Stanley J. Korsmeyer

The scientific community has been saddened and diminished by the loss of Stanley J. Korsmeyer, M.D., who died of lung cancer last month at the age of 54. Over the last 25 years, Korsmeyer had been an international leader in the fields of cancer biology and programmed cell death (apoptosis). Through his studies of apoptosis, Korsmeyer helped revolutionize our concepts of carcinogenesis. Korsmeyer, a medical oncologist by training, also helped translate this knowledge into the development of novel cancer therapeutics that are just now entering into human clinical trials.

Stan didn't start out to be a research scientist. He grew up the oldest of four on a livestock farm in southern Illinois. It was his involvement in the 4-H club that spawned his interest in science. From the beginning, his scientific experiments met with success. The pair of Hampshire Hogs he raised at age 14 were named Grand Champion at the Illinois State Fair, and Stan went off to the University of Illinois determined to become a veterinarian. However, on the advice of one of his veterinary mentors, he switched to pre-med. Following receipt of an M.D. degree from the University of Illinois and an internship and residency at UCSF, he arrived at the NIH as a Research Fellow at a time when molecular biology was just beginning to revolutionize the study of human disease. There, under the tutelage of scientists like Tom Waldmann and Phil Leder, Stan soon joined the vanguard of research scientists characterizing the molecular features of the chromosomal translocations that had been observed in patients with leukemia/lymphoma. Over his career, Stan contributed to the characterization of a variety of chromosomal translocations and identified several widely studied oncogenes including MLL, AF-4, and Ttg-1 (rhombotin).

Although he had many accomplishments, Stan will be best known for his contributions to the discovery and characterization of the role that programmed cell death plays in the pathogenesis of cancer. In 1985, the Korsmeyer laboratory was one of three laboratories to describe the molecular aspects of a chromosomal translocation between chromosomes 14 and 18 observed in the majority of patients with follicular lymphoma. This translocation placed the immunoglobulin gene enhancer from chromosome 14 in close proximity to a previously uncharacterized gene on chromosome 18 that was given the name Bcl-2. From the beginning, Bcl-2 was a problem. It didn't score easily in any of the assays usually used to characterize oncogenes. In 1988, a group from The Walter and Eliza Hall Institute reported that Bcl-2 could promote the survival of hematopoietic cells in culture. Shortly thereafter, Korsmeyer, who had been pursuing an independent investigation to determine whether Bcl-2 overexpression could alter B cell development and/or transformation in vivo, confirmed and extended this observation. Korsmeyer demonstrated that a Bcl-2 transgene expressed under the control of an immunoglobulin enhancer led to the progressive accumulation of B cells in vivo. The transgenic B cells were characterized by an extended cell survival, and this extended survival led ultimately to an increased incidence of B cell lymphomas in the mice. These studies provided the first evidence that inhibiting cell death by apoptosis could contribute to development of cancer.

Following his pioneering discoveries of the role of Bcl-2 in preventing programmed cell death and in promoting carcinogenesis, Stan remained at the forefront of apoptosis research. Not only did he demonstrate that overexpression of Bcl-2 could enhance lymphocyte survival in vivo, he also demonstrated that Bcl-2′s endogenous role was to regulate cell survival. He showed that Bcl-2-deficient mice were unable to maintain the survival of mature lymphocytes. Bcl-2-deficient animals developed profound immunodeficiency soon after birth. Korsmeyer also led investigations to identify how Bcl-2 proteins work. His laboratory localized Bcl-2 to the mitochondria; discovered Bax, a Bcl-2 homolog whose function was to execute cells rather than keep cells alive; and cloned Bad and Bid, two BH3-only-containing Bcl-2 homologs that modulate the functions of other family members. In recent years, many others have contributed to the current understanding of apoptosis regulation, but Stan continued to be a leading figure. As the Bcl-2 family expanded to include a dizzying array of death inhibitors and death effectors and their intermolecular regulatory network became increasingly complex, it was Stan who came up with a simple model of Bcl-2 function that focused on the family's central activity. Stan proposed that the combined activities of Bcl-2-related proteins acted like a rheostat to regulate a cell's sensitivity to apoptotic stimuli. He hoped to take advantage of this by

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developing cancer therapeutics specifically designed to either inhibit the antiapoptotic members or activate the proapoptotic members.

Stan's ability to reduce problems to first principles kept the field's attention focused on the big picture. Stan's summation to a science writer of his interest in the Bcl-2 family said it best: "It turns out to be a family in which there are good guys and bad guys." Last year, Stan's laboratory collaborated with investigators in the Harvard Chemistry Department to develop peptide mimetics of the BH3 proteins that suppress the antiapoptotic function of Bcl-2. Using a chemical technique called hydrocarbon stapling, they replaced the natural amino acids within a BH3 peptide sequence to produce a stable helical structure with enhanced killing activity and provided preliminary evidence that treatment of cultured leukemia cells with these modified peptides led to selective inhibition of leukemic cell survival. Treatment of mice with leukemia with these new compounds slowed disease progression. In addition, Stan's collaboration with a company he helped found, Idun Pharmaceuticals, and Abbott Laboratories has led to the development of small molecule inhibitors of antiapoptotic Bcl-2 proteins. These mimetics appear to shift the Bcl-2 rheostat in favor of the proapoptotic family members and induce programmed cell death in cancer cells with elevated levels of antiapoptotic Bcl-2-related proteins. Ironically, in a paper soon to be published, these new Bcl-2 inhibitors are shown to have single agent activity in treating lung cancer cells.

As numerous and significant as Stan's scientific achievements were, what those of us who worked with him will remember is the enthusiasm and perspective that he brought to his research. No matter how competitive the situation, he always reminded his own laboratory, collaborators, and competitors that the important goal was to focus on developing a deeper understanding of cancer and utilize that information to improve cancer treatment. Stan's dedication to science was surpassed only by his dedication and love for his family. Despite being a nonsmoker, he developed lung cancer. Even his illness couldn't change his approach to life. Right through the final stages of his treatment, he faced his illness with courage and optimism, actively participating in the choice of therapy he received. Stan was never one to stay on the sidelines.

Stan's contributions to cancer research were recognized widely in his lifetime. He was appointed a tenured Professor, first at Washington University and then at Harvard. Stan was appointed an Investigator within the Howard Hughes Medical Institute at both universities. He was elected to membership of the National Academy of Sciences, the Institute of Medicine, and the American Philosophical Society. His awards for cancer research include the Bristol Meyers Squibb Award for Distinguished Achievement in Cancer Research, the Charles S. Mott Prize of General Motor Cancer Research Foundation, the 2000 Louisa Gross Horwitz Prize, the Stratton Medal from the American Society of Hematology, the Leukemia and Lymphoma Society deVilliers International Achievement Award, and the International Award for Cancer Research from the Pezcoller Foundation and the American Association for Cancer Research. Nevertheless, those of us who knew him will remember Stan best for his qualities as a colleague, mentor, and friend. When Stan Korsmeyer died on March 31, 2005, we lost one of the good guys.

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