

## Profile of Karolin Luger

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As a postdoctoral associate in 1997, biochemist Karolin Luger helped vault nucleosomes into the spotlight (1) when she and colleagues revealed via X-ray crystallography the three-dimensional (3D) structure of this fundamental component of chromatin, the chromosome-forming material, in eukaryotic cells (2). The nucleosome was then the largest, most complex protein–DNA assemblage ever to have been crystallized. Luger, a professor of biochemistry at the University of Colorado Boulder, continues to analyze the structure and function of chromatin, which is a mixture of DNA and proteins that forms chromosomes and shapes gene transcription, DNA replication, and DNA repair. Luger's team has conducted seminal research on nucleosome evolutionary origins, chromosomal proteins, and chromatin remodeling factors, including enzymes that serve as targets in the treatment of cancers involving deficiencies in DNA repair through homologous recombination. Elected to the National Academy of Sciences (NAS) in 2018, Luger and colleagues (3) review findings on compounds called primary poly(ADP-ribose) polymerase (PARP) inhibitors (PARPi) in her Inaugural Article, which provides insights into the development of next-generation drugs to treat several types of cancer.

### Budding Scientist

Luger was raised in Austria by parents who encouraged their three children to strive for excellence but not to get discouraged when losses happen. She learned to have a “plan B” when things did not work out. This advice served her well as a scientist and when she competed in athletics. She says, “I realize now that this is a really valuable lesson that many of our undergrad and sometimes even grad students learn way too late in life.”

Luger's father and older brothers were interested in engineering and electronics, topics that dominated dinner-table discussions. Luger was also interested in gardening as a hobby, and this sparked her desire to learn about mechanisms underlying plant growth and contributed to her interest in molecular biology during high school. There, a teacher attempted to explain protein synthesis. Luger says, “It didn't make sense to me how the amino acid ‘knew’ onto which transfer RNA (tRNA) to attach itself, and this is when I realized there was a lot that was still unknown about stuff that is in textbooks. This also brought up the concept of recognition (in particular, in the context of tRNA synthases) and this interest in molecular recognition has stayed with me, not that I could have put it into such technical terms at that time.”

Luger decided to pursue a career in science after being offered a position as an undergraduate researcher with her own project at the University of Innsbruck, where she earned a Bachelor's degree in biology/microbiology in 1983 and a Master's degree in biology/biochemistry in 1986.



Karolin Luger. Image credit: Glenn Asakawa, University of Colorado Boulder.

Bernhard Auer, a professor of biochemistry at the university, was an early mentor. She says, “I remember, in the early days, doing a miniprep in his lab and I was so excited that I could hardly contain myself. This is a big reason why I take on so many undergrads now, so that I can pass along this joy.”

Luger moved to Switzerland for her doctoral work at the University of Basel, where she earned her doctorate in biochemistry/biophysics in 1989. Her advisor, the late biophysicist Kasper Kirschner, gave her free rein in selecting projects. She says, “He lent his enthusiastic support to all of my and my peers' crazy ideas.” One was to make a circularly permuted gene to see if the protein would fold (4). Luger continues, “It worked, and this has since influenced homology searches (because it has been shown to occur in nature) and also affected the way protein genes can be patented.”

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## Nucleosome Structure and Stability

Drawn to X-ray crystallography because of its “beautiful diffraction patterns” and utility, Luger chose to study structural biology at the Swiss Federal Institute of Technology (ETH) under the guidance of crystallography expert Timothy Richmond. After completing her postdoctoral stint in 1994, she served as a research assistant professor at ETH Zürich for 5 years and continued to work with Richmond. For 8 years the team strove to uncover the 3D structure of the nucleosome core particle of chromatin and finally succeeded in 1997 (2). Luger says, “For the first time we could see how histones intertwine and form a protein spool around which the DNA is wrapped.” The work garnered the team international acclaim.

Two years later, Luger was named a Searle Scholar, received 3 years of flexible funding, and accepted an assistant professorship in the department of biochemistry and molecular biology at Colorado State University. Luger says she appreciated the department’s vision for building a state-of-the-art macromolecular X-ray crystallography facility. She later oversaw the creation of that facility and advanced to a full professorship in 2015. Since 2005, she has also been an appointed investigator at the Howard Hughes Medical Institute.

Luger has always valued collaboration. With California Institute of Technology chemist Peter Dervan and colleagues, she helped construct a “nucleosomal staple” out of synthetic ligands that stabilized the nucleosome (5). She and her team later formulated a method for measuring nucleosome stability (6). With infectious disease specialist Kenneth Kaye at Brigham and Women’s Hospital, Luger showed how the Kaposi sarcoma virus uses the nucleosomal surface to attach its genome to chromatin (7). Through this effort, the researchers determined the structure of the nucleosome-interacting protein.

## Histone Modifications and Variants

For more than two decades, Luger has explored proteins called histones, the modifications of which influence gene expression, such as by altering chromatin structure. Her first article from her independent laboratory, a collaboration with David Tremethick of the Australian National University, described how the histone variant H2A.Z modulates nucleosome structure (8). She and colleagues subsequently found that histone posttranslational modifications lead to changes in chromatin’s higher-order structure (9).

Luger’s laboratory uses a wide range of technologies, including cryogenic electron microscopy (cryoEM), which reveals structures at atomic resolution. She says, “Keda Zhou, one of my postdocs and currently an assistant professor at the University of Hong Kong, solved the first cryoEM structure in my lab.” A collaboration with cell biologist Andrea Musacchio of the Max Planck Institute of Molecular Physiology, this study shed light on the centromeric nucleosome—key to mitosis and meiosis—through analysis of a histone variant’s structure (10). A graduate student working in Luger’s laboratory, Young-Jun Park, also achieved a milestone when he determined the crystal structure of a nucleosome assembly factor (11).

## Mechanisms of Nucleosome Assembly and Disassembly

Park’s achievement is one of many from Luger’s laboratory concerning the mechanisms by which nucleosomes are assembled and disassembled. Histone chaperones—proteins that bind histones and regulate nucleosome assembly—have been a primary focus. Luger and colleagues (12), for example, elucidated how the histone chaperone Nap1 (nucleosome assembly protein) interacts with other proteins to regulate the availability of histones for chromatin assembly.

With University of Texas at Dallas chemist and former Luger postdoctoral associate Sheena D’Arcy, Luger and her team solved the structure of the ubiquitous histone chaperone FACT (FAcilitates Chromatin Transcription) (13).

Additionally, Luger’s team has investigated the ATP-dependent chromatin remodeler SMARCAD1, a protein that acts on nucleosomes during DNA replication, repair, and transcription. Luger’s former graduate student Jon Markert coauthored a study characterizing SMARCAD1 and revealing how it binds to the nucleosome (14).

## Eukaryotic Nucleosome Origins

Another interest of Luger’s laboratory is the evolutionary origin of the nucleosome. In collaboration with microbiologist John Reeve of The Ohio State University and Colorado State University biochemist Thomas Santangelo, as well as then-postdoctoral associates Francesca Mattioli, Sudipta Bhattacharyya, and Samuel Bowerman, Luger elucidated the structure of Archaea chromatin (15, 16).

Such work led her team to investigate giant viruses, which are believed to be evolutionary bridges between living and nonliving organisms. Collaborating with geneticist and virologist Chantal Abergel of the Centre National de la Recherche Scientifique and the Genomics and Structural Information Laboratory in Marseille, Luger and colleagues found that histones are essential for viral fitness and organize DNA in the viral capsid (17).

## Effort to Improve PARP Inhibitors

Since PARP is abundantly bound to chromatin, helps recognize DNA damage, and initiates the DNA damage response, Luger and her team are interested in this nuclear enzyme, an important target in the treatment of certain ovarian, breast, prostate, and other cancers. There are currently more than 100 clinical trials underway for PARPi as a monotherapy or in combination with other agents.

In a study led by enzymologist Johannes Rudolph, Luger and her team showed that PARP1, which has multiple DNA binding domains, moves rapidly through chromatin via a “monkey bar mechanism” that enables it to swing from one DNA segment to the next (18). With graduate student Megan Palacio, Rudolph, Luger, and colleagues identified a previously unknown DNA binding domain on PARP1 that contributes to the monkey bar movement (19).

Luger’s Inaugural Article (3)—coauthored with Rudolph and undergraduate student Karen Jung—is a review article concerning studies on PARP, but it also offers extensive data analysis relevant to the development of next-generation PARPi

cancer treatments from the viewpoint of PARP structure-activity relationships and mechanistic enzymology.

"We address the issue of comparing *in vitro* and *in vivo* potencies and the biochemical underpinnings of PARP trapping," Luger says. "Our insights are meant to point out new angles that need to be considered by drug designers who are trying to develop the next blockbuster drug and, in general, help steer the field towards the development of PARPi that are truly novel and not subtle variations of the same old theme." Her laboratory is now directly involved in that effort.

## Invested in Mentoring

In recognition of her achievements, Luger was invited to be the national lecturer for the Biophysical Society in 2013. She says, "To speak in front of around 6,000 biophysicists and tell them about my journey was just mind-blowing and such an honor." She is grateful for other honors, including

her election to the NAS and being elected in 2017 as a member of the American Academy of Arts and Sciences.

She is also thankful for her team and students. Luger has trained dozens of graduate students and postdoctoral associates and mentored numerous undergraduates. She says, "I have always believed that my primary job is to train the next generation of scientists and to help them on their journey. I have been fortunate to work with many interesting people who taught me so much. I am also grateful to have several people in my lab who have been with me for as long as I have had my lab, and these individuals are as dedicated to the success of the lab and to our overall mission as I am."

Her daughter and husband have also been steadfast supporters. "My husband has always been hugely supportive, and not the least of it was his willingness to move between cities and, ultimately, continents several times to accommodate my job," says Luger.

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