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Obituary

A death in the family: Stanley J Korsmeyer (1950–2005)

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Stan Korsmeyer

The cell death research community, in particular, and science in general, lost an honored friend on March 31, as Stanley J Korsmeyer died at the age of 54 from lung cancer. Never a smoker, Stan fell victim to the rising trend of lung cancers in nonsmokers. Scientifically, Stan made important contributions to several areas in cell and developmental biology through identifying novel oncogenes from chromosomal translocations in lymphoid tumors and their analysis in transgenic mice. However, he is most remembered for his seminal work with Bcl-2 and apoptotic cell death.

Stan was born in 1950 in Beardstown, IL, into a family of German homesteaders. His father, Willard, continued the family hog farm started by his great-great grandparents and fought as an airman in World War II, imprisoned at Stalag Luft I in WWII. His mother, Carnell, is a past president of the National Pork Board and one of the founding members of the Beardstown Ladies Investment Club. Stanley Joel was their sole boy among four children. At age 14, Stan became the youngest person ever to show a Grand Champion pair of Hampshire Hogs at the Illinois State Fair, receiving the Governor's trophy. He had an early interest in veterinary medicine, but switched to pre-med on the advice of a local veterinarian. He pursued undergraduate studies at the University of Illinois at Urbana-Champaign, achieving a BS in Biology in 1972. His first exposure to research came as a James Scholar at UIUC, working with Ralph Williams and Reg Strickland on lymphocytotoxic antibodies in patients with systemic lupus erythematosis and inflammatory bowel disease. He moved upstate to the University of Illinois, Chicago for his MD studies, where he acquired an interest in hematology from Dr. Paul Heller. He completed an internship and residency program in internal medicine at the University of California Hospitals in San Francisco where he met an ICU nurse and his future wife, Susan. Stan then decided on a research fellowship at the National Cancer Institute instead of subspecialty training. He served as a clinical associate from 1979 to 1982 at the National Cancer Institute in Tom Waldmann's Metabolism Branch. This was a time of rapid discovery of immunoglobulin and T-cell receptor genes, and with the help of Phil Leder, Korsmeyer and Waldmann pioneered the analysis of receptor gene rearrangements to classify T- and B-lymphoid tumors. The influence of Bob Good, Leder and Waldmann, as scientists interested in the study of clinical 'experiments of nature', led naturally to Stan's interest in cancer-associated chromosomal translocations as signposts for new oncogenes. Leder, in particular, was working on the 8;14 translocation involved in Burkitt's lymphoma at this time. In 1982, Stan was promoted to senior investigator. While at NCI, Stan began studies to identify the genes involved in the 14;18 chromosomal translocation that is associated with follicular lymphoma. The analysis of this translocation will mark his entire scientific career in that it led to the identification and molecular cloning of Bcl-2.

In 1986, he moved to Washington University in St. Louis. At Washington University, Stan initiated studies to characterize the function of Bcl-2 and its role in lymphoma development. During this period, studies in Stan's laboratory revealed the mitochondrial localization of Bcl-2 and a role for Bcl-2 in the inhibition of programmed cell death induced by growth factor withdrawal and lymphoid survival *in vivo*. Other critical discoveries at Washington University by members of his laboratory were the identification of Bax, the first proapoptotic Bcl-2 family member, and BAD, the first BH3-only protein identified. The discovery of Bcl-2 family proteins with opposite biological activity regulated through heterodimerization was a seminal finding in the field. This 1987–1995 period represented the early stages of the Bcl-2 field and Stan's laboratory was a main force driving it forward.

In 1998, Stan was recruited to the Dana-Farber Cancer Institute in Boston, where he was named as Sidney Farber Professor of Pathology and Medicine and Director of the Program in Molecular Oncology. With a new crop of postdocs and graduate students, his productivity accelerated. Important discoveries included the direct action of mitochondrial-targeted tBID to oligomerize the multimeric BAX or BAK proapoptotic factors, and the general requirement for BAX and/or BAX as downstream effectors of BH3-only death promoters. Antiapoptotic BCL-2 and BCL-X_L proteins were shown to sequester BH3-only proteins, preventing their interactions with BAX/BAK. Discrete BH3-only peptides could be classified as activators or sensitizers of cell death, based on their affinity for BAX-like or BCL-2-like multidomain proteins. Korsmeyer's group also extended our knowledge of the cell biology of apoptosis, identifying remodeling of mitochondrial cristal junctions with the intermembrane space during apoptosis, and a regulatory role for BAX and BAK in calcium homeostasis in the endoplasmic reticulum. Perhaps most surprisingly, his laboratory discovered an important role for BAD in glycolytic control through targeting of glucokinase. Another important finding demonstrated the critical role of the third antiapoptotic family member, MCL-1, in lymphocyte development and hematopoietic stem cells. The Korsmeyer lab had also made important progress toward development of novel therapeutics targeting antiapoptotic proteins in cancer, demonstrating the efficacy of a hydrocarbon-stapled BH3 helix in animal tumor models.

In addition, Stan continued work initiated at Washington University to explore the cellular functions of other genes identified in the context of chromosomal translocations, including Hox11 genes *t(10;14)* and MLL *t(4;11)* that have provided new insights into chromatin regulators of morphogenesis and hematopoiesis.

Throughout his career, Stan's youthful appearance belied his increasing stature internationally as a leading researcher in the molecular and cellular biology of apoptosis. Stan retained his enthusiasm and, at times, his impish delight in 'pulling a fast one', as in his accidental 'discovery' of Doug Green's high school 'Hall of Fame' at the last Cold Spring Harbor Programmed Cell Death meeting.

Multiple honors and awards recognized Stan's contributions to science. He was elected to the National Academy of Sciences (USA) and Institute of Medicine, received the Bristol-Meyers Squibb Award for Distinguished Achievement in Cancer Research, the General Motors Mott Award, the Wiley Foundation Prize in Biomedical Research and the Pezcoller Foundation-AACR International Award. Stan was widely recognized as a generous and willing collaborator. Despite short-tracking his oncology training, he led the successful efforts at Washington University to establish the Siteman Cancer Center. At DFCI, he was chair of the Executive Committee on Research. In this role, he fostered efforts to bring genomic, computational and chemical resources in the Harvard system to bear on developing new treatments for cancer. Ironically, Stan would use all the resources of this program to fight his own cancer.

A cancer diagnosis is a major blow to anyone including Stan. He decided to fight his illness with a high level of endurance and positive attitude in spite of the difficult outlook. Unfortunately, the cancer had spread and was difficult to control, even with the most advanced therapeutic tools available at DFCI. Stan continued to work at the laboratory until the final days, despite not feeling well. This perseverance was a reflection of his tremendous work ethic, and at the same time his concern for the future and well-being of his postdocs, graduate students and technicians, whom he considered as his extended family. His beloved family survives Stan, including his wife of 25 years, Susan, and his sons Jason and Evan, his parents Willard and Carnell, sisters Lynn, Janet and Karen, and his grandfather Carl.

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