productive students, mainly Elitza Deltcheva and Krzysztof Chylinski, and to have collaborated with the group of Joerg Vogel in Germany on this study. A year later, we were indeed able to demonstrate that CRISPR-Cas9 is a dual-tracrRNA-CRISPR RNA enzyme that cleaves DNA sequence-specifically. The system was then developed into a precise gene-editing tool that can correct defective DNA, much like a text editing software can edit or correct typos in a document. The details of the DNA targeting mechanism by the CRISPR-Cas9 system and the guidelines how to use it as a versatile genetic tool were published in the journal Science in 2012 within the frame of a collaboration with Martin Jinek in Jennifer Doudna's laboratory in the US.

These ground-breaking findings in the field of RNA-mediated regulation based on the CRISPR-Cas9 system have revolutionized life sciences research and are opening whole new opportunities in biomedical gene therapies. Just a couple of months after the 2012 Science article, a number of studies were published, demonstrating the success of CRISPR-Cas9 as a technology that modifies DNA in human cells, plants and model organisms such as zebrafish and flies. The field of CRISPR-Cas9 continues to develop at dazzling speed, with exciting new developments emerging almost weekly.

At the same time, my career as a senior scientist was evolving very fast. Between 2013 and 2015, I was Professor at the Medical School of Hannover in Germany and established a new research department as Head of the Department of Regulation in Infection Biology at the Helmholtz Centre for Infection Research, Braunschweig. In 2013, I was honored with an Alexander von Humboldt Professorship, which I held in 2014 and 2015. In 2015, the Max Planck Society appointed me Scientific Member and Director of the Department of Regulation in Infection Biology at the Max Planck Institute for Infection Biology in Berlin, Germany. This meant that I had to move my laboratory for the third time in only a few years. A year later, I became Honorary Professor at Humboldt University.

When I left France and went to the United States, I lost a part of myself, but more importantly, I gained something new. I left America and moved to Vienna; I kept the best of the United States, and left the rest behind. Although not easy, it is important to find the right balance between staying true to oneself and avoiding complete assimilation on the one hand, and respecting and integrating into a new environment on the other, at the same time building on and being receptive to new ideas. A few iterations of this cycle – five in my case – and one is left with the essence of self that is imbued with one's experiences. This has helped me realise what my core values are as a person and as a scientist.

My restless years, in which I changed institutions and countries, have now come to an end. I have found a home in Berlin and within the Max Planck Society. In early 2018, I founded a new institute, the Max Planck Unit for the Science of Pathogens which allows me to expand my research on the fundamental processes of infection and immunity to other types of pathogens as well. I am very happy and extremely grateful to create a completely new institute from the very beginning, and I hope it will give a home to many talented and ambitious young scientists from all over the world to work on the many questions of basic biological research on pathogens that are still unanswered.

People outside science are often surprised when they learn that the discovery of the CRISPR-Cas9 gene editing technology is a result of basic science. Being a microbiologist, I sometimes see my field of research overlooked or not given the public attention and funding it deserves. But, the CRISPR-Cas9 discovery is a very good example why basic science is fundamentally important. Without the deep understanding of its basic mechanisms, we would not have been able to develop it into the innovative technology it is today.

The fact that the work of my laboratory was honored with numerous prizes all over the world makes me very happy, not only on a personal level, but also because it gives fundamental research the public attention and recognition it needs. Despite the fact that it is arduous work, experiments fail on a regular basis, and it often takes years until results are finally visible. I would like to motivate the new generation of researchers to be persistent, curious and passionate about basic science. I would like to encourage them to take risks and cross as many borders as they possibly can – because what lies behind these borders, expands your mind-set and is a very enriching experience. For me, it was a process of refinement and has made me the scientist I am today.