

Rolf Peter Hilgenfeld (1954–2025)

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Keywords: obituary; Rolf Hilgenfeld.



Photograph: Thomas Berg/University of Lübeck

1. A life dedicated to science

Rolf Hilgenfeld was born in Göttingen and, after grammar school, he temporarily moved to Finland as a German teacher for the Goethe-Institute before studying chemistry (1973–1980) at the Albert Ludwigs University Freiburg and the Georg August University Göttingen, working on the X-ray structure elucidation of crown-ether compounds in Wolfram Saenger's group at the Max Planck Institute for Experimental Medicine. After Göttingen, he continued his studies in West Berlin and completed his doctorate in 1986 at the Institute of Crystallography at the Free University of Berlin. From 1986 to 1987 he was the laboratory chief of the newly established protein crystallography unit at Hoechst AG (now Sanofi), Frankfurt am Main. He temporarily relocated to Switzerland for a postdoc at the Biozentrum of the University of Basel and returned to Hoechst AG as the group leader of the Structural Biology and Drug Design unit. HIV protease, insulin and EF-Tu were some of the proteins he worked on. With a solid track record outside of academia, he applied for a professorship in Jena. He became full university professor (C4) of structural biochemistry (1995–2002) and head of department at the Institute of Molecular Biotechnology (IMB). From 1998 to 2000 he served as Scientific Director of the IMB. Next, Rolf applied for and became full professor of biochemistry and Director of the Institute of Biochemistry at the University of Lübeck (2003–2020). From 2020 onwards, he continued to

work as a senior professor and head of an independent research unit. In short, he lived a life in the fast lane, devoted entirely to science, in which he absorbed a wealth of knowledge, conscientiously created new knowledge and passionately passed it on to his students.

2. West Berlin

The research group of Wolfram Saenger, who was one of the early crystallographic pioneers along with Robert Huber, Johann Deisenhofer and Hartmut Michel (Munich) and Georg E. Schulz (Freiburg), moved from Max Planck in Göttingen to the Free University of Berlin in 1982. Rolf played a key role in the relocation and laboratory construction activities as well as in setting up the IT infrastructure. From thereon he worked on the X-ray structure elucidation of the plant cysteine protease calotropin D1, and this without protein-sequence information (Heinemann *et al.*, 1982). At that time no service documents were allowed to be stored in West Berlin, and Rolf and his colleagues had to operate the '3D' computer, a PS 300 from Evans & Sutherland, intuitively. Back then, the DORIS storage ring in Hamburg was (until 1993) used for high-energy physics experiments, and synchrotron radiation was produced in the so-called 'parasitic' mode. Users of synchrotron radiation were, compared with today's number of users, rare, *i.e.* they were tolerated. Data collection took days or even weeks, using X-ray film and crystals mounted in thin quartz capillaries, and 'short' breaks in the operation of the ring could last for several days. Traveling from West Berlin, surrounded by the Wall, to Hamburg by car on the famous 'transit highway' was adventurous. Many anecdotes are still told among former colleagues. Imagine having to explain to the border police of the German Democratic Republic (DDR) what goods were inside those Styrofoam boxes and why there were so many large magnetic tape rolls stashed in the trunk of the car. A somewhat witty response to the interrogations was sometimes advantageous, but above all serenity was crucial. Rolf preferred working at night, experimenting and programming in the laboratory until the early morning hours, exhaustively mastering the scientific methods and procedures of protein crystallography. He was awarded the Tiburtius Prize by the Berlin Senate for an outstanding dissertation (1987). Despite his life's commitment to science, Rolf found time to meet up with colleagues, not only to perform or discuss research, but also to philosophize about life over an appropriate beverage late into the night.

3. Hoechst AG

Most of his colleagues expected him to pursue a career in academia, but Rolf went into the pharmaceutical industry. He was given the job of starting a protein crystallography unit at Hoechst AG, Frankfurt am Main. Once the construction work started on the new research building that would also house the protein crystallography unit, Rolf temporarily went to Switzerland for a postdoc at the Biozentrum of the University of Basel. Once the construction work was finished, he returned to

Hoechst AG and started to equip the unit with computers and an X-ray source and to recruit personnel. The unit has since been involved in about 25 different pharmaceutical projects, and over the years has focused on structural biology contributions to the interdisciplinary team named New Insulins. Rolf was involved in the development of the long-acting insulin glargine (Hilgenfeld *et al.*, 2014), the active molecule, in essence a crystal contact engineering endeavor, of the blockbuster drugs Lantus and Toujeo. With annual sales of up to 6.5 billion euros, Lantus has been one of the world's top ten best-selling compounds for many years. He never lost his interest in proteases, and with the advent of AIDS, many pharmaceutical companies, including Hoechst AG, worked on the development of HIV protease inhibitors. His office was a library, full of knowledge, with shelves, tables and the whole floor filled with piles of papers. When he was traveling, he would occasionally call his closest coworker to telefax him a specific publication from one of those piles. Obviously, there was some kind of order in what looked like chaos to most people. He himself was a walking library; he had a profound knowledge of chemistry, a great overview of the literature and an amazing memory. Besides pharmaceutical targets, Hoechst AG and Goethe University permitted him to supervise students to obtain a PhD or Diploma. This 'EF-Tu' side path started promisingly with a *Nature* publication (Berchtold *et al.*, 1993) and over the years many papers on EF-Tu followed (see, for example, Vogeley *et al.*, 2001). In 1994, a comprehensive restructuring process was initiated at Hoechst AG that was later followed by mergers and finally led to the formation of Sanofi-Aventis in 2004. Rolf had already decided in 1994 that it was time to move on.

4. University of Jena and the IMB

With his curriculum vitae, *i.e.* a qualification equivalent to a habilitation, Rolf applied for a professorship in Jena (1994). Because of laboratory construction work, new coworkers for Jena initially joined him at Hoechst AG. Early in 1995, they relocated to Jena and started to build up the laboratory, computing and X-ray facilities at the IMB. Rolf was appointed full university professor of structural biochemistry and head of department at the IMB and joined a few months later. He continued to work on proteins such as blood coagulation factor XIII, HIV protease and EF-Tu. The science behind crystal growth became, in close collaboration with Christian Betzel of the University of Hamburg, an important field of research for him, which ultimately led to the development, marketing and sales of the XtalController (Meyer *et al.*, 2012) after they launched the company Xtal Concepts GmbH in Hamburg. To gain regular and fast access to X-ray synchrotron radiation, Rolf and Christian acquired a stake in the EMBL X13 PX beamline at DESY through grants from the state of Thuringia and the Federal Ministry of Education and Research (BMBF). Rolf initiated the first Heart of Europe bio-crystallography (HEC) meeting back in 1998, with the intention of starting a series of down-to-earth low-budget meetings organized by PhD students, with contributions from

PhD students, for PhD students. This year marks the 27th edition (HEC27). Following the first HEC meeting, the collaboration with the Academy of Sciences of the Czech Republic was intensified: together with colleagues, *i.e.* friends, from Spain and Czechia, he initiated and co-organized many FEBS, and later FEBS-Instruct, hands-on advanced crystallization courses (Havlickova *et al.*, 2024). For his activities and commitment, Rolf was awarded a visiting professorship in biophysics (2003), followed by a *doctor honoris causa* (2009), from the University of South Bohemia in Budweis. The joint EU-wide research initiative on HIV PR inhibitors (Fifth Framework Programme) was the first in a series of projects funded by the European Commission in which Rolf was involved. The National Contact Point European Research Counsel (NCP-ERC) proposed him as scientific director of the ESRF in Grenoble, but ultimately Rolf declined because he was not content to pause or slow down his own research at the IBM for a five-year period. From 2001 to 2005 he was elected Chairman of the European Structural Biology Forum (ESBF). Rolf was a gifted conference organizer, with a fine eye for detail and care. Looking back at the extraordinary ICCBM-9 conference in Jena in 2002, there has not been a larger conference with parallel sessions on crystallogenesis since (see Chernov & DeLucas, 2002). During this conference, the International Organization for Biological Crystallization (IOBCr) was founded, with him as its first president. Research on proteases of small RNA viruses increasingly moved into the foreground, including those of coronaviruses. The Scientific Advisory Board of the IMB suggested that he narrow his research focus and give up coronaviruses, because back then it was considered to be niche research. Then, a wind of change, aging instead of structural biology, struck the IMB and Rolf decided that it was again time to move on.

In the nineteenth century, Jena's bourgeoisie included many professors and merchants. They had a major influence on daily life, urban development and local politics. These included the Hilgenfeld family, for example theology professor Adolf Hilgenfeld (1823–1907), who was made an honorary citizen in

1901. The city council also named a street after the family name.

5. University of Lübeck

Rolf applied for and became full professor of biochemistry and Director of the Institute of Biochemistry at the University of Lübeck (2003–2020). With the *Science* publication on the X-ray structure of inhibited SARS-CoV-1 main protease (M^{Pro}; CL3 pro; Anand *et al.*, 2003) he experienced a strong debut, and events came thick and fast. The publication appeared amidst the SARS outbreak in 2003, and Rolf was one of the intrepid German scientists who volunteered to travel to China to support research there. This also meant that he was then confined to a university campus for several weeks, a measure to contain the SARS-CoV-1 epidemic. Funding but also traveling increased, the research group grew, laboratory space became scarce and more publications on viral proteases followed, with a strong focus on inhibitor design. Rolf was awarded a Visiting Fellowship from the Japan Society for the Promotion of Science (JSPS). He was mentioned in daily newspapers and seen on television and in governmental committees. Over the years, Rolf made roughly 400 national and international media appearances and contributions, from newspaper articles to radio programs and television appearances. Unusually – and there are only a few examples, such as for hemoglobin, the DNA double helix and insulin – one of his structures formed the basis for the bronze sculpture *SARS Inhibited* (by Mara G. Haseltine) that has been on display at the Biopolis in Singapore since 2006 (Fig. 1). Rolf committed himself to organizing small workshops/conferences, with the working title 'emerging viruses', on the African continent together with African scientists. He considered it very important to support research into viruses on the African continent in this way. Two Visiting Professorships, one at the Beijing Genomics Institute (2007) and one at the Shanghai Institute of Materia Medica for high-ranking foreign researchers (2010–2012), and the Ge Hong Medal of the

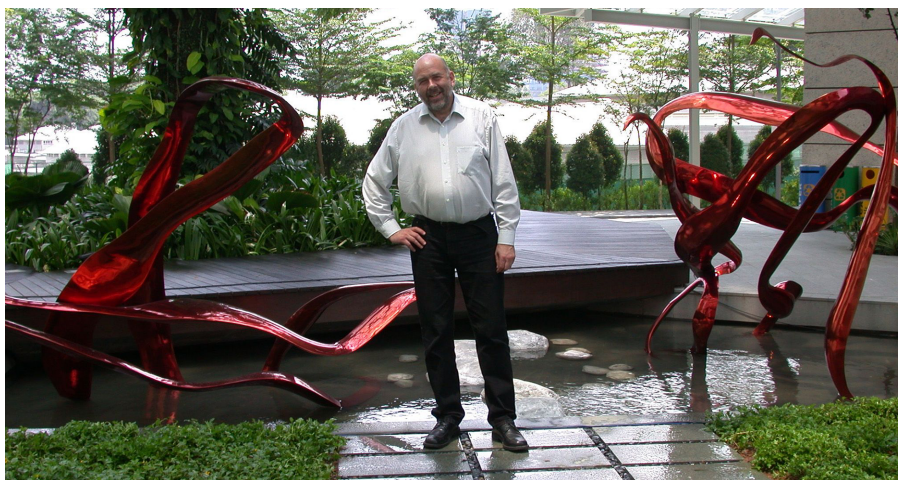


Figure 1
Rolf at the bronze sculpture *SARS Inhibited* (by Mara G. Haseltine), Biopolis, Singapore.



Figure 2

Rolf at the yellow-colored banners and T-shirts protest parade, fighting with the students against the dissolution of the University of Lübeck (2010). Photograph: Angelika von Keiser.

Institute of Virology in Wuhan (2015), were awarded to him. Unfortunately, he lost the sight in one eye during one of his trips abroad, which eventually made future travels abroad particularly difficult. Like his debut, his time at the Institute ended with a leading-edge *Science* publication on α -ketoamide-inhibited SARS-CoV-2 protease (Zhang *et al.*, 2020). Merely one in 4000 publications reach the threshold of being cited more than 1000 times; the two *Science* publications on SARS-CoV-1 and SARS-CoV-2 are among these, making him one of the world most influential researchers in his field.

Personally, he loved traveling by train, especially on steam-powered trains. No matter which continent he traveled to, he took the opportunity in his free time to travel on historic or narrow-gauge railroad lines and to visit railroad museums. Besides trains, he was a big fan and friend of the hard-rock band Steppenwolf and whenever possible attended their gigs as a backstage special guest.

And then there was the fight, together with all of the students at the university, against the dissolution of the University of Lübeck (2010). In protest, he moved his biochemistry lectures to an open-air forest stage in the neighboring federal state, organized a private train to transport all of the students to the yellow-colored banners and T-shirts protest parade in the state capital (Fig. 2) and was willing to personally pay for Lübeck's city signs to include the words 'University City' and read 'Hanseatic City – Lübeck – University City'.

From 2020 onwards and with support from the Possehl Foundation and the federal state's Structure and Excellence

budget, he was able, not yet ready for retirement, to actively continue to work as a senior professor and head of a small independent research unit at the University of Lübeck. For his life's work he was bestowed the prestigious Carl-Hermann-Medal of the German Crystallographic Society (2023). During the interview in preparation for the Laudation, Rolf spontaneously acknowledged that he stood on the shoulders of competent coworkers and collaborators. Rolf's activities and commitment to technology transfer was honored with the Thomas-Fredenhagen-Prize of the Lübeck Merchants' Association (2025).

In retrospect, protease research and drug development have dominated his entire scientific career. His interdisciplinary approach was the magic ingredient, and his legacy will have a lasting impact on the field of emerging virus research. Rolf will be greatly missed by many and leaves behind a daughter and two grandchildren.

Acknowledgements

The author, a long-term coworker and deputy to Rolf, gratefully acknowledges the contributions from Harald Berchtold (Rolf's first PhD student; formerly Hoechst AG/Sanofi; currently at Goethe University, Frankfurt am Main) and Christian Betzel (University of Hamburg) and thanks all friends, students, colleagues and collaborators worldwide for expressing their condolences to his family, coworkers and students. Disclaimer: this article is written by the author to the best of his knowledge and belief.

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