Apoptosis is one of the most tightly regulated pathways in cells," says HHMI investigator Hermann Steller, "because if you make a mistake, you can’t undo it. Dead cells can’t come back to life."

Steller, at the Rockefeller University, has spent the past three decades trying to understand these strict levels of regulation. Now, he’s translating those findings into developing small molecule drugs for two diametrically opposed purposes: healing wounds and treating cancer. Abrasions and burns heal faster, he’s found, when cellular suicide is turned down. By turning up apoptosis, however, he can treat cancers by killing off the cells that drive their growth.

At the crux of Steller’s research is a family of proteins called IAPs (inhibitors of apoptosis proteins) that put the brakes on cell death. In humans, there are eight IAPs, with different effects throughout the body so that long-living cells, like neurons, don’t die as easily as those with a short lifecycle, like skin cells. Other proteins, in turn, regulate the IAPs: in humans, Smac and ARTS do the job; in fruit flies, it’s the aptly named reaper, hid, and grim, discovered in part by Steller’s lab group in the 1990s. ARTS, reaper, hid, and grim all encourage cell death by blocking IAPs.

"These are the brakes and the accelerators of cell death," Steller says. "They hold the keys to controlling the whole pathway."

Scientists studying acute lymphoblastic leukemia had found that in many instances of the disease, ARTS expression was diminished. Steller wanted to know whether a lack of ARTS was sufficient to cause cancer, so he blocked expression of the protein in mice. A third of the mice developed leukemia or lymphoma within 15 months, his lab group reported in *Genes & Development* in October 2010. Without the cellular suicide pathway kicking in, their low apoptosis threshold allowed cancer cells to thrive. But when the researchers also blocked expression of a key IAP protein, the effect was reversed—apoptosis could proceed, killing off cancer cells.

"The ideal cancer drug would block the IAPs, as ARTS normally does, or restore ARTS expression," says Steller. With his sights set on such a drug, he’s collaborated with clinical scientists to find out how ARTS is silenced in leukemia and to develop molecules to block IAPs. In work published September 2010 in the *Journal of Cell Biology*, Steller and his colleagues concluded that reaper and hid—the functional equivalents of ARTS in the fly—work by clustering on the mitochondria, a cellular organelle critical to apoptosis. Now they’re
developing a small molecule based on a conserved region of reaper and grim, and they’re tacking on a protein sequence that sends the molecule to mitochondria. A version to treat cancer is in early animal trials.

“The rationale for these drugs seems strong and the promise great,” says H. Robert Horvitz, an HHMI investigator at the Massachusetts Institute of Technology who also studies the cellular suicide pathway.

Turning up apoptosis, however, has a drawback. When Steller blocked ARTS expression in mice, the tumor-ridden animals had one health advantage over their cancer-free counterparts: speedy wound healing. With impaired apoptosis, wounds heal faster—good for healing nasty cuts and burns. Likewise, Steller has shown that when cell death is increased, wounds heal slower.

“This means if people have a major wound, you can stimulate pathways to heal them faster,” says Steller. “But in a cancer patient you want to diminish those same pathways. It’s this slider between cancer and regeneration.”

But the dividing line may not be so clear-cut, he’s found. When a cell undergoes apoptosis, it also sends out signals to nearby cells encouraging them to divide, Steller has found. “The cell is saying ‘look, I’m going to die, you need to replace me,’” he explains. For wound healing, this means some level of apoptosis actually helps the process of healing. But in cancer, it introduces a problem: more apoptosis may increase the signals that tell nearby cells—including cancerous ones—to multiply.

This may mean that radiation therapy (which kills cancer through inducing widespread apoptosis) or one of Steller’s new small molecule compounds could force a cancer to spread at the same time it’s killing a primary tumor. If researchers like Steller can tease apart these growth-causing signals—called mitogens—from the rest of the apoptotic pathway, they’d be able to pick and choose which ones to turn on. For cancer, the ideal mix would be more apoptosis with no mitogens. For healing, the goal would be less apoptosis and a surplus of mitogens.

“Steller’s recent work,” says Horvitz, “is novel, important, and intriguing in the context of possible novel therapeutics.”

And whether or not his findings lead rapidly to therapeutics, his research is helping scientists understand how to control a cell’s most fundamental decisions: whether to live or die. —SARAH C. P. WILLIAMS