An Artist in Gene Editing

Sometimes a single discovery can change a whole life. For Emmanuelle Charpentier, deciphering the functioning of an enzyme previously known only to experts was such a moment. The trio comprised of one enzyme and two RNA molecules and known as CRISPR-Cas9 made headlines far beyond the world of science. Since then, a lot of things have changed in the French woman’s life. She became a Director at the Berlin-based Max Planck Institute for Infection Biology in early October 2015.

TEXT UTA DEFFKE
group in Berkeley, California to combine the two RNA molecules into one molecule. This step simplified the application of the CRISPR-Cas9 tool, since it meant that researchers only needed to program one RNA molecule in the gene sequence that Cas9 was to cleave.

In order for the DNA to be cut at a desired location, only the relevant gene sequence needs to be known and a matching RNA molecule manufactured. Researchers can then insert a new DNA snippet at the cut and thus switch genes on or off.

Since the discovery of the CRISPR-Cas9 mechanism, the molecular scissors have taken laboratories by storm: in 2012, 127 publications covered the subject of CRISPR-Cas9; by 2013 the figure had risen to 277. In 2015, the number skyrocketed to almost 500, and could rise to more than 1,100 studies this year. Scientists from all over the world are now taking a closer look at CRISPR-Cas9 and want to develop it further. But they are using it mainly as a tool to study genes. As it is much more precise, efficient and cost effective than previous methods, it is already a vital addition to many labs.

To date, all experiments involving plant, animal and human cells have been successful. CRISPR-Cas9 therefore has the potential for an extremely diverse range of applications: from plant breeding and the breeding of transgenic laboratory mice to treatments for a multitude of diseases. Doctors could use it to correct mutations and cure genetic diseases. It is already being used in HIV and malaria research.

Finally here: Emmanuelle Charpentier moved to the Berlin-based Max Planck Institute for Infection Biology in October 2015. Her objective was to begin working on her research as soon as possible after the move.
An immune mechanism in bacteria, until recently known only to hardcore microbiologists, could soon become a medical treatment for millions of patients. CRISPR-Cas9 is therefore a prime example of one of Charpentier’s core beliefs: “Basic research is essential for progress,” she stresses at every opportunity—a view that resonates perfectly with the Max Planck Society, of course.

The driving force behind Charpentier’s research is, above all, an unquenchable curiosity about the world and its complex relationships, a characteristic that she displayed even as a child. Charpentier grew up south of Paris, where she was exposed to a multifaceted range of interests. Her mother worked in psychiatry; her father was responsible for planning green spaces in the city. One of her sisters began her studies at university just as Emmanuelle started school, and from then on, one thing was clear to her: she wanted that, too. Even more so than school, university seemed to her to be the place of learning and intellectual debate.

**FROM MUSIC TO BIOLOGY**

That she would one day be a biologist, however, wasn’t determined until later. “According to my mother, when I was 11 or 12 years old, I told her that I would work at the Pasteur Institute—and that is where I actually did my doctorate,” she recalls with a smile. “But I actually enjoyed all my subjects at school. So I could have also followed a very different path.”

In her spare time, Charpentier enjoys art, music and dance. She played the piano and practiced ballet and modern dance for several years—a good exercise, not least for discipline and creative power. As she herself says: “Art has had a significant influence on my scientific career: you need to be rigorous, but you also need to be able to let yourself go.”

But she didn’t want to make a career out of this talent: not only because it is difficult to make a living from it, but, for dancers in particular, their active years are soon over. Scientists, on the other hand, can always keep making progress, even as they get older.

Biology, with its complexity and direct relationship with people, was the area that fascinated her most. Biochemistry was the area she initially focused on, but bacteria soon took over the main role in her life as a researcher. In her doctoral thesis, she examined mechanisms that lead bacteria to develop resistance to antibiotics. It was already apparent back then that the number of multi-resistant pathogens would rapidly increase.

At the same time, there was a growing awareness that we could also learn a lot from them. Thus, the research that was conducted on bacteria in the 1970s resulted in important new laboratory techniques, such as the gene cloning.
It is surprises like these that she finds so exciting in her discipline. This is also what motivated her at an early stage, following her studies and her doctoral work, to continuously embark on new adventures – both geographically and in terms of subject matter. She began her scientific pilgrimage with a postdoctoral position in New York. On the day she arrived, she found out that her working group would be moving to Memphis, Tennessee. “At that moment, I remembered something that my aunt, a missionary, had once predicted for me as a young child: that I would have an adventurous life with constant change. Up to then, it didn’t mean very much to me. But since my arrival in New York, I have actually been constantly on the move.”

This is also a source of inspiration for Charpentier. After all, leaving different places also means constantly leaving her comfort zone, scrutinizing and tweaking her own work. “This is probably exactly what I need for my work,” she says, also recommending it to her students. Similarly, she didn’t want to restrict herself in terms of subject matter, even if that was sometimes viewed critically by scientific colleagues. After all, in the scientific world, it’s important to find one’s niche.

Leaving home initially also meant leaving her bacteria. Charpentier turned instead to their hosts, and carried out research on mice, focusing on skin development and how microorganisms trigger skin infections. In doing so, she learned how arduous it was to modify the mouse genome in such a way as to make the animals suitable as model systems for diseases. This experience ultimately brought the researcher back to bacteria, as they were frequently a starting point for new gene manipulation tools.

After six years of postdoctoral work in the US, she was offered the opportunity to establish her own research group in the Biocenter at the University of Vienna. This was a real incentive to return to Europe. “Vienna offered strong basic research and outstanding colleagues, and I could choose my own subjects and work completely independently. I learned to think on a larger scale, to apply for research funding, as well as to manage with scant resources.”

In 2009, Charpentier moved from Vienna to Umeå University in Sweden. More than a few people thought she was a bit crazy at the time. “The move to Umeå was certainly risky,” she admits. “But ultimately it was exactly the right decision.” Not least because she came up with the radical idea of bringing together CRISPR and RNA while on the plane during her initial commutes between the two locations.

It then took her almost a year to find a student who also wanted to implement her idea in the lab. Her master’s student Elitza Deltcheva played an important role in encouraging other colleagues in the group to take an interest in CRISPR-Cas9.

Charpentier has now been researching in Germany since 2013. The country has always been a presence in her life. Her parents experienced the Second World War, she herself learned German at school, and as part of a student exchange, she got a taste of life in the country by living with a German family in a small town in the Rhine region for two weeks. Many of her friends and colleagues in the US, Austria and Sweden were also from Germany.

The Helmholtz Centre in Braunschweig and the Hannover Medical School enticed her with, among other things, an Alexander von Humboldt professorship. The connection with the
refuse to do,” clarifies Charpentier. Ul-
timately, it is the responsibility of pol-
icy makers to ensure that the enor-
mous potential of the DNA scissors
isn’t abused to create designer babies.

Charpentier is looking forward to
the new challenge at the Max Planck
Institute in Berlin. The location offers
the ideal conditions for her research: “I
have always looked for a place where I
can freely develop my ideas and prac-
tice science under excellent conditions.
And I have always dreamed of working
in a major city like Paris, London or
Berlin.” In particular, the unconven-
tional spirit of the city on the Spree Riv-
er resembles her own, and could inspire
her research.

For the time being, however, the
daily commute to the institute may
well have to suffice, as she will have
very little time to enjoy the cultural life
of Berlin in the coming months. After
all, it’s full steam ahead for the estab-
lishment of her new “Regulation in In-
fection Biology” department, and it’s
something that will require a huge
amount of energy: labs will be modi-
fied, and some of her colleagues who
are coming with her from the Helm-
holtz Centre will be busy setting up the
labs so that the research can continue
as seamlessly as possible. At the same
time, she also wants to cultivate con-
tacts with colleagues from the neigh-
boring institutes of the two universities
in Berlin and Charité.

In terms of subject matter, under-
standing regulation mechanisms in
pathogens will continue to be the focus
of her attention. First and foremost, she
wants to finish what she started with
CRISPR-Cas9. Her main objective is to
gain an even better understanding of
the biochemistry, specificity and effi-
ciency of the system: “We can see that
it works and we understand the funda-
amentals, but we’re still studying the de-
tails of how the DNA sequences are
identified and how the cutting works.”
She also wants to investigate other
CRISPR-Cas systems, as there may be
other cutting tools in the realm of bac-
teria that are even more suitable for
studying genes.

On top of all that, Charpentier wants
to strengthen the field of microbiology
at the institute and attract excellent ju-
nior scientists to this biological disci-
pline. This is also a matter of urgency,
as many microbiologists will be retiring
in the coming years. Compounding
this is the fact that microbiology isn’t
exactly seen as a discipline with a great
future. Charpentier is convinced this
is an error of judgment – one that she
hopes to correct.

Hannover Medical School gave Char-
pentier access to clinical practice – a
connection that she would now like to
build on in a similar way at Charité. But
she still stays in touch with her col-
leagues in Hanover.

LEGAL FRAMEWORK ABSENT
IN MANY COUNTRIES

In addition, two of the companies that
she co-founded are driving the devel-
opment of CRISPR-Cas9: CRISPR Ther-
apeutics was set up to make the tech-
nology commercially viable as a meth-
od of treatment for genetic diseases.
The company wants to remove cells
from patients, treat them with CRISPR-
Cas9, and then return them to the
body. Alternatively, CRISPR-Cas9 could
also be inserted into the body via spe-
cific transport containers, such as fat
bubbles or nanoparticles. Charpentier
also helped co-found ERS Genomics,
and has transferred the licenses for use
on other organisms to the company.

However, it will still be a few years
before humans can be treated with
CRISPR-Cas9. Before that, more clari-
ty about potential risks is needed. Al-
though CRISPR-Cas9 is considerably
more precise than other techniques, it
still makes mistakes and occasionally
cuts the genome at the wrong place.

Added to this are ethical issues that
the use of CRISPR-Cas9 could raise.
Chinese researchers recently modified
the genes in human embryonic stem
cells. While the embryos weren’t viable,
the experiments nevertheless show that
society and policy makers urgently
need to dictate what is and isn’t al-
lowed. “CRISPR-Cas9 can deliver huge
benefits to humanity, but of course we
need to handle it responsibly. Inter-
ventions into the human germline, for
instance, which would influence the
genome of future generations, is some-
thing that I and most of my colleagues
refuse to do,” clarifies Charpentier. Ul-

GLOSSARY

CRISPR-Cas9: CRISPR stands for “Clustered Regularly Interspaced Short Palindromic
Repeats” and describes a genome sequence in bacteria. Cas9 is an endonuclease – an
enzyme that cuts DNA. In viral infections, the bacteria cut sequences out of the viral
genome and insert them into the CRISPR sequence. The bacteria can use the resulting
transcribed CRISPR-RNA and an additional RNA molecule to identify the viral genome
if it attacks again. They can cut through it, incapacitating the pathogen. In this way,
the CRISPR-Cas9 system provides the bacterial immune system with a kind of memory.

RNA: The DNA molecule contains the assembly instructions for all proteins in an
organism. These instructions aren’t translated directly into proteins, but rather are first
transcribed into individual, much shorter RNA molecules. The chemical structure of
RNA, which is a single-stranded nucleic acid, is somewhat different from that of DNA.
There are various types of RNA molecules: some serve as a template for the production
of proteins, while others control gene activity.
Wer begleitet mich auf meinem Karriereweg?

Die Antwort: academics.de, der führende Stellenmarkt für Wissenschaftler

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