Fooling Cancer With Tech Wizardry

Using drugs that kill tumor cells while sparing normal cells is one way of decreasing the toxic effects often seen with cancer therapy, scientists noted last week when describing their latest studies using toxins attached to cell-growth factors and viruses grown in cancer cells as cancer treatments.

Recently, scientists have created anticancer drugs called oncotoxins by attaching compounds that kill cancer cells to monoclonal antibodies against those cells – based on the theory that, after the antibodies bind to cell surfaces, the toxins then destroy the cells. Now researchers at the National Cancer Institute (NCI) in Bethesda, Md., are studying a new family of related agents, which goes beyond the initial antibody-plus-toxin concept.

Using a powerful toxin produced by the bacterium *Pseudomonas*, Ira Pastan and his co-workers have modified the oncotoxin approach, hoping to make even more selective agents. The scientists developed a gene that codes for a toxin incapable of binding to cell surfaces, including those of normal cells. They then spliced this altered gene to others coding either for a growth factor like transforming growth factor alpha (TGFα) or for interleukin-2 (IL-2). Both of these substances bind to cell-surface receptors, which certain cancer cells have in numbers many times those seen on the surface of normal cells. This quantitative difference is the key to selective killing of cancer cells, says Pastan.

In *in vitro* experiments, oncotoxins made of TGFα have been "extremely active in killing T-cell leukemia cells," Pastan said last week at the American Cancer Society's 30th science writers' seminar in Daytona Beach, Fla. He says other possible targets include squamous cell carcinoma and bladder cancer, because those cancer cells have excess receptors for the so-called epidermal growth factor. Only one molecule of the toxin – so potent that a dose the size of a salt grain will kill a human – is needed to kill an individual cell.

The *Pseudomonas* toxin also is the assassin component of OVB3-PE, the institute's earlier oncotoxin based on monoclonal antibodies against cancer cells. Studies in mice injected with human ovarian cancer cells had shown that mice without OVB3-PE treatment died within four to five weeks, while treated mice survived up to six months. The substance has just entered a preliminary clinical trial, says Pastan. To date, only four women with ovarian cancer have joined the preliminary study. Because the initial doses are much lower than those predicted to be effective against tumors, Pastan says it may take up to a year of gradual dosage increases before the scientists can draw any clinically significant conclusions.

Although the newer oncotoxins based on growth factors and IL-2 are less well-studied than OVB3-PE, Pastan and others suspect that this second generation of chimeric anticancer agents will prove superior. The approach is "a very devilishly clever idea," says NCI Director Vincent T. DeVita. "I think there's going to be a real future for this kind of approach. [It] is potentially cleaner [more specific] and quicker [than using monoclonal antibodies]." He adds, however, that more work must be done to ensure that the oncotoxins do not significantly harm normal cells.

Instead of using toxins to destroy tumor cells, Ralph S. Freedman and his colleagues at M.D. Anderson Hospital and Tumor Institute in Houston have resurrected the idea of viral oncolysates—viral products that somehow destroy tumors. Scientists noted in the late 1950s that the injection of extracts from viral-infected, laboratory-grown cancer cells might stimulate a patient's immune system to fight the same type of cells in the body.

Freedman reported injecting such an extract, made from an influenza A virus, into 40 women with advanced ovarian cancer. The results, published in the latest issue of GYNECOLOGIC ONCOLOGY, showed a reduction of tumor size in nine of the patients. Although a minority of the patients responded in this manner, Freedman says enhanced cellular immunity and IL-2 levels following injection suggest that oncolysates might be used to augment other therapies. *– D.D. Edwards*

Cold probe reduces preemie blindness

A procedure that freezes the surface of the eye can cut by half the risk of "severe vision loss" among premature infants with the vision-threatening disease called retinopathy of prematurity, scientists said this week in announcing a recently completed study at 23 U.S. medical centers.

A disease that causes vision loss in 2,600 U.S. infants annually, the retinopathy is caused by abnormal branching of blood vessels in the underdeveloped eye that intertwine and prevent normal vessel growth throughout the retina, which lines the eye's interior. Eventually, if the condition does not spontaneously reverse itself (which occurs in about 50 percent of cases), the retina becomes detached, causing either total or partial blindness. But, say the scientists, if the area is frozen, the progression to blindness often can be halted by removing barriers to normal growth.

Sponsored by the National Eye Institute in Bethesda, Md., the study of 172 very low birthweight infants (below 2.76 pounds at birth) with early stages of the disease found that a probe cooled to −80°C – when touched to the outside of the eyeball – apparently removes the twisted abnormal vessels. "Each [frozen] spot is two to three millimeters in diameter, and approximately 50 of them are distributed like polka dots in a belt around the front part of the retina," says Earl A. Palmer of Oregon Health Sciences University in Portland, chairman of the study. He and other researchers presented the results this week at a news briefing.

In the study, one eye was treated, the other left untreated. In the treated eyes, only 21.8 percent progressed to an "unfavorable outcome," compared to 43 percent of untreated eyes. An unfavorable outcome was defined as retinal detachment or folding. A favorable outcome, says Palmer, means the infant will likely have better vision than that considered legally blind. He says that no significant side effects were noted during the study, but that the technique will likely cause some loss of peripheral vision due to scarring. Not all infants are candidates for cryotherapy – but when it is used, timing is critical, says Palmer, because it is too late once the retina detaches.

Because of the dramatic results, which will appear in the April ARCHIVES OF OPHTHALMOLOGY and the May PEDIATRICS, a monitoring committee halted the study before its original completion date. On Feb. 12, study coordinators mailed a "clinical alert" to 2,300 specialists in the United States, recommending referral of patients to one of the 23 participating centers until publication of the final results. Although the therapy has been used for years in other countries – in Japan since 1972 – with apparent success, Palmer says U.S. clinicians did not adopt the procedure pending more definitive results of a large, controlled clinical trial like the one just completed. *– D.D. Edwards*