Stefan Jentsch (1955-2016) Obituary

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Stefan Jentsch
(1955-2016)

Stefan Jentsch, whose unusual creativity and trailblazing work changed forever the fields of ubiquitin biology, DNA repair, splicing, and autophagy, sadly passed away in Munich on October 29 after a short and severe illness.

Stefan was born in Berlin on May 29th 1955. Following his school and university years, Stefan also embarked on his graduate thesis in his still divided hometown and joined Thomas Trautner's group at the Max Planck Institute of Molecular Genetics. His dissertation work on DNA modifications by methyltransferases, completed in 1983, already focused on one of his life-long scientific passions, the intricate crosstalk between DNA and proteins.

On the hunt for the "gold mines of cell biology", as he would call it, the freshly minted PhD moved to Boston, where he joined Alex Varshavsky's lab at the Massachusetts Institute of Technology. In the exciting years to follow, Stefan and his colleagues identified key players of the ubiquitin pathway and thus laid the foundation for our current understanding of how this essential modification is being implemented in cells. Bucking the trend in a genetics laboratory, Stefan chose a biochemical approach to purify enzymes of the ubiquitin cascade, and a few 150-liter fermenters later he managed to track down the first E2 ubiquitin-conjugating enzyme. As this was decades before the emergence of streamlined protein identification by mass spectrometry, Stefan subjected the key band of his purification gel to good old Edman sequencing, and right after obtaining his coveted result, he raced to call his postdoc advisor Varshavsky. Only then did he realize that it was four o'clock in the morning… Stefan's excitement was justified, as the first E2 enzyme turned out to be RAD6, which immediately linked the DNA repair and ubiquitin fields.

Already at the forefront of a budding field, Stefan moved back to Germany, where the Max Planck Society had convinced the rising star to accept a group leader position in their Institute of Developmental Biology in Tübingen. There, Stefan set out to use yeast genetics to discover new E2 enzymes and cellular functions for the ubiquitin pathway.

One of these projects led to the realization that unfolded proteins of the endoplasmic reticulum are returned to the cytoplasm for ubiquitylation and degradation, a pathway that has become known as ER-associated degradation or ERAD. ERAD protects cells from the accumulation of unfolded secretory or membrane proteins, and interference with this process likely contributes to the therapeutic benefits of the proteasome inhibitors that have revolutionized the outlook for myeloma and leukemia patients. For this fundamental work, Stefan soon received the Gottfried Wilhelm Leibniz Prize, the highest recognition awarded by the German Science Foundation.

Moving up through the ranks of academia, Stefan left Tübingen for Heidelberg, where he became a professor at the Center for Molecular Biology. One of his hallmark contributions of this time was the insight that ubiquitin chain formation can occur in distinct initiation and elongation steps, with the latter being catalyzed by an enzyme they coined E4. His findings did not remain unnoticed, and in 1998, Stefan moved back to the Max Planck Society, this time joining the Institute of Biochemistry in Martinsried near Munich as one of its Directors. He spent the longest time of his career there and left a strong mark at this institute; indeed, his taste for classic Bauhaus architecture and Le Corbusier and Breuer furniture is on display for everyone walking through the halls of his former workplace. In Martinsried, Stefan continued to recruit the most talented students and postdocs, but now he was also able to support young group leaders, giving them a head start into the German academic system. The atmosphere in his lab was truly unique, and many long lasting friendships have their roots in these formative years of being a student in Stefan's group. To many of us, one of our most cherished friendships was that with Stefan.

During the Martinsried years, Stefan's lab made several seminal discoveries. To name but a few, they revealed proteasomal cleavage as a mechanism to activate, rather than inhibit, membrane-bound transcription factors. This work led them to discover that p97/CDC48, a protein mutated in neurodegenerative diseases, acts as a "segregase" that takes apart protein complexes in a ubiquitin-dependent manner. They found roles for ubiquitin-like proteins, including NEDD8, which they showed to modify and regulate the large family of CULLIN-RING ligases, or HUB1, which controls alternative splicing without being attached to target proteins. Recently, they had identified receptors for ubiquitin-dependent autophagy in yeast, a pathway that had been well studied in higher

eukaryotes but had evaded recognition in yeast, and they isolated the essential players of a DNA repair pathway that detects covalent adducts between DNA and proteins.

One of Stefan's major findings in Martinsried, acknowledged with a Louis-Jeantet Prize, led him back to his scientific roots. While searching for proteins decorated with the ubiquitin cousin SUMO, Stefan and his team circled in on the DNA polymerase processivity factor PCNA. During their analysis of cells exposed to DNA damage, they noticed that some modified species of PCNA were not lost upon mutation of the SUMOylation enzymes. Stefan immediately suspected that the recalcitrant gel bands were ubiquitylated forms of PCNA, ultimately allowing his lab to identify PCNA as the critical substrate of the same E2 enzyme RAD6 that he had discovered many years before. The finding of PCNA ubiquitylation and its roles in the DNA transactions that guide repair or recombination is one of those landmark discoveries that fundamentally changed a whole scientific field. Based on the work of Stefan and others, PCNA ubiquitylation is now known to endow cells with the ability to switch DNA polymerases at distinct stages of repair, a feature that is critical for successful elimination of mutagenic DNA lesions. SUMOylation of PCNA turned out to be important in its own right, as it coordinates important events in DNA replication.

Throughout his career, Stefan was an incredibly creative scientist who always had the "big picture" in mind. He never compromised on the quality of his science and continually thought in terms of the complete stories he wanted to tell. He could mull over the perfect title for papers and taught his students to write abstracts that read like detective stories, and so his manuscripts are gems in how science can be described. The same was true for his presentations, which had Stefan's telltale style, a product of endless time spent drawing and revising models. It is no surprise that one can see many signs of Stefan in the papers and presentations of his students, postdocs, or group leaders. One of the last examples of his unique ability to distill perplexing results into coherent models was his "SUMO spray" idea. It had frustrated many in the field that mutation of lysine residues modified with SUMO could result in weak phenotypes. Armed with quantitative mass spectrometry data, Stefan proposed that this might be due to multiple modification events that occur in parallel on many subunits of protein complexes and that substitute for each other, a "SUMO Velcro" holding together large protein assemblies as those that drive DNA repair.

A scientist and world citizen in the Humboldtian sense, Stefan liked to explore not only in the lab but also through his travels. Often joined by his brother Thomas, Stefan ventured out to destinations off the beaten path, including many African countries and – as he would describe it with his unique sense of irony and humor - his “axis of evil” North Korea, Pakistan, and Iran. Stefan carefully prepared for these trips and exchanged literature with local archeological experts. After he had returned, he loved to share his experiences and provided captivating accounts of his adventures to anyone fortunate enough to engage him in a conversation about Africa. An avid collector of African artifacts and with a keen interest in archeology and photography, Stefan would often take the opportunity of scientific meetings to introduce his students to the art and culture he loved. In fact, it had become a highlight of ubiquitin meetings to be out with Stefan searching for churches, museums, and, of course, authentic bars. Those cultural excursions turned into a cherished opportunity to learn about places and people, but also to catch up with old friends from the Jentsch lab days.

Despite his many fundamental and trailblazing discoveries, Stefan had an unpretentious and humble personality. One of us vividly remembers the day of his interview for a graduate student position in Stefan’s lab, when he expected an awe-inspiring German professor clad in suit and tie, but met a gentle person wearing his characteristic chucks, black jeans and shirt, holding up his avant-garde black and white coffee mug, and welcoming the nervous undergrad with “Hi there, I am Stefan.” As one friend described him, Stefan has been a true scientist, and never was a politician. He deeply cared about his science, but in the same way looked out for his mentees, turning them into independent thinkers and helping them to start their own careers and to succeed in life. Stefan was a wonderful and inspiring mentor, and to many, he became a true friend. Stefan left us much too early, and his illness struck when he was in the prime of his scientific work. The empty footsteps that are left behind by those chucks, in science and life, are impossible to be filled. Stefan will be missed incredibly.

Thomas Sommer, Thorsten Hoppe, and Michael Rape

Stefan Jentsch