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IN MEMORIAM

Angelika Amon (1967–2020): Breakthrough scientist, extraordinary mentor, and loyal friend

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When asked to write a tribute to our mentor and friend, Angelika, 20 years of memorable, funny, and exciting anecdotes came to mind, some of which we recount below.

Angelika Amon was born in Vienna, Austria on January 10, 1967, and was attracted to science for as long as she could remember. Passionate, exuberant, and incorrigibly curious, it is easy to imagine young Angelika bursting with "why" questions. Brought up in a family fostering her love for animals and nature, she aspired to be a zoologist at first, but ended up devoting her life to discovering the fundamental concepts of biology. In high school, a black and white movie from the fifties showing chromosomes splitting apart enchanted Angelika and drew her to molecular biology and genetics. "The way nature works is unmatched and cells work perfectly," she used to say with contagious enthusiasm. Determined to pursue her dream, for her undergraduate thesis she marched—no doubt about that—into Kim Nasmyth's office at the Institute of Molecular Pathology in Vienna. At that time, Kim was new to the city and country, and, by Angelika's account, it was her knowledge of the Austrian waltz and German language that won her a place in his laboratory. She remained there for her PhD, graduating in 1993. From the early days in Kim's laboratory, Angelika distinguished herself as one of the brightest minds of the cell cycle field. Using the elegant genetics of budding yeast, Angelika made key contributions to our understanding of cell cycle control. She showed that cyclins are confined within precise cell cycle windows by a combination of transcriptional and posttranslational regulatory mechanisms. On the one hand, cyclins self-regulate at the transcriptional level via sophisticated feedback loops; on the other, they undergo ubiquitin-mediated degradation to allow exit from mitosis. She went on to show how this degradation is turned off to allow entry into the next cell cycle (1).

Following her stellar PhD, and fascinated by the elegant genetics of the fruit fly, *Drosophila melanogaster*, Angelika landed in Cambridge, MA, where she began a postdoctoral position in Ruth Lehmann's laboratory, marking what was to become a permanent move to the Massachusetts Institute of Technology (MIT). However, soon after, Ruth relocated to New York, and, realizing that *Drosophila* did not suit her, Angelika chose not to follow. Instead, in 1996, recognizing her potential, the Whitehead Institute appointed Angelika as a Fellow. This launched an independent career that, from the very beginning, had a major impact on science and all that were lucky enough to interact with her. In 1999 she accepted a faculty position in the MIT Department of Biology and Center for Cancer Research, which later became the Koch Institute. A Howard Hughes Investigator since 2000, she was also the Kathleen and Curtis Marble Professor in Cancer Research.

Angelika Amon, Whitehead Institute, 1997. Photo taken by Susanne Prinz.

Passionate about puzzles and brain teasers, when starting her laboratory, she returned to yeast, recognizing in this organism the perfect toy to unravel the mysteries of life. "What's so incredible about yeast is that the rate-limiting step is your brain. You can do anything you can think of very cleanly and precisely," she used to say, and there is no doubt that she fully exploited this power. Initially, Angelika turned her attention to a question that had captivated her since graduate school: How is the cell cycle reset at the end of mitosis? With the field focused on inactivation of kinase activity, Angelika had the key insight

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that a phosphatase could be important, leading to the identification of the budding yeast Cdc14 phosphatase as a central player in mitotic exit (2). Together with her first postdoc (R. Visintin), Angelika next demonstrated that relocation of Cdc14 out of the nucleolus is under control of a signaling cascade called the mitotic exit network (MEN) and is the critical step in mitotic exit. MEN is a GTPase kinase cascade related to the Hippo pathway that controls organ size in metazoans and remained an important focus of Angelika's laboratory for the next two decades. She made numerous fundamental discoveries that provided insight into how signaling networks operate, including understanding how spatial cues elicit cellular decisions, how scaffolds facilitate signaling assemblies, and how signals are translocated across cellular compartments.

Every five years, Angelika would start something new. One of her first new directions was into meiosis, inspired by her final year at the Institute of Botany in Vienna and friendship with Franz Klein and Susanne Prinz, who later became her second postdoc. Angelika's intuition was to look at meiosis with the eyes and the tools of a cell cycle scientist (3). Her approaches and findings brought a breath of fresh air into a field dominated by homologous recombination studies and accelerated the field enormously. Frustrated by the lack of sophisticated genetic tools in yeast for studying meiosis compared with mitosis, she devised a suite of clever approaches and rapidly and generously shared them with the community, revolutionizing the field. Her scientific accomplishments on meiosis were diverse, ranging from understanding how cell cycle and chromosome segregation pathways are rewired, through demonstrating translational control by an amyloid and revealing the rejuvenating, anti-aging ability of gametogenesis.

Angelika's work on mitosis and meiosis revealed potential reasons for unequal distribution of chromosomes between daughter cells during cell division. This condition, known as aneuploidy, is characteristic of cancer cells and is one of the leading causes of miscarriages and developmental defects when occurring in germline cells. It was clear that aneuploidy is detrimental at organismal levels, but the effect on individual cells was unknown. This mystery perplexed Angelika such that she set out to purposefully generate yeast, mouse, and human cells with defined aneuploidies. In landmark studies, her group found that, rather than conferring a proliferative advantage, aneuploidy generally decreases fitness (4). In subsequent studies, they showed that altered gene dosage in aneuploid cells profoundly impacts protein composition. Misfolding of proteins that lack their binding partners aggregate, which allows for dosage compensation but also leads to proteotoxic stress. Therefore, aneuploidy impacts protein quality control pathways and alters cellular metabolism, resulting in a higher energy requirement. These common properties of aneuploid cells prompted Angelika to ask whether they could be exploited for selective elimination. Indeed, her group showed that aneuploid cells are sensitive to conditions that interfere with protein translation, folding, and degradation and identified energy and proteotoxic stress-inducing compounds that selectively inhibit proliferation of aneuploid cells. Remarkably, signatures of aneuploid cells may also make them a target for the immune system. By transplanting aneuploid fetal hematopoietic stem cells into a wild-type mouse, Angelika's group found evidence that aneuploid hematopoietic stem cells were selected against by the immune system. Collectively, these studies presented a paradox: If aneuploidy causes a decrease in fitness, why are cancer cells so frequently aneuploid? Angelika's group found that aneuploid yeast cells are prone to genetic instability, showing increased chromosome loss and impaired DNA damage repair. Furthermore, the same defined aneuploidies show variability in cell cycle progression and response to environmental perturbations, findings that were recapitulated in trisomic mice. Taken together, these findings indicate that cells encounter selective pressure to adapt for aneuploidy tolerance, increasing variability and providing the opportunity for advantageous traits to evolve. Angelika proposed that it is this flexibility of aneuploid cells that provides the opportunity for rare variants to emerge, offering a survival advantage that allows the aggressive proliferation of cancers.

Mitosis, meiosis, and aneuploidy can be considered Angelika's signature fields of interest, but she never missed the chance to approach a new exciting biological question. Her broad scientific influence is exemplified by the range of fields where she made a substantial impact. In all of her endeavors, she designed clean, unambiguous experiments, applying the logical thinking she had honed as a yeast geneticist to tackle the most complex problems. She chose systems that were as representative of the in vivo system as possible, preferring whole organisms over cell culture. Using organoid culture systems, she demonstrated the importance of tissue architecture for accurate chromosome segregation. Her work on cell size showed, using budding yeast, that DNA content becomes limiting as the amount of cytoplasm increases, reducing proliferative potential and contributing to senescence. A recent preprint from her group reports that increased cell size is also detrimental to mouse and human haemopoietic stem cell function and, as in yeast, is associated with aging (5), another of her key interests. She also worked on mitochondria, where she identified a surveillance mechanism that monitors protein import to protect mitochondrial function. In all the fields she chose to study, her work has left a lasting legacy both through her documented work and the people from her laboratory and beyond who have been influenced by it.

Angelika's impressive scientific achievements were recognized with many awards, including the 2003 National Science Foundation Alan T. Waterman Award, the 2007 Paul Marks Prize for Cancer Research, the 2008 National Academy of Sciences (NAS) Award in Molecular Biology, the 2013 Ernst Jung Prize for Medicine, the 2015 Women in Cell Biology Senior Award, and the 2018 Vanderbilt Prize. In 2019, the Carnegie Corporation of New York included Angelika on their list of Great Immigrants. She won the 2019 Breakthrough Prize in Life Sciences and the 2019 Vilcek Prize in Biomedical Science. In 2020, she won the Human Frontier Science Program Nakasone Award and the Ernst W. Bertner Memorial Award, delivering her acceptance lecture only six days before her death. She was a member of the NAS (2010) and the American Academy of Arts and Sciences (2017).

Angelika's impact on creating an equitable scientific culture extended beyond her laboratory. She was fair, generous, and

committed to making a difference wherever she could. In recent years, she applied her understanding of the basic cellular biology of aneuploidy toward the goal of increasing "health, autonomy, and inclusion of people" with Down syndrome through her co-directorship of the Alana Down Syndrome Center. She was a strong advocate of women in science long before it became fashionable and was not afraid to speak out when she felt something was not right. She was also a vocal supporter of fundamental science; her own career is a case in point for how research on simple budding yeast is critical for informing molecular processes relevant to disease.

Angelika is world renowned for her razor-sharp mind, elegant experiments, intoxicating laugh, and sense of humor, but those who were fortunate enough to be trained by her know that she was much more than that. First and foremost, she was a devoted mother and wife: her love for her family was evident in everything she did. She cared deeply about her students and colleagues; her generosity and loyalty distinguished her. Many around her benefited immensely from Angelika's (often invisible) support and her encouragement to pursue a scientific career or to simply "keep going." She had a remarkable ability to bond with each individual and nurture diverse personalities. The environment she created was open and inclusive, making us feel part of a family, which we like to call the "Amonites." We shared so many "lightbulb" moments with Angelika. Rushing into her office with a new result and watching her come up with the next experiment barely before we had connected the dots was electrifying. Both of us were lucky enough to observe her still working at the bench, which was mesmerizing and incredibly fun. She would run the craziest time courses to the rhythm of the Rocky Horror Picture Show or the Rolling Stones, and we would karaoke and dance. "Persistence is everything" was her motto and she truly lived up to it.

Group meetings were accompanied by the hiss of the Diet Coke can (which many attendees of scientific meetings will also remember) and obligatory apple strudels. Always looking for the decisive experiment, and impatient during circular discussions, her mantra was "just do the experiment." She delivered advice in a persuasive and direct, but always encouraging, manner. And persuasive she was for sure; the memory of all the laboratory members dressed in Elvis costumes for Halloween still brings laughter. She loved talking about politics, TV series, celebrity gossip, sports, and books and giving us all (often hilarious) relationship advice. The group camping and ski trips are legendary, and we treasure the memory of wonderful summer and holiday parties with her family. We remember fondly the bespoke goodbye presents collectively made by group members and even the "surprise" birthday cakes along with (often awkward) group singing. A fierce supporter of all her trainees, the support, mentorship, and friendship continued after leaving Angelika's laboratory. This atmosphere was evident at the 50th birthday symposium and party, a wonderful reunion of nearly all laboratory members past and present from around the globe who did not want to miss the chance to be there.

She truly loved her job and her people. In accepting the Breakthrough Prize, Angelika said, "Making a discovery is the best feeling in the world. It's like Christmas when you were five. Eureka moments are rare but when they happen, feelings are priceless. The beauty of experimental science is that these eureka moments are often shared with other scientists, and I'm privileged to have experienced this." We believe that this sentence fully captures her passion and generosity. No matter how well known she became, she preserved her sparkling enthusiasm and humbleness.

With great admiration and gratitude for the opportunities and example that Angelika gave us, we will "keep going." As we do, we'll cherish the picture of her smiling, joyful and enthusiastic like a kid in a candy store. We will remember her kissing her "magical" hands, in celebration of her perfectly executed experiments, as we continue to be inspired by her. We cannot but wonder what would have come next in her scientific life. Archeology? Fossils? Life on other planets? We don't know, but we are certain there was no limit to her creativity. We'd like to think of her somewhere surrounded by the rarest varieties of orchids, discussing crazy experiments and big theories with her heroes.

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