the genes uncovered, a skeptic might still judge the screen and its results to have uncertain physiological significance without additional data. In bolstering the case for selected gene candidates, DasGupta and co-workers made a wise choice in exploiting genetic approaches to pursue the notion that some genes uncovered by the screen will have conserved Wnt signaling function in multiple species and models. (Models included reporter gene assays in mammalian cultured cells, development of *Drosophila* wing imaginal discs, and zebrafish morphogenesis.) Indeed, the authors demonstrate the importance of several new Wnt pathway components—Rab5, the serine-threonine kinase Lats/Warts, and a pairlike homeobox gene (CG4136)—in multiple settings.

Almost certainly, a subset of candidate Wnt pathway components identified by DasGupta *et al.* will be major players in one or more cell types, although many candidates may regulate the Wnt pathway indirectly. No doubt it will take Wnt researchers time to assess the in vivo relevance of the candidate Wnt pathway genes highlighted by the study and to determine their biochemical connection to the pathway. The list of candidate Wnt pathway components generated by DasGupta *et al.* is remarkable, but it is certainly not complete. For example, some components known to act redundantly, such as APC1 and APC2 (*9*, *10*), were missed. Also, the model reporter genes used in the screens bear minimal similarity to endogenous genes dependent on β-catenin–TCF complexes. Thus, the screens may be more informative about factors acting upstream of Arm/β-catenin. However, given that straightforward modifications can be made to reporter gene constructs and assays, it should be easy to develop additional screens to fill apparent gaps. Among the major challenges will be integrating the abundance of candidate components into useful working models of Wnt pathway function. Given the importance of Wnts in development and disease, future studies are sure to identify links between some of the new pathway components and essential developmental processes and diseases such as cancer. Such discoveries will only serve to increase the glow surrounding the Wnt signaling pathway.

References

1. L. Lum *et al.*, *Science* **299**, 2039 (2003).
2. K. Boutros *et al.*, *Science* **303**, 832 (2004).
3. K. Berns *et al.*, *Nature* **428**, 431 (2004).
4. S. Cherry *et al.*, *Genes Dev.* **19**, 445 (2005).
5. R. DasGupta, A. Kaykas, R. T. Moon, N. Perrimon, *Science* **308**, 826 (2005); published online 7 April 2005 (10.1126/science.1109374).
6. C. Y. Logan, R. Nusse, *Annu. Rev. Cell Dev. Biol.* **20**, 781 (2004).
7. R. T. Moon *et al.*, *Nat. Rev. Genet.* **5**, 691 (2004).
8. T. B. Chou, N. Perrimon, *Genetics* **144**, 1673 (1996).
9. Y. Ahmed *et al.*, *Development* **129**, 1751 (2002).
10. K. Akong *et al.*, *Dev. Biol.* **250**, 91 (2002).

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RETROSPECTIVE

Stanley Joel Korsmeyer (1950–2005)

Timothy J. Ley

Stanley Korsmeyer died from lung cancer on 31 March 2005, at the age of 54. He had never smoked. He grew up on the family farm in southwestern Illinois. Given his farming roots, he thought about becoming a veterinarian. But one of his early mentors, a local vet named Robert Goodin, advised him to think more about a career in biological sciences. What an incredibly good piece of advice that would turn out to be. Stan didn't really know how to pursue such a goal—he had no role models and no connections. But he had desire and determination, and a very supportive family. His parents prepared him for life with the bedrock values of farming: thoughtful preparation, hard work, personal integrity, and neighborly kindness. These values would serve him well throughout his life.

After majoring in biology at the University of Illinois at Urbana-Champaign, Stan went to the University of Illinois medical school in Chicago. Here, he met the great hematologist Paul Heller, who recognized Stan's potential. Heller encouraged Stan to pursue a research career and facilitated his first research experience, with Robert Strickland at the University of New Mexico. Stan studied lymphocytotoxic antibodies in the families of patients with inflammatory bowel disease and, while still a medical student, was the first author of a *New England Journal of Medicine* paper. His love of immunology was set in stone.

CREDIT: STEVE GILBERT

While a medical resident at the University of California, San Francisco, he met a gifted oncology nurse named Susan Reynard, whom he married. In 1979, Stan joined the laboratory of Tom Waldmann at the National Institutes of Health. In a spectacular collaboration with Phil Leder's group, Stan and his colleagues defined immunoglobulin gene rearrangements in normal and diseased B lymphocytes. Using the molecular reagents generated by these studies, Bakhshi and Korsmeyer described the breakpoint region of a translocation between chromosomes 14 and 18 that is found in most follicular lymphomas. The translocation juxtaposed regulatory elements from the immunoglobulin locus with a previously undescribed gene, which they called *Bcl-2*. The *Bcl-2* gene was not altered in any obvious way, suggesting that its expression was simply dysregulated in B cell lymphomas. However, this gene did not resemble traditional oncogenes, and its link to pathogenesis was uncertain.

In 1986, Stan moved his laboratory to the Department of Medicine at Washington University medical school in St. Louis, where he became a Howard Hughes Investigator. He set up a highly focused and robust laboratory within a year, and began to attract the best and the brightest. His drive and focus were nothing short of incredible. Within a few years, Stan and his colleagues made transgenic mice that overexpressed the Bcl-2 protein in B lymphocytes. These animals developed follicular hyperplasia not because of excessive B cell proliferation, but rather because the B cells failed to die on schedule. These long-lived B cells went on to acquire additional mutations that ultimately led to the development of high-grade lymphomas in mice. This finding demonstrated that "wild-type" Bcl-2 could prevent cell death and lead to the development of cancer. The link with cancer was expected, but the mechanism was not. In the mid-1980s, cancer was thought to be a disease of increased cellular proliferation. The idea that it might be caused by reduced cell death was not

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recognized. The data from Stan's group were compelling and incontrovertible, launching Bcl-2 as the founding member of a new class of oncogenes. The earlier proliferative paradigm of cancer pathogenesis was not wrong, but was simply incomplete. Dysregulated programmed cell death would soon be demonstrated in many tumors, and the word "apoptosis" would become part of the vernacular for all biomedical scientists.

For the rest of his life, Stan embraced the key scientific question posed by these studies: How does Bcl-2 block programmed cell death? He and his colleagues defined the physiological roles of Bcl-2 in B cell memory and T cell development, and showed that this protein was required for the survival of many cell types during normal development. Stan and his collaborators demonstrated that Bcl-2 is only one member of a large group of related proteins with conserved homology domains. Moreover, he and others showed that these proteins interact and subserve both pro- and antiapoptotic functions that regulate cell survival by affecting critical mitochondrial functions.

For these many remarkable observations, Stan was elected to the National Academy of Sciences at the age of 45. He proceeded to win the Bristol-Myers Squibb Award, the Mott Prize of the General Motors Cancer Research Foundation, the Pezcoller Foundation–American Association for Cancer Research International Prize, and the Stratton Medal from the American Society of Hematology, to name but a few of his many awards. David Nathan and the leadership at the Dana-Farber Cancer Institute recruited him to Harvard in 1998. There, he continued his extraordinary science and acted as a senior scientific leader of the institution until his untimely death.

Stan was one of the most highly cited scientists of our time. He published more than 250 peer-reviewed papers that were cited, in total, more than 40,000 times. Remarkably, 23 of his publications were cited at least 500 times; 11 were cited more than a thousand times. His papers reflect his experimental precision and creative genius; they were impeccably edited, understated, and a joy to read.

Stan's most enduring scientific legacy—and the one of which he was proudest—was that of his trainees. Forty of his former postdoctoral fellows now hold faculty positions at universities around the world. Stan never ran a mega-lab, because he worried too much about the well-being of every person that he mentored. When a graduate student told Stan that he was struggling, Stan smiled and replied, "Okay, let's struggle together," and he meant it. He brought out the best in every person he trained, and he served as a wonderful role model for future generations of physician-scientists. Most appropriately, he won the Barger Award for Excellence in Mentoring at Harvard last year.

A spirit of caring and humility pervaded all that Stan did. Despite his many scientific accolades, his source of greatest pride was his family. His wife of 25 years, Susan, and his sons, Jason and Evan, were the most important people in his life. The lessons of his parents and the farm in Beardstown, Illinois, were never far from his mind, and they kept him grounded. Although he was a visionary scientist and a natural leader, he was even more so a compassionate human being whose mission was to heal. He had an ever-optimistic view of life, and a broad, genuine smile that could light up a room. He embodied the spirit of Wordsworth, who wrote: "That best portion of a good man's life, his little, nameless, unremembered acts of kindness and of love." To Stan Korsmeyer, that was the best portion indeed.

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ATMOSPHERE

Air Pollution–Related Illness: Effects of Particles

André Nel

Worldwide epidemiological studies show a consistent increase in cardiac and respiratory morbidity and mortality from exposure to particulate matter (PM) (*1*–*3*). PM is a key ingredient of polluted air and is estimated to kill more than 500,000 people each year (*4*). To prevent this staggering loss of life we must understand the characteristics of the toxic particles and gain insight into how these characteristics are related to adverse health effects (*5*). As our understanding increases, we can use this knowledge to develop biomarkers in the hope of identifying susceptible individuals and reducing their exposure to PM.

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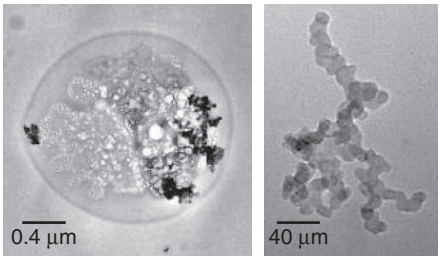
PM is composed of solid and liquid particles that come from sources such as vehicle exhaust, road dust, smokestacks, forest fires, windblown soil, volcanic emissions, and sea spray (*6*). Particle size, surface area, and chemical composition determine the health risk posed by PM (*7*). PM can be classified into coarse, fine, or ultrafine particles (*6*). Coarse particles, which have a diameter of more than 2.5 μm, are mostly derived from soil and sea salts. Fine particles (0.1 to 2.5 μm in diameter) and ultrafines (<0.1 μm in diameter) are predominantly derived from combustion of fossil fuel (see the first figure). Combustion particles have a core of elemental carbon that is coated with a layer of chemicals, including organic hydrocarbons, metals, nitrates, and sulfates. All of these components may play a role in particle toxicity (*7*).

Currently, government and air-quality monitoring agencies track and regulate 10-μm-diameter (PM10) and 2.5-μm-diameter (PM2.5) particles. Unfortunately, the unregulated ultrafine particles are potentially the most dangerous. Ultrafines are the major component in vehicle emissions—the largest source of air pollution in urban areas (*8*)—and they have the largest surface area and highest content of potentially toxic hydrocarbons among all PM sources. They can also penetrate deeper into lung tissue than fine or coarse particles (*8*).

Pulmonary effects of PM include the triggering of inflammation in the smaller airways, which can lead to the exacerbation



Dangerous dirt. (**Left**) Electron micrograph of a fine mode particle collected by an impactor from air outside an engineering laboratory at the University of California, Los Angeles. A halo surrounds residues of what are probably inorganic salts and polar organic compounds dissolved in the original aqueous droplet. Sootlike particles are also present. (**Right**) Aggregates of ultrafine particles collected on the last stage of an eight-stage impactor. These are soot particles emitted from diesel engine sources such as buses. More volatile particles may have evaporated in the electron microscope.

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