



**Among proteins that control cell death "there are good guys and bad guys," says Stanley Korsmeyer.**

in cell culture just like the Smac protein. What's more, studies of laboratory-grown cells showed that the compound readily passes through the cell membrane and targets only cancer cells, leaving normal cells healthy. That's probably because normal cells don't rely on these anti-apoptotic proteins to survive, the scientists say.

#### TO DO THE "HONORABLE" THING

According to Korsmeyer, normal cells have a variety of anti-death mechanisms at their disposal. Cancer cells, on the other hand, tend to be specialized at making excessive amounts of a specific anti-death protein and therefore become highly vulnerable in its absence. His group is developing agents, different from those studied by Wang and colleagues, that can target the BCL-2 family of apoptotic proteins.

Several years ago, Korsmeyer discovered that certain lymphoma cells specialize in making BCL-2, the founding member of a large family of proteins now known to orchestrate the cell-death machinery. "It turns out to be a family in which there are good guys and bad guys," says Korsmeyer, noting that some members activate

death while others work to block it.

Through his studies, Korsmeyer has untangled the complex signaling system that family members use to communicate among themselves and with mitochondria. For example, a series of molecules—which go by the names of BID, BAD, and BIM—function as antennae for death signals or cellular damage, and spur cell death by communicating the pro-death message to mitochondria, which can respond by releasing their pro-death agents. This subclass of BCL-2 family proteins, referred to as BH3-only, contain an important peptide subunit, called BH3, that allows them to block inhibitory proteins such as BCL-2 or, in some cases, directly activate additional pro-death proteins, named BAX or BAK. Based on this mechanism, he and his colleagues have developed a modified BH3 peptide that initiates apoptosis in leukemia cells.

"The problem with simply using the natural BH3 peptide is that it has a critical three-dimensional spring-like structure that unfolds when taken out of context from the whole protein," says Loren D. Walensky, a biochemist and pediatric oncologist at Dana-Farber who helped develop the agent. To create a stable, biologically active compound, the researchers used a chemical technique called hydrocarbon stapling, developed by Gregory L. Verdine of Harvard University, that allowed them to replace some of the natural amino acids within the BH3 peptide sequence with artificial ones that react chemically to form a sturdy linkage. Applying this strategy, the group was able to brace the peptide from within, restoring its helical structure and enhancing its killing activity, Walensky says.

Experiments with cultured leukemia cells showed that the modified peptides hit their target at the mitochondria, causing the cells to self-destruct. Furthermore, leukemic mice treated with the new compounds showed regression of their malignant cells and survived longer than untreated control animals.

In a separate study, Korsmeyer and Anthony Letai of Dana-Farber demonstrated that when mice with leukemia were stripped of their BCL-2 armor, their cancer cells receded and the mice lived longer than their BCL-2-making counterparts. This experiment, according to Korsmeyer, is the first to show that simply removing the barrier to cell suicide can kill cancer in animals.

"These cancer cells may be somewhat predisposed to doing the 'honorable' thing if we could roust some of those BH3-only proteins out of the BCL-2 pockets," he says.

—SUSAN GAIDOS

## Cranial Explorations in the Splash! Class

*On a weekend afternoon they're unlikely to forget, teenagers practice brain surgery at MIT.*

**O**n the Saturday before Thanksgiving, two dozen grade-school students, scalpels in hand, line up at laboratory countertops at the Massachusetts Institute of Technology (MIT) for the highlight of their three-hour neuroanatomy workshop—dissecting sheep brains. Fifty chilled, preserved brains were shipped in a white bucket from the biological specimen company and are shared in the lab to encourage group discovery and collaboration.

The work is unfamiliar and potentially gross, and the students show a range of responses as they try to muster some professionalism. "It's like a butcher house," says Tyler Quinn, who carefully organizes pieces of gray and white matter to preserve "a bit of dignity" for the formerly vital organ. Quinn, 12, attends Elm Street Middle School in Nashua, New Hampshire.

"I feel like I should be remorseful because I'm cutting through a brain," says Sarah Gulick, 14, sitting at the next lab bench over. "But it's so beautiful." She slices the bumpy cortex with surgical precision, revealing the smooth contours of the curved hippocampus underneath. "It's like butter," Gulick says. Across the room, another team struggles to find the small almond-shaped amygdala located at one end of the hippocampus.

The course is part of a program called Splash!, designed for students in grades six through twelve and run by an MIT student club. Every fall, some 1,000 young people—many of them home-schooled or gifted—attend more than 200 weekend classes ranging from international finance to the art of comics.

Splash! classes appeal to students who want to sample an MIT education or are simply seeking new and stimulating learning environments, says program director Michael Shaw, an MIT sophomore with a double major in math and physics.

*Neville Sanjana and Emily Hueske help grade-school students understand the brain—"the amazing computers inside our heads."*



Most of the participants live in the New England area; a few come from as far away as Texas and Oregon. Some of them not only return year after year but also enjoy its benefits during the time in-between. "Last year, I pretty much made half of my friends here," says Gulick, who attends the Commonwealth School in Boston.

The neuroanatomy class begins in a seminar room with a slideshow—a whirlwind tour of the central nervous system. "We teach this class over three months to MIT undergraduates," says instructor Neville Sanjana, whose graduate education is supported by a HHMI predoctoral fellowship. "We'll teach you in three hours." Sanjana works in the lab of HHMI investigator H. Sebastian Seung, a professor in the departments of brain and cognitive sciences and physics at MIT, who has covered most of the workshop costs.

Sanjana and co-instructor Emily Hueske, a fellow graduate student, focus on three major parts of the human brain—the cerebral cortex, the limbic structure, and the brainstem. "The smart stuff is divided into four lobes," says Sanjana, who then points out the sections of the cortex that handle vision, hearing, touch, smell, motor skills, personality, and social behavior.

A lot of what scientists know about the

brain, say the instructors, comes from studies of people whose brains were damaged. Hueske relates the gruesome but fascinating tale of Phineas Gage, foreman of a railway construction gang in Cavendish, Vermont, who survived a 13-pound iron rod being shot through his frontal lobe in a blasting accident on September 14, 1848—though his dependable and congenial personality changed for the worse.

Discussing the hippocampus, which plays a crucial role in the storage and retrieval of memories, Hueske observes that much of what is known about that seahorse-shaped structure comes from studies of a patient known as H.M. In 1953, when doctors attempted to cure his epileptic seizures by removing about one half of his hippocampus, they inadvertently destroyed his ability to encode new memories. Every day he wakes up and does not know what day, month, or year it is, says Sanjana. Now 78, H.M. has lived in New England all his life and is still followed closely by MIT researchers.

After the slideshow, Sanjana and Hueske pick up two trays of expertly dissected sheep brains in the back of the room. The students don lab coats and latex gloves to preview the structures they will be discovering in the lab. Down the hall, after the brains and scalpels

have been distributed, the instructors prepare their students for the main event, including a reminder to be respectful of the specimens as parts of former living creatures. Sanjana demonstrates each maneuver on an overhead projector, while Hueske circulates to provide encouragement and advice. "A good rule," she says, "is to make as few cuts as possible. Long straight cuts are better than a lot of little ones." Some of the students follow this and related guidance with cooler heads and steadier hands than others, but virtually all agree that the workshop and its *pièce de résistance* are nothing short of "awesome," to use a favorite word of their contemporaries.

It's an awesome experience for the instructors as well, both of whom note that this is their second year teaching this Splash! workshop. Sanjana had in fact participated in the program when he was an undergraduate at Stanford.

"The most important thing about this class is that it be fun," he says. "It's certainly fun for Emily and me. We go to work every day and have a great time in lab—we think this is the most interesting problem of our time. So we want to share with [the students] how much we have figured out about the amazing computers inside our heads." — **CAROL CRUZAN MORTON**