A Pocketful of Protein

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Seizing the time-honored Trojan Horse strategy, scientists from Washington University School of Medicine have found a way to sneak death-dealing molecules into cells infected with HIV. Call it a triumph of outside-the-box thinking: While everyone else was developing compounds to *inhibit* the protease enzyme that HIV needs to replicate, chief researcher Steven Dowdy, PhD, came up with the idea of *exploiting* the protease to trigger cell death via a protein his team devised called TAT-Casp3. It contains two separate parts of caspase-3, a molecule that promotes cell suicide. But then Dowdy faced the problem of transporting these proteins—hundreds of times larger than the molecules currently used in drugs—into the cell. Riding his bike to work one day, Dowdy envisioned the breakthrough: a way to “fold” the protein that allows cellular entry. Once the TAT-Casp3 is inside, the scissorslike HIV protease goes about its usual business of cutting up proteins into the pieces it needs to reproduce. But—surprise!—when it slices open the TAT-Casp3, the freed caspace-3 parts activate the body’s own caspace-3, spawning thousands of murderous molecules. The result: In the test tube, 100 percent of HIV-infected cells die within 16 hours. Since uninfected cells don’t contain HIV protease, they are unaffected, making this a potentially non-toxic therapy. And the speed at which TAT-Casp3 destroys infected cells makes Dowdy believe resistance is unlikely to develop. If the animal research now underway confirms the promise, human tests using the protein against HIV via an aerosol to the lungs might begin next year. And the research won’t stop there. Dowdy says, “It’s a brave new world of protein therapy. We can now introduce things into cells that we never could before, opening up possibilities for nontoxic therapies a thousand times more efficient and extremely specific for many diseases. This approach may be able to work against hepatitis C, malaria, herpes and other infections, as well as some kinds of cancer cells.”

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