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Architect in the **Cellular Cosmos**

Elena Conti used to entertain the notion of becoming an architect. The fact that she decided to study chemistry in the end detracted nothing from her passion for the subject. As Director at the **Max Planck Institute of Biochemistry** in Martinsried, she studies the architecture of molecular machines in the cell – and is fascinated by the sophisticated structures in miniature.

TEXT **ELKE MAIER**

A black leather sofa, metal furniture, large-format images – Elena Conti has a fine sense of esthetics and clean lines. That is immediately clear from the decor of her office. To the left are classic black-and-white architectural photos: New York buildings, a memento of the city in which she did her postdoc work; to the right are white canvases covered by sinuous rows of colored dots.

"Those are artistic representations of an X-ray diffraction pattern inspired by the dot paintings of Damien Hirst," she says. On a table is more artwork: a shining yellow sun, a green meadow, an apple tree. A photo of the artist is hanging next to the computer: Elena Conti's five-year-old daughter Lucia …

Elena Conti has been Director at the Max Planck Institute of Biochemistry in Martinsried since 2006. Since 2007 she has also been an honorary professor of chemistry and pharmacology at Ludwig-Maximilians-Universität in Munich. The 47-year-old Italian-born scientist heads the Department of Structural Cell Biology at the institute in Martinsried. Together with her team, she studies the structure of molecular machines in cells that recognize undesirable or defective RNA molecules and renders them harmless. Once again, architecture – but this time on an atomic scale.

THE AGONY OF CHOICE BEFORE STUDYING

Her enthusiasm shines through when she speaks. Her fluent English has the lilt of a southern European accent. The petite, graceful scientist likes to speak with her hands, and she speaks rapidly. "I do everything quickly," she says, and laughs. Sometimes she is even reprimanded by her young daughter because of this: "'*Caaaaalma*, *caaaaalma*, *mamma*,' she says to me!"

Elena Conti hails from Varese in Lombardy, where she grew up as an only child. Her father works for a chemical company, her mother for an aircraft manufacturer. "When I was growing up in Italy, it was quite normal for women with children to pursue a career," she says. "My grandparents helped out – I recall the time I spent with them with great fondness."

Throughout her childhood there was no indication that she would one day become a scientist. Toward the end of her schooling, when it came time to choose a subject to study, she vacillated between chemistry and architecture, her two favorite subjects. "But at the time I thought I didn't have enough talent to become an architect." She opted for chemistry – not least because of her inspiring chemistry teacher and the prospect of being able to follow in her father's footsteps.

In 1986, Elena Conti enrolled in Pavia University. She won a scholarship

Ordered structures: Elena Conti is interested in the structure and function of molecular machines that are vital to a cell's survival. Investigating these structures requires sophisticated laboratory work.

Photo: Axel Griesch

"That's the most exciting part of the day:" Elena Conti looks forward to her daily round through the laboratory. Here, she and her colleague Eva Kowalinski (left) are standing in front of a chromatograph, which is used for purifying proteins.

from Collegio Ghislieri, a renowned institution founded in the 16th century that supports highly talented students. She actually wanted to specialize in organic chemistry, but then discovered that theory, especially the theory of molecular structures, was far more exciting to her than laboratory work.

Her faculty included a young professor who was investigating the structure of macromolecules, and Elena Conti completed her undergraduate work with him. Only then did the idea of going into science take shape. Coincidentally, the professor, Martino Bolognesi, had studied under Nobel laureate Robert Huber in Martinsried. At the time, Conti had no inkling that fate would one day land her there, as well.

For her doctoral work, Elena Conti traveled to the Imperial College of Science, Technology and Medicine in London, where she devoted herself to studying the enzyme that is responsible for the symphony of blinking lights we enjoy in gardens on sultry summer evenings. The title of her dissertation was *The Structure of the Glow-Worm Luciferase*, a somewhat arcane topic: "Because it's a niche field without much competitive pressure, I had enough time to learn the methods thoroughly," she recalls. To this day, her doctoral supervisor Peter Brick is one of her closest friends, as well as being her most exacting critic: "My research group loves it when he appears at one of our conferences and makes my life difficult," Conti says.

SCIENCE THAT RAISES THE ADRENALIN LEVEL

She acquired the biochemical tools for her later work while doing a postdoc at Rockefeller University in New York. There, she studied how proteins are transported from cellular plasma to the nucleus. "The time I spent at Rockefeller University opened my eyes," she recalls. "I moved from a small research group with leisurely tea breaks and Wimbledon games playing on the TV to a big, busy laboratory with exciting biology going on all around me. My adrenalin level was correspondingly high. It was quite normal to work during Christmas and Easter."

The hard work paid off: she discovered how a certain identifying pattern that occurs in many proteins in the cell nucleus is recognized by matching receptors – a key piece of the puzzle to better understand processes by which proteins are transported from the nucleus to the cell plasma.

After this accomplishment, Elena Conti was fully captivated by biochemistry. When she saw an ad for a position at the European Molecular Biology Laboratory (EMBL) in Heidelberg, she jumped at the chance and moved to Germany in 1999. It wasn't easy to leave New York after two and a half years. "New York has so much energy," she rhapsodizes. "But I knew that the EMBL is one of the best institutions for setting up my own working group." With a small team, she set out to investigate how RNA molecules are transported from the nucleus to the plasma and, in the process, are inspected for errors – a topic that still fascinates her to this day.

Photo: Axel Griesch

RNAs are a family of thread-like macromolecules that carry out vital functions in the cell. The so-called messenger RNAs – a special class of RNA molecules – act simultaneously as copiers and couriers. They are responsible for copying the blueprints for proteins that are coded in the nuclear DNA and for conveying the information to ribosomes, protein factories in the cell that then build the proteins according to the blueprints.

During this process, reliable quality control is vital for the cell, as any of the steps can result in errors. Errors lead to defective RNA molecules and incorrect blueprints with potentially fatal consequences for the cell and the body as a whole. It would be equally disastrous if blueprints that are no longer required were allowed to accumulate uncontrollably in the cell.

Elena Conti wasn't the only person at the EMBL who was active in this research field. Elisa Izaurralde, now Director at the Max Planck Institute for Developmental Biology in Tübingen, also focused on RNA transport in Heidelberg. Not only did the two scientists have the same research interests, they also complemented each other in their methodologies. "Whereas Elisa looked at the biological side, I sought to answer the structural questions," Elena Conti says.

The two became good friends outside of work, and twice a week, their agendas included a joint visit to a fitness studio. "After a workout, we used to discuss science and experiments in the sauna," Conti recalls, laughing. "People must have thought we were crazy!"

But it was definitely worthwhile: the two researchers characterized a number of factors that are involved in the transport and quality control of RNAs. In 2008, the two women shared the Leibniz Prize.

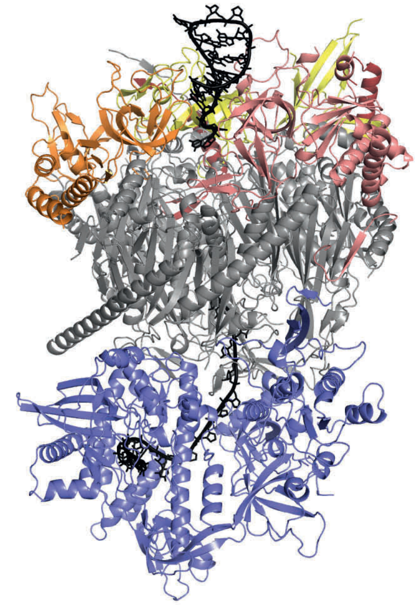
Elena Conti had already moved to the Max Planck Institute two years before. She was increasingly intrigued by the question of what happens when the cellular quality-assurance mechanism identifies defective or superfluous RNAs: How does the cell manage to get rid of such molecules? Together with her team, she began to research how the elaborate machinery picks out RNA molecules and destroys them, similar to a paper shredder.

A PRIMORDIAL MICROBE IN THE RESEARCH SPOTLIGHT

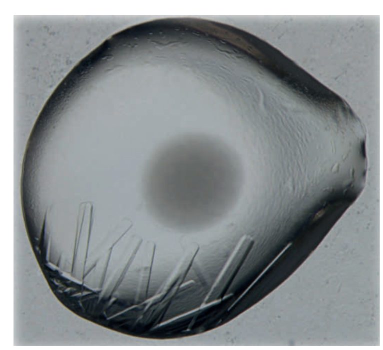
One focus of her work is to decipher the mechanism of action of the exosome, a molecular complex whose job is to break down RNAs. The exosome occurs in all eukaryotes, or organisms whose cells possess a nucleus. It is also present in simplified form in prokaryotes, organisms that lack a nucleus. At first, Elena Conti and her colleagues concentrated on the exosome of *Sulfolobus solfataricus*, a prokaryote.

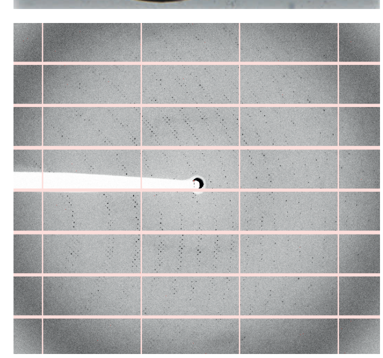
This primordial microbe belonging to the Archaea group of organisms was discovered by Wolfram Zillig, then Director at the Max Planck Institute of Biochemistry. He discovered the heat-loving microbes in sulfurous pools around Mount Vesuvius, near Naples. In comparison with higher organisms, its exosome consists of just a few proteins. And because they are adapted to the harsh environment in which the microbes thrive, they are particularly robust. This makes them easier to handle for research purposes.

Conti's team showed that the exosome of *S. solfataricus* has a hollow cylindrical structure. Inside it is the heart of the mechanism: the active centers at which RNA breakdown takes place. The eukaryote exosome is similar in



Top: A yeast exosome complex in action, shown at atomic scale: An RNA molecule (black) is transported through the barrel-like structure (gray) to the subunit that will break it down (purple). Middle: To investigate the atomic structure of protein complexes, the researchers grew crystals from pure proteins. Each crystal contains around a trillion regularly ordered identical molecules. Bottom: The scientists can view individual molecules with the help of X-ray diffraction.





Photos and graphic: Makino et al., Nature 2013 (top), MPI of Biochemistry (bottom, 2)

A weakness for design: Elena Conti's flair for esthetics and clean lines is reflected in the decor of her office. She abandoned her original notion of studying architecture in favor of chemistry.

structure. It, too, comprises nine protein subunits that form a barrel-like structure, but without the active centers. Instead, a tenth subunit that is absent in *Sulfolobus* is responsible for the shredding work.

THROUGH THE JAWS OF THE SHREDDER

The result is astonishing: Why has such a complicated structure been conserved over billions of years, from prokaryotes to eukaryotes? And why is it so vital that the cell would perish without it? "At that point, it was clear that we would have to tackle the more complicated eukaryote exosome," Conti says.

With the help of sophisticated biochemical methods, the researchers finally succeeded in visualizing the complex in action. "Isn't it beautiful?" asks Elena Conti, as she points to the three dimensional atomic model of a eukaryote exosome on the computer screen. It was captured precisely at the moment when an RNA molecule docked and was about to disappear into the jaws of the shredder.

"The RNA is transported through the central cavity of the barrel structure and finally lands at the subunit responsible for breakdown," the scientist explains, as she rotates the model with a click of the mouse. "Even though the barrel has lost its enzymatic function over the course of evolution, the RNA binding sites and the mechanism that transports the RNA through the complex are essentially still the same."

For the RNA to fit through the channel, it first has to be unfolded and pass through a narrow opening. What initially appears to be very complex turns out to be a stroke of genius. In this way, only those RNA molecules that are actually supposed to be broken down enter the shredder. This prevents a potentially dangerous machine like the exosome from indiscriminately chopping up RNA molecules in the cell.

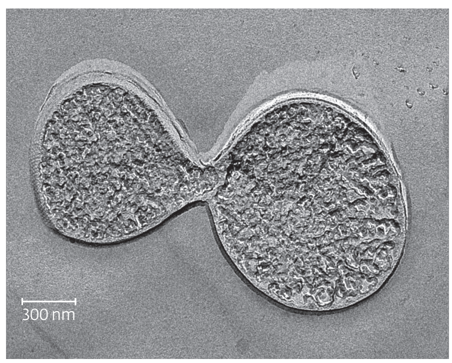
But how does the cell recognize which RNA molecules are destined for the molecular garbage can? And how does it ensure that defective molecules are reliably destroyed before they can cause harm? The Max Planck researcher is currently addressing these questions. One thing is certain, though: The exosome must cooperate and communicate with many other molecular machines in the cell.

This ensures, for example, that messenger RNAs can't be broken down until other machines have snipped off a characteristic structure at one end of the thread-like molecule. Conti and her colleagues are investigating how the entire process works. "You can think of it as a sort of assembly line," the scientist explains. "Each machine carries out a highly specific task before passing the workpiece on to the next. It all has to be finely orchestrated. We want to understand the information flow in the process."

The fact that problems with RNA metabolism are also implicated in many diseases shows just how important these processes are. In recognition of her work

Photo: Axel Griesch

» The two most important things are my family and my work. Even if the day had more than 24 hours, I would still divide my time between the two.



Hot springs like the Grand Prismatic Spring in Yellowstone National Park (left) contain heat-loving microbes of the Archaea group of organisms. Among these primordial organisms is *Sulfolobus solfataricus*. Discovered by former Max Planck Director Wolfram Zillig near Mount Vesuvius in the 1980s, it is now a popular model organism. On the right is an *S. solfataricus* cell undergoing division, which the researchers were able to visualize using a technique known as freeze etching.

in this field, Elena Conti was awarded the 2014 Louis-Jeantet Prize for Medicine, one of the most prestigious distinctions in biomedical research.

Elena Conti no longer works alone at her laboratory bench. She therefore looks forward all the more to her daily tour of the laboratory and takes the opportunity to chat with her colleagues and find out what has and hasn't worked. "That's the most exciting part of the day," she says. "I've got a great lab team! When I suggest an experiment, more often than not, it turns out that they already thought of it long ago and the experiment is already half complete."

Does she also think of other things with so much enthusiasm when she leaves the institute in the evening? "It's difficult to switch off," she admits. As Maria Callas said in a famous quote: "An opera begins before the curtain goes up and first ends long after it has come down!" This sentence rings particularly true if your partner is also a scientist, as in Elena Conti's case: Jürg Müller leads a research group at the Max Planck Institute in Martinsried that is investigating chromatin, the material of chromosomes, and how genes are read.

A ROUTINE FAMILY DAY WITH GENES AND MOLECULES

Not surprisingly, genes, RNAs and molecular complexes are often part of life at home. "It's a bit of a challenge as far as family life is concerned," says Elena Conti. But her partner's critical opinion is very important to her: "As you get older, your colleagues become younger and younger, and sometimes you don't feel able to speak your mind frankly," she muses.

Elena Conti and Jürg Müller met at the EMBL in Heidelberg. When their daughter was six months old, he also moved to Munich. During Lucia's first year, a nanny helped out with childcare. Since then, Lucia goes to the institute's nursery. When Elena Conti and Jürg Müller attend different conferences at the same time, the grandparents are happy to lend a hand and look after Lucia. "I would like my daughter to have as close a relationship with her grandparents as I had with mine," she says. Elena Conti knows precisely where her priorities lie: "The two most important things are my family and my work. Even if my day had more than 24 hours, I would still divide the time between the two." Elena Conti and her family live in the western part of Munich. They have annual passes to the Botanical Garden, Hellabrunn Zoo and Lenbachhaus art museum, where the three can often be found on weekends. The fact that Conti suddenly also remembers a little chocolate shop behind Munich's Viktualienmarkt ("You really must go there!") shows that art isn't the only thing she appreciates.

Otherwise, there's not much time left over for leisure activities, and she manages to make it to the fitness studio only once a week now. "My work is my hobby," she says – almost apologizing. But it's a privilege when one's work is also one's passion. Or in Elena Conti's case, two passions: architecture and chemistry. ◄