IMMUNITY TO CANCER MEETING

INTERFERON AUGMENTS TUMOR ANTIGENICITY...

WILLIAMSBURG, Va.—Tumor heterogeneity presents one of the toughest obstacles to treating cancer. In fact, the diversity of cells within a tumor undermines the very advantage of monoclonal-antibody therapy: specificity.

But new strategies are finding ways around the problem that not all malignant cells express large quantities of the expected "tumor-specific" antigen. One approach is to use a "cocktail" of monoclonals to attack cells that may produce high levels of one tumor antigen but not another. A second technique employs antibody-

radionuclide conjugates that can kill cells 5–50 cell diameters away from where the conjugate binds. And a third strategy is to use low, sub-cytotoxic doses of interferon to induce tumor cells to express higher quantities of antigen, thereby allowing monoclonal antibodies to find and bind these cells more easily. Jeffrey Schlom, chief of the National Cancer Institute's (NCI, Bethesda, MD) Laboratory of Tumor Immunology and Biology, described recent work on adding interferon to cell cultures derived from human biopsies at the "Second Conference on Immunity to

Cancer." Held here in November, this well-attended meeting was sponsored by NCI's Biological Response Modifiers Program and the Society for Biological Therapy.

According to Schlom, approximately 50 percent of human colon carcinoma cells express measurable levels of the TAG-72 antigen on their surface. Treatment with recombinant human alpha-interferon (clone A) or with gamma-interferon increases this figure *in vitro* to 98 percent. Although the approach doesn't work with all tumor types—it's useless for tumor cells that lack interferon receptors, for example—it does seem to be a fairly general phenomenon.

Schlom stresses that the treatment only *augments* antigen production—if a cell produces absolutely no antigen prior to interferon administration, then it will produce no antigen after treatment. This means that normal cells will not be influenced to produce tumor antigens; however, if a particular tumor cell does not produce any of the desired antigen, the treatment won't help.

Schlom says that the next step is human clinical trials, scheduled to begin during the first half of 1988.

—Arthur Klausner

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REASONS

Cell-sorter analysis shows that recombinant alpha-interferon increases tumor antigen expression. *Left:* A colon cancer cell line sorted with an anti-cancer monoclonal antibody registers about half the cells as positive (vertical axis). *Right:* When the cells were first treated with interferon, however, some 98 percent of the cells are positive, and more of them show a higher intensity of antibody binding (horizontal axis).

CLINICAL TRIALS

...BUT IT CAN ALSO PROVOKE ANTIBODY RESPONSE

WASHINGTON, D.C.—Clinical use of interferon apparently elicits an immunogenic response among a fraction of patients, according to reports made by several researchers at the Annual Meeting of the International Society for Interferon Research (ISIR), held in November. And this antibody reaction just might explain some of the unsuccessful cases of interferon therapy. Although not considered a cause for major alarm, the findings have been described as an early "warning flag" needing evaluation.

Specific "neutralizing antibodies" that interfere with interferon's biological activity appear in as many as 20 percent of cancer patients receiving alpha-interferon, according to Jorge Quesada and Jordan Gutterman at M.D. Anderson Hospital and Tumor Institute (Houston, TX) and their collaborators, and also to Peter von Wussow and his colleagues at the Med. Hochschule (Hannover, F.R.G.). In addition, antibodies have been observed among patients receiving alpha-interferon for other conditions, such as viral infections, and

also, reportedly, in patients given recombinant interleukin-2.

Since 1982, the Texas group has used alpha-interferon to treat more than 100 people suffering from hairy cell leukemia. Among these, Quesada reports, five of the relapses occurred in patients who had generated neutralizing antibodies. Similarly, the West German group reports the appearance of neutralizing antibodies in five of 25 interferon-treated patients with chronic myelogenous leukemia. The antibodies "can abrogate therapeutic effects," von Wussow notes.

And findings were not limited to cancer patients. According to Phillip Weck of Burroughs Wellcome (Research Triangle Park, NC), patients under treatment for papillomatosis virus infections are more likely to develop interferon antibodies if their lesions appear in the respiratory tract rather than as genital warts.

Such observations have prompted ISIR's new president, Ernest Borden (University of Wisconsin, Madison), to appoint a committee to study the antibody question. The first phase of committee activity will be to alert fed-

eral and international agencies, such as the National Institutes of Health (NIH, Bethesda, MD) and the World Health Organization, and to find a sponsoring organization to coordinate efforts. Dependable assays and reagents must be developed before investigators can determine the extent of the problem.

Currently, clinical researchers say it is striking how *seldom* neutralizing antibodies have been observed among patients in clinical trials of recombinant proteins, according to committee chairman Sidney Grossberg of the Medical College of Wisconsin (Milwaukee), who has developed standardized interferon reagents under a contract from NIH. "The numbers are very small, and the antibody titers that appear in patients are very low, so it's crucial to determine what's really significant," he adds. "The route of administration [of the drug] appears to make a tremendous difference" as to whether antibodies form. The researcher cautions, however, that "everything about this is tentative."

—Jeffrey L. Fox