Developmental Cell

CellPress

Obituary

Angelika Amon

Angelika Amon: Cell Division Supernova

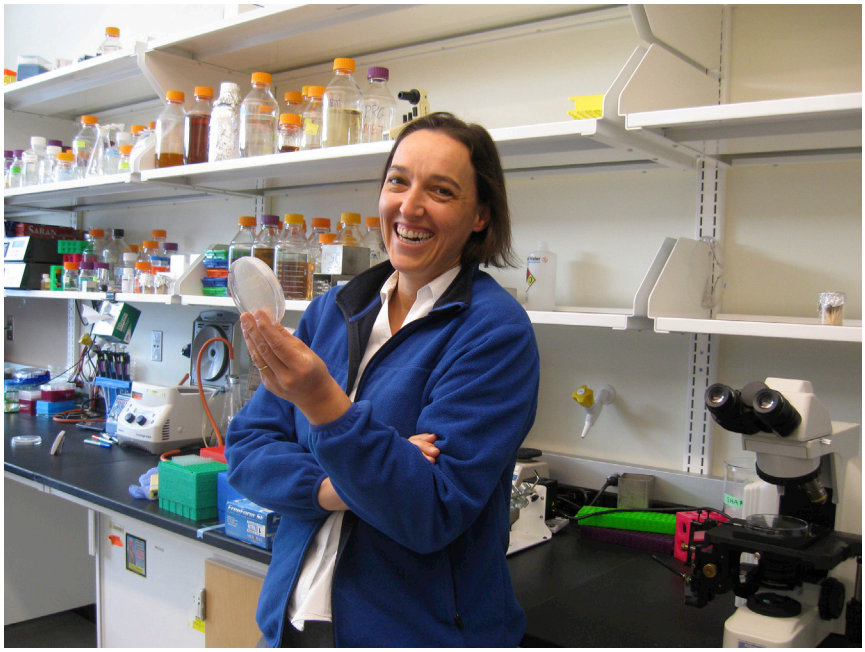
In 2015, Angelika Amon presented a seminar as part of the prestigious Harvey Society lecture series (https://harveysociety.org/videos/video.php?series=110&lecture=4), describing the breakthrough that cemented her iconic status in the cell cycle field. Together with her postdoctoral fellow Rosella Visintin, Angelika had shown that exit from mitosis and return to G1 was mediated by the regulation of the phosphatase Cdc14, which antagonizes cyclin-dependent kinase (CDK) activity and resets CDK-based marks when it is released from inhibitory tethering to a protein partner in the nucleolus. In this lecture, she explained the results of two seminal papers (Visintin et al., 1998, 1999) concisely and brilliantly: *they reduced the abstract idea of mitotic exit to a simple problem of regulating one protein-protein interaction*. Much of the "mitotic exit network" (MEN) regulation that her lab led the way in defining, based on these initial inroads, would subsequently be found to be conserved in the Hippo pathway, which controls tissue growth and size control in animals. This set of findings, and her description of them, encapsulate Angelika's science. Over her far too short 23-year career as an independent PI, she tackled complex but fundamental questions with rigor and enthusiasm, carefully unearthing clear principles that became foundations for emergent fields. Her ability to derive and communicate clarity from complex biological systems was unparalleled, and her loss will be felt in many facets of biological research.

The Birth of a Star

Angelika Amon was born and raised in Vienna, Austria where she was the eldest of four siblings. Angelika's fascination with biology was sparked at an early age, initially fueled by her love of nature and animals. In middle school, learning about the Austrian geneticist Gregor Mendel and watching the waltz of chromosomes in a movie of a dividing plant cell solidified her pursuit of a career in science. "They were amazing black-and-white movies from the sixties, long before fluorescence microscopy and the fancy techniques we use today. Plant cells have these large chromosomes, and I just loved seeing the cells divide" she recalled (Vilcek and Nair, 2019). We witnessed Angelika share this story on multiple occasions and her sense of awe never diminished.

After completing her undergraduate degree in biology at the University of Vienna, Angelika started her doctoral studies at the Institute of Molecular Pathology. At IMP she joined Kim Nasmyth's laboratory, where she made fundamental discoveries in the cell cycle, earning her an early reputation in the field. As a graduate student, Angelika studied the regulation of cyclins, a family of proteins that control cell cycle progression by activating cyclin-dependent kinases. In landmark papers (Amon et al., 1993, 1994), Angelika revealed an intricate interplay between different groups of cyclins, with G2 cyclins not only activating their own expression but also playing a crucial role in repressing G1 cyclins. She further found that cyclins must be degraded before cells make the transition from mitosis to G1, and importantly, the destruction of these mitotic cyclins continues throughout the G1 phase and ceases as cells enter S phase, when DNA is replicated. Importantly, Angelika's studies established the logic of the cell cycle, explaining how the previous phase sets the stage for the next one.

In meetings with her trainees, Angelika would at times joke about how well her papers from graduate school had withstood the test of time. This was not meant to be boastful, but rather to emphasize her philosophy that it is important to be rigorous, self-critical, and to make the extra effort to "get things right" rather than "get there fast." Angelika advocated for strategies to seek clear "black & white" results, which prevent wasted time in analyzing uninterpretable data from poorly designed experiments. Clarity, she believed, was the goal, independent of whether the outcome would support or refute a favored hypothesis. Throughout her career, she took pride in being agnostic to results and letting the data direct her path to discovery.



Angelika Amon

After earning her doctorate degree, Angelika moved across the Atlantic to start her postdoc with Ruth Lehmann at the Whitehead Institute in MIT. Little did she know at the time that MIT would become her permanent scientific home. In Ruth's lab, Angelika set out to study the germplasm in fruit flies with a particular emphasis on post-transcriptional gene regulation. However, she soon realized that the work was not for her. In her words, "Ruth was an amazing role model and mentor, and I learned so much from her. But I soon found out that I didn't like working with flies. Back then, once you had worked with yeast, you were spoiled; the only rate-limiting step in working with yeast was your brain" (Vilcek and Nair, 2019).

Amon Lab Research: Illuminating Cell Division and Its Consequences

Angelika was not even 30 years old when she was recruited to start her own lab as a fellow at the Whitehead Institute at MIT, diving back into understanding how budding yeast cells progress through the cell cycle and partition their chromosomes. Angelika's team at the Whitehead included two other young scientists, Rosella Visintin and Susanne Prinz, who became integral parts of her scientific and personal life. Based on their series of remarkable discoveries together, within a few years Angelika became a tenure-track faculty member in the MIT Department of Biology, rising quickly through the academic ranks to become one of the most esteemed of an illustrious group of professors. She was an investigator of the Howard Hughes Medical Institute since 2000 and the 2003 recipient of the NSF Alan T. Waterman award, the highest American honor for a scientist under the age of 40. Her discoveries continued to garner prestigious accolades throughout her career, including the Vilcek Prize in Biomedical Science for extraordinary immigrant biologists and the Breakthrough Prize in Life Sciences in 2019.

Research in the Amon lab included three main directions: the mechanisms of mitotic exit, the regulation of meiosis, and the core cellular effects of aneuploidy. Her lab uncovered key principles governing the cell cycle and was first to demonstrate a direct link between completion of chromosome segregation and initiation of mitotic exit. Beyond illuminating the mechanisms that reset cells for the next stage of the cell cycle, Angelika's research also defined core mechanisms that are broadly applicable to many signaling pathways in diverse cell types and organisms, including showing how spatial cues can be converted into a temporal, decision-making signal and how signaling information can be conveyed across different cellular compartments. Angelika had remarkable intuition, making her an excellent detective of biology. She knew exactly how to listen to and learn from the cells, and how to extract coherent information from seemingly disconnected clues, to identify the general patterns and principles that they pointed to. The unusual beauty of her papers is a testament to these qualities, the clarity of her logic, and her extraordinary communication skills.

Although Angelika remained interested in explaining the core mitotic principles throughout her career, she also saw important mysteries in the control of meiosis, the cell division responsible for gamete production. She tackled the mysteries of meiosis with similar approaches as she had applied so elegantly to her studies of mitosis. Her lab made key discoveries in this new area, including the regulation of meiotic cohesin and cyclin activity. The biggest impact of her work on meiosis, however, may have been the development of invaluable tools. These included synchronization protocols and meiotic conditional alleles, which enabled highly controlled molecular studies of meiosis rivaling what was possible in mitosis. These approaches accelerated the field, catalyzing waves of discovery from dozens of labs and, together with her charismatic personality, made her a central figure in the tight-knit community of meiotic researchers.

In studying mitotic and meiotic cell division, Angelika became accustomed to the explanation that the fidelity of these processes was critical to prevent aneuploidy, or chromosomal imbalance. This piqued her interest from an early stage, as she noted that everyone accepted that aneuploidy was catastrophic, but no one really understood why. She decided to try to define the molecular consequences of aneuploidy, first as a side project that she tinkered with whenever she could find a few hours to dedicate to benchwork, and later as a major focus of her group. Angelika's work in this area built up and defined a field, starting from an array of systematically constructed disome strains in budding yeast, and extending to aneuploidy studies in mice and human cells. These studies led to many discoveries, including a common signature of cellular stress that results from aneuploidy, regardless of the specific chromosomes that are imbalanced. Angelika had recently expanded her studies of aneuploidy further, focusing on cases in which chromosomal imbalances offered cells an advantage, an area with important implications for understanding cancer and its treatment.

While the core research in her lab focused on these three aspects of cell division, Angelika always devoted a portion of her lab to new topics. Each of these topics were hard problems, and more than enough to seed labs of their own. And yet, she was able to make profound contributions to fields ranging from transcription to aging to cell size control to mitochondrial biology. Angelika's instinct was always to follow interesting science wherever the big questions were. As she explained it, "I like a good mystery" (Amon, 2013).

A Mentor Who Lit the Way with Energy, Structure, and Humor

Angelika's remarkable scientific impact was made possible by her singularly incisive mind, but also her approach to mentorship. She enabled the careers of dozens of young scientists, including ours, by providing a training atmosphere that was exciting, well-structured, and supportive. The feature of Angelika's style that is most memorable, and the one that drew many to the lab, was her exuberance. Her entry into a room was often preceded by the sound of her voice remarking enthusiastically about a new result or inquiring about yesterday's experiment. Her genuine curiosity, whether asking an undergraduate researcher about their PCRs at the bench or a Nobel laureate about their research in a packed lecture hall, was invigorating and infectious. This, coupled with her ability to bond with everyone she met, made Angelika magnetic. Sometimes this bonding was through scientific

discussion, but often it was through conversations about family, food, celebrity gossip, or sports. Each lab member had a connection to Angelika, something that they looked forward to hearing her brutally honest—often hilarious—opinions about. In turn, she made everyone in the lab feel that they were supposed to be there, and the Amon lab a fun place to do science. Even if your current project was in a rut, this atmosphere and Angelika's excitement about the next potential result kept you engaged. "Just do the experiment, okayyy?!" she loved to say when someone was feeling discouraged, perhaps agonizing over all possible caveats of a new approach, and the infectious laugh that followed more than counterbalanced whatever concerns remained. Angelika was proud of this ability, mentioning wryly after an appropriately effusive introduction to a seminar that she gave in October that her one true talent was actually being the world's best cheerleader. Her enthusiasm was indeed remarkably motivating, especially when paired with her refrain "You're a superstar!" when a particularly cool result came in.

Amon lab group meetings reflected Angelika's enthusiasm and the camaraderie that she fostered, with lively discussions that sometimes extended for hours after the official meeting was over. Each lab member felt an obligation to others, and to upholding the high standard that Angelika had established. Angelika made a place for everyone to feel invested in her lab because she believed deeply that science has a place for anyone who cares to be a part of it, regardless of how they fit the traditional mold of what a scientist should be. In support of this idea, she often exclaimed that if she could do it, anyone could, because she wasn't very smart. A ridiculous statement, of course, but disarming and inspiring to many a young and insecure graduate student.

That Angelika shared her unfiltered views about everything gave young scientists a valuable glimpse into the sometimes challenging aspects of a scientific career—including publication, competition, and sexism—that could otherwise only be gained through their own trials and missteps. Much as she demystified complex scientific topics with her incisive mind, she also demystified the process and the politics of the scientific endeavor with honest and open communication. And beyond just telling us how a life in science worked, Angelika invited lab members into her family. Through regular potluck celebrations at her home that sometimes involved karaoke, and annual lab camping trips that sometimes involved cocktails, we all had the chance to get to know and admire her beloved husband Johannes and daughters Theresa and Clara. Angelika believed strongly in the importance of family. Her perspective, which she emphatically conveyed to both male and female trainees, was that the exceptional flexibility of scheduling in academic research enables family life by allowing parents to modify their schedules to accommodate childcare responsibilities.

If Angelika's exuberance was the motor of her lab, her high degree of organization formed its framework. She believed that logical, well-documented infrastructure was key to the lab's success and imparted this belief to each new lab member. Strains and plasmids, for example, were archived meticulously, allowing a new trainee to do careful work from the start, learning from former lab members they may have never even met. Experimental strategies were designed with high standards in mind, involving testing by complementary approaches to avoid being misled by a single result. Each meeting with Angelika resulted in a written summary of experimental priorities, which she photocopied and kept in a dedicated folder, so that the next meeting could pick up exactly where the last left off. This, along with her razor-sharp mind, allowed Angelika to successfully manage more than 20 disparate projects at once. Each project began with a clear plan on day 1. When the first key result came in, she would say "Let's write a paper!" and hand draw a set of potential figures, to help illuminate the missing pieces. She encouraged her trainees to take the driver's seat in their projects, to anticipate holes and make a plan to address them, and most importantly, to learn to articulate ideas in a clear, concise, and logical framework. She believed that curiosity-driven, basic science is at the root of important discovery, but a larger context must always be kept in mind. As she liked to say, "if you can't explain your project to your grandma, either you don't understand it or it's not important."

The depth of Angelika's commitment to trainees was only made clearer by her devastating diagnosis of stage III ovarian cancer in 2018. She continued to teach and mentor with her characteristic intensity and enthusiasm, even if it meant teaching yeast genetics at Cold Spring Harbor between rounds of chemotherapy or holding lab meetings from a hospital bed.

Angelika's support for her team members has already led to many impactful careers, including 22 academic PIs and over a dozen leaders in industry. The loyalty that her dedication engendered in former trainees is expressed in the 57 pages of grateful and humorous tributes that make up the book given to Angelika for her 50th birthday in 2017, also commemorating the 20th anniversary of her lab. Appropriately, this milestone included multiple celebrations, because one cannot properly describe Angelika without mentioning that she was fun, and outrageously funny. She enjoyed parties, dancing, science, and life, all with confidence and a wide smile. She made others laugh as hard as she made them think, sometimes with her comically loud "whisper" from the back of a packed seminar room and other times with a well-crafted joke. Angelika ended her masterful formal seminar for the Harvey Lecture series, for example, by mentioning that the purple ball gown she was wearing was borrowed from her friend, Vicki Lundblad. As she flipped to the last slide, she revealed a US Weekly-style "Who wore it best?" mock-up with Vicki's votes at 99% and Angelika's at 1%. "That 1% is my husband, I love him very much," she quipped, to roaring laughter.

Commemorating Angelika Amon is a particular challenge because her leadership, insight, mentorship, and even her sense of humor meant so much to so many people. She was a three-dimensional person who shared all of her dimensions unabashedly. If you met her once, you certainly remember it. Those of us who were fortunate enough to train with her now have the heavy honor of carrying this immense legacy forward,

to share Angelika's joyous and brilliant vision of science and life with future generations.

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