Compelling cancer cells to self-destruct

A cell's surface begins to blister, its nucleus disintegrates and the surrounding cytoplasm shrinks. Finally, with its DNA breaking into short "ladders," the cell dies. This phenomenon, called programmed cell death, occurs naturally in developing embryos, skin and metamorphosing insects – wherever certain cells are no longer needed (SN: 12/5/87, p.360).

Now West German researchers have triggered programmed cell death in human tumor cells. Using a monoclonal antibody with no attached drug or toxin, the scientists killed malignant B-cells *in vitro* and caused striking regression of human tumors growing in immunologically weakened "nude" mice.

The newly engineered antibody, called anti-APO-1, may eventually offer a novel approach for treating some cancers, says study coauthor Peter H. Krammer. But its therapeutic potential, he cautions, "very much depends on how much any normal tissue is affected [by the antibody]." He and his colleagues at the German Cancer Research Center and the University of Heidelberg are now testing anti-APO-1 for ill effects on noncancerous tissue.

To produce the deadly antibody, Krammer's group injected normal mice with cancerous human B-cells, a type of white blood cell. They then extracted and cultured antibody-secreting cells from the mice and tested antibodies from more than 10,000 cell cultures. Antibodies from one culture completely blocked growth of the cancerous cells, they report in the July 21 SCIENCE.

Under the microscope, the cancerous cells revealed blisters and other changes suggesting programmed cell death. In contrast, cells killed by antibody-actuated immune proteins swell and burst. The scientists also measured the cells' broken DNA, finding the 180-base-pair ladders characteristic of programmed cell death.

The mechanism of this destruction remains unknown. Krammer notes that the immune system's killer T-cells and some cytotoxins such as tumor necrosis factor (SN: 8/31/85, p.132) can also induce programmed cell death.

When anti-APO-1 attaches to a cell surface, "the cell goes berserk," says Krammer. It appears unlikely that the antibody's attachment site – a protein dubbed APO-1 – is the receptor for tumor necrosis factor, he adds. But he speculates that APO-1 may be a receptor for killer T-cells or part of a family of receptors that trigger programmed cell death when stimulated.

The West German group also found APO-1 on some noncancerous immune cells from humans. And that may bode ill for the monoclonal antibody's use in cancer treatment. "It's worrisome that [APO-1] is found on active B- and T-cells," says Ralph Reisfeld of the Research Institute of Scripps Clinic in La Jolla, Calif. If it destroys normal, active immune cells, this could prevent physicians from using the antibody with other treatments, he says. Noting that many newer cancer therapies work by activating killer T-cells to attack tumors, Reisfeld says administering anti-APO-1 in conjunction with these treatments could "throw a monkey wrench into the process."

Still, Reisfeld joins Karl Eric Hellström of Oncogen in Seattle in calling the work "exciting." Anti-APO-1 is one of only a few antibodies with direct antitumor effects, says Hellström, who describes the tumor reduction in nude mice as "quite remarkable." Hellström says he thinks "it would be worthwhile to try to follow up in some clinical model." But he emphasizes the necessity of looking first for toxic effects on normal tissue. – *S. Hart*

Zeroing in on the Z° mass

In the race to determine the key properties of the Z° subatomic particle, two research teams dashed to the forefront last week, describing the most precise measurements yet of the particle's mass. Scientists working with the Mark II detector at the Stanford (Calif.) Linear Collider reported data showing the Z° has a mass of 91.11 billion electron-volts (GeV), roughly 100 times a proton's mass. The finding is consistent with a concurrent announcement from a team of scientists operating a detector at the Tevatron accelerator at Fermilab in Batavia, Ill., who put the particle's mass at 90.9 GeV. The short-lived Z° particle is one of three carriers of the weak nuclear force, which governs certain kinds of radioactive decay.

The Mark II data are based on 106 events resulting from high-speed collisions between electrons and positrons (SN: 4/22/89, p.245). The Fermilab results are based on studies of 500 events involving Z° particles created in collisions between protons and their oppositely charged, antimatter counterparts.

By varying the energies of the colliding particle beams, physicists can map the energy range over which Z° particles are created. They see a broad peak covering the range of energies (or masses) that Z° particles can have. Last week's mass estimates represent the position of that peak. Even more important, however, is the peak's width, which may provide clues to how many families of fundamental particles ought to exist. Determining that width precisely requires far more data than are presently available.

The Mark II researchers hope to detect at least 1,000 Z° particles before the end of September. By that time, the recently completed Large Electron-Positron accelerator at the European Laboratory for Particle Physics (CERN) in Geneva, Switzerland, will probably be in operation, also generating large numbers of Z° particles. Scientists are now testing the new accelerator in preparation for experiments that may begin as early as next month. □

AIDS drug shows promise

People infected with the AIDS virus showed signs of improved immune function after taking an experimental drug called dideoxyinosine (DDI), researchers report in the July 28 SCIENCE.

Robert Yarchoan of the National Cancer Institute in Bethesda, Md., and his colleagues studied 25 men and one woman infected with the virus, known as HIV. All subjects had evidence of a damaged immune system that is characteristic of HIV infection, and 10 had turned to DDI as a last resort when they could no longer take the drug zidovudine (AZT) because of severe side effects such as anemia.

The pilot study demonstrates that DDI can shore up an ailing immune system without the toxic effects of zidovudine. By the sixth week of the study, subjects who got the highest drug doses (at least 1.6 milligram per kilogram of DDI intravenously every 12 hours) showed an increase in their CD4-positive T-cells, infection-fighting white blood cells targeted by HIV. The researchers say most patients tolerated DDI well, though a few reported headaches and insomnia.

DDI works by blocking HIV replication, Yarchoan says. The team found that by the sixth week of DDI treatment, high-dose subjects showed declines in an HIV protein component that can be measured in the blood. This suggests DDI may help AIDS patients stave off opportunistic infections and live longer, but further studies must prove DDI's performance, Yarchoan says.

The pilot study is part of a multicenter research effort to show DDI is safe before scientists go on to Phase II clinical trials to test the drug's efficacy. DDI manufacturer Bristol-Myers Co. of New York City says Phase II trials will begin in September. The company says it will distribute DDI free to AIDS patients who do not qualify for clinical studies at that time, a plan that fits with the recent Public Health Service proposal to establish a separate program enabling AIDS patients who don't meet Phase II trial criteria to obtain promising drugs from their doctors (SN: 7/1/89,p.6). □