

OCTOBER 07, 2002

Horvitz Wins 2002 Nobel Prize in Physiology or Medicine

H. Robert Horvitz, a Howard Hughes Medical Institute investigator at the Massachusetts Institute of Technology, is one of three scientists who were awarded the 2002 Nobel Prize in Physiology or Medicine for discoveries concerning the genetic regulation of organ development and programmed cell death.

Horvitz shared the prize with Sydney Brenner of The Salk Institute in La Jolla, Calif., and the Molecular Sciences Institute in Berkeley, Calif., and John Sulston of the Sanger Centre in Cambridge, England. The three scientists were honored for identifying key genes regulating organ development and programmed cell death and for showing that corresponding genes exist in higher species, including man.

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— H. Robert Horvitz

Programmed cell death is the natural, necessary death of individual cells for the good of the organism as a whole. It is a well-orchestrated process, very different from the kind of cell death that results from direct injuries. During development, literally billions of cells die as the body sculpts its proper shape—for example, to eliminate webbing between the fingers of a hand.

Much of what is known about programmed cell death comes from pioneering studies by Horvitz and his colleagues, who have explored the genes that control this program in the nematode worm *Caenorhabditis elegans*. This worm is a marvelous animal for developmental geneticists to work with because the lineage—and fate—of every one of the worm's 1,090 cells is known. This has made it easier to identify many of the genes that control the

cells' developmental history and function.

Researchers have learned that 131 of the worm's cells die or "commit suicide" during normal development. Horvitz and his associates showed that two genes, *ced-3* and *ced-4*, are required for these deaths, while another gene, *ced-9*, prevents them. They also found that, once a cell is committed to a programmed cell death, it follows a reproducible pathway of events.

"That pathway can be said to consist of three sequential stages," said Horvitz. "First, killing the cell. Next, getting rid of the body. And third, destroying the evidence. Basically, you have a corpse and you must do something with it, so a neighboring cell swallows the corpse to remove it from the animal. But then the corpse must be degraded. This sequence, which we have defined in the worm, looks as if it will prove to be universal among organisms, including ourselves." Upstream of these steps, Horvitz said, is the decision about cell death: "Do it, or don't do it."

Horvitz and his collaborators discovered that *ced-9*, which protects the worm against cell death, is similar to *Bcl-2*, a human oncogene discovered by HHMI investigator Stanley Korsmeyer in patients suffering from follicular lymphoma. Unlike other oncogenes, *Bcl-2* does not promote the growth of cells; instead, it blocks cell suicide. And when *Bcl-2* is deregulated, as in follicular lymphoma, it extends the survival of cells that normally would die.

"We normally think of cancer as too much cell division," Horvitz explained, "but cancerous growth really is a change in an equilibrium. The number of cells in a tissue is maintained by two opposing processes: one of cell addition, by cell division; and one of cell deletion, by cell death. If you have too much cell division, you get an increase in cell number; if you have too little cell death, you also get an increase in cell number. Either can lead to cancer."