Angelika Amon (1967–2020)

On 29 October 2020, Massachusetts Institute of Technology (MIT) biologist Angelika Amon passed away at the age of 53 after a two-and-a-half-year battle with ovarian cancer. Cell biology lost a brilliant scientist, and the community lost a vibrant and highly original voice.

Angelika grew up in Vienna, Austria, the oldest of four children. At an early age, she was captivated by science and developed a fascination with chromosome segregation after viewing a classic cell division video. She pursued this in earnest as a graduate student with Kim Nasmyth at the Institute of Molecular Pathology in Vienna, where she made several major discoveries. These included advances on the regulation of cyclin-dependent kinase, an understanding of the transcriptional feedback circuits that control cyclin expression, and the discovery that mitotic cyclin proteolysis promotes irreversible mitotic exit. I am still struck by the elegance of these early papers, whose precision and rigor carried over into all of Angelika's later work on cell cycle, meiosis, and aneuploidy.

Angelika did a brief postdoctoral fellowship in *Drosophila* genetics with Ruth Lehmann at the Whitehead Institute at MIT before reverting to type and rekindling her passion for the yeast cell cycle. As a Whitehead Fellow, and later as a MIT faculty member, she got off to a fast start: she discovered substrate-specific activators of the E3 ubiquitin ligase that drive anaphase onset and mitotic exit (the anaphase-promoting complex). With Andrew Murray, she showed that one of these activators, Cdc20, was the target of the spindle assembly checkpoint.

Angelika's laboratory then led the way in deciphering the intricate signalling network that controls the exit from mitosis in budding yeast (the mitotic exit network or MEN pathway and the related pathway she dubbed "FEAR"). She co-identified the protein phosphatase Cdc14 as the central downstream effector of the pathway and showed that MEN signalling activates Cdc14 by liberating it from the nucleolus. She and others showed that the MEN cascade is initiated when the mitotic spindle enters the new daughter cell, bringing a centrosome-bound G protein in contact with its activator on the daughter-cell cortex. This elegantly explains how a cell can sense the position of its mitotic spindle and enforce a 'spindle position checkpoint', ensuring proper chromosome segregation. Although the MEN pathway is unique to budding yeast, this work highlighted universal themes: the centrosome's role as a signalling hub, spatial regulation of signalling molecules, and feedback mechanisms to drive irreversible cell cycle transitions.

Credit: Image courtesy of Theresa Weis

In addition to these discoveries on mitotic chromosome segregation, Angelika's group made many important contributions toward understanding how this machinery is adapted for meiotic chromosome segregation.

In recent years, Angelika focused on the consequences of aneuploidy, the presence of an abnormal number of chromosomes in a cell, which causes human genetic disease and is common in cancer. Since the dawn of the modern era of biology, it was appreciated that aneuploidy generates pathological phenotypes, and these observations became lynchpins for the chromosome theory of inheritance. Nevertheless, the cellular consequences of aneuploidy, particularly whether all aneuploidies induce a common set of physiological alterations, remained unclear.

Angelika had the insight to use yeast genetics to systematically dissect this problem. In a landmark 2007 paper, her group constructed a near-complete series of haploid yeast strains containing extra copies of individual chromosomes. Analysis of these strains showed that aneuploidy was deleterious, slowing cell proliferation due to a G1 cell cycle delay. Gene expression in aneuploid cells was mostly proportional to chromosome number, leading to gene expression imbalance, abnormal protein complex assembly, and proteotoxic stress. Her subsequent studies confirmed these findings in mammalian cells and demonstrated that extensive aneuploidy-induced expression imbalance compromises DNA replication and repair, generating additional genome instability and mutagenesis.

This clear demonstration of the deleterious impact of aneuploidy on cell growth still left the field with a paradox: why are the vast majority of rapidly dividing cancer cells aneuploid? Part of the answer is that cells can acquire aneuploidy-tolerating mutations, some of which Angelika's group identified. Additionally, aneuploidy-induced instability may drive the acquisition of other tumour-promoting mutations. Finally, as shown by Angelika and others, aneuploidy can itself promote growth and tumourigenesis in certain contexts. With much thanks to Angelika, we now think of aneuploidy as a large-effect mutation, which, although usually deleterious, can sometimes increase fitness and drive proliferation.

Angelika was highly celebrated for these seminal discoveries. She was the Kathleen and Curtis Marble Professor of Cancer Research at the Koch Institute at the Massachusetts Institute of Technology and an Investigator of the Howard Hughes Medical Institute. She received numerous awards, most recently the Breakthrough and Vilcek prizes. She was a member of the US National Academy of Sciences and a fellow of the American Academy of Arts and Sciences.

If many scientific leaders have large personalities, Angelika's was outsized squared! She was funny, boisterous, and sharp. She did not do circumlocution but went right for the point. At conferences, her incisive questions, usually fired from the back of the auditorium, could be intimidating. She was the life of any party or conference, regaling her audience with stories of all her latest passions and obsessions, be it American football, Candy Crush, People Magazine, or her 23andMe report. I vividly recall a skeet shooting outing that Angelika organised during a Federation of American Societies for Experimental Biology meeting. Scientists are generally not experienced or handy with shotguns, but Angelika was a natural talent. I cannot forget the look of predatory joy that

came with each clay pigeon Angelika blew out of the Georgia sky—the very same look she had when, as a starting Fellow, her film came off the X-Omat showing that Cdh1 triggered cyclin degradation.

Angelika had charming small vices and eccentricities. She lived on Diet Coke and lugged a couple of six packs to each scientific conference lest God forbid the hotel ran out. Before she quit, she smoked cigarettes with the same gusto that she had for everything else. As a postdoc, I indulged in many cigarettes with her sitting on the front steps of the Whitehead Institute, talking science, getting instruction on how to best organise my personal life, and watching the clouds roll over the Kendall Square cityscape.

Although far too short, Angelika Amon's life was full. Her scientific career is an inspiration for its impact and originality. She was a wonderful mentor, and many of her trainees are now leaders in their fields. She was a role model for many women in science. In addition to her professional accomplishments, she married her high school sweetheart, dearly loved her two daughters, and had a rich family life. She reminds us that professional accomplishment does not preclude personal warmth or a fulfilling private life.

My family recently got me to swear off Diet Coke, but now I think I'll go back. An occasional can will not harm me, and I am going to raise a defiant toast to Angelika. Perhaps the quiet moment will also help me better appreciate the other colleagues, students, and friends who enrich my own journey through science and through life, as Angelika did. Hopefully this small indulgence in a shared transgression will remind me to live my own life on the larger scale, with the same passion and purpose that Angelika brought to hers. ❐

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Published online: 8 January 2021
https://doi.org/10.1038/s41556-020-00612-7