Waving a Red Flag Against Melanoma

For years, a dilemma has stymied scientists' attempts to create a successful "vaccine" for treating cancerous tumors: In order to work, the vaccine would have to rally the patient's immune system into launching a more vigorous attack against cancer cells, but it would also have to leave normal cells unscathed.

Most cancer researchers agree that the key component of an anticancer vaccine would be an immune-stimulating protein, or antigen, that exists only on the surfaces of cancer cells. Now, European scientists report the discovery of such an antigen on tumor cells taken from people with malignant melanoma.

In a complex series of laboratory experiments, the team identified a protein that serves as a red flag to incite the killer instincts of the melanoma patient's own cancer-fighting cells. They also identified the gene that codes for the protein's production.

"This is the first time that a [cancer-cell] antigen recognized by [immune-system cells] has been identified," asserts Thierry Boon, of the Ludwig Institute for Cancer Research in Brussels. Boon, who directed the new study, speculates that injections of human cells bearing this protein might help fend off the disease in up to 10 percent of all Caucasian melanoma patients.

Malignant melanoma, which affects the skin's pigmented cells, will strike an estimated 32,000 people in the United States this year. Most melanoma victims are Caucasian. In the earliest stage of the disease, patients develop one or more irregularly shaped, varicolored spots that grow progressively larger.

Melanoma is the deadliest form of skin cancer, killing one-fifth of its victims within five years despite surgical removal of the lesions, chemotherapy and radiation treatment. Oncologists estimate that only 30 to 40 percent of all melanoma patients derive any benefit from standard chemotherapy, and most of those eventually suffer fatal recurrences.

This dire prognosis has spurred attempts by researchers worldwide to create a vaccine for melanoma patients. Last year, a California group eliminated skin tumors in all 25 participating melanoma patients by injecting the lesions with monoclonal antibodies against a particular fatty molecule sometimes present on the surfaces of cancer cells, although most of these patients later died from other melanoma tumors (SN: 5/26/90, p.324). Other research teams have shrunk melanoma tumors by inoculating them with killed melanoma cells, which apparently bolster the body's immune response (SN: 3/30/91, p.207).

Boon and his colleagues predict that their newly discovered protein will trigger a more specific antitumor response, potentially lengthening patients' lives. "The idea [to develop a melanoma vaccine] is certainly not new," Boon concedes. "But what is new is that we may now be able to vaccinate with a given antigen a person who we know carries this antigen on his tumor," thereby stimulating the immune system more effectively.

In the Dec. 13 SCIENCE, his group reports finding the antigen on some tumor cells taken from melanoma patients. They discovered the distinctive protein wedged into the cells' major histocompatibility complexes (MHC) — clumps of outer-membrane proteins that body cells use to tell each other from foreign cells.

In laboratory tests, the researchers found that the immune-system cells of patients with a particular type of MHC, known as HLA-A1, could detect tumor cells bearing the novel protein, recognize these cells as foreign, and kill them. The immune-system cells, called T-cells, ignored normal cells carrying HLA-A1 but lacking the tumor antigen.

HLA-A1 occurs in 25 percent of Caucasians but is less common in blacks and Asians.

Boon's group now plans to give immune-system cells to melanoma patients with HLA-A1 whose tumors make the newly discovered protein. However, he cautions, "we have no proof that this is going to work" to bolster the patients' rejection of their tumors.

Steven A. Rosenberg of the National Cancer Institute in Bethesda, Md., praises the new discovery. "This is an excellent piece of work," he says. "I'm thrilled."

Rosenberg and his colleagues are testing several gene-therapy treatments for melanoma, including one using tumor cells engineered with genes that code for two naturally occurring anticancer substances. Last May, he announced that his group was close to finding the gene for a melanoma tumor antigen (SN: 5/25/91, p.326). But he concedes that the European scientists got there first. — *C. Ezzell*

Software failure: Counting up the risks

When Boeing's new 777 airliner first takes to the skies in a few years, computers will control such crucial functions as setting flaps and adjusting engine speed. Electrical circuits will relay a pilot's actions to these computers, where complicated programs will interpret the signals and send out the instructions necessary for carrying out the appropriate maneuvers. Pilots will no longer fly the aircraft via direct electrical and mechanical controls, except when using an emergency backup system.

Because of the disastrous consequences of even a single fault, the software for such a computer system must be extremely reliable. A new analysis, however, demonstrates that testing complex software to estimate the probability of failure cannot establish that a given computer program actually meets such high levels of reliability.

The analysis also affirms that using multiple programs, which independently arrive at an answer to a given problem, doesn't necessarily guarantee sufficiently high reliability.

"This leaves us in a terrible bind," say Ricky W. Butler and George B. Finelli of the NASA Langley Research Center in Hampton, Va., the computer scientists who performed the analysis. "We want to use digital processors in life-critical applications, but we have no feasible way of establishing that they meet their ultra-reliability requirements."

In a paper presented last week in New Orleans at the Association for Computing Machinery's conference on software for critical systems, they argue: "Without a major change in the design and verification methods used for life-critical systems, major disasters are almost certain to occur with increasing frequency."

Many military aircraft and the European-built A320 airliner already use computer-controlled "fly-by-wire" systems. Computers also play important roles in medical technology, transportation systems, industrial plants, nuclear power stations and telephone networks — realms in which a software failure can cause tragedy (SN: 2/16/91, p.104).

"I think this is . . . an important paper," says David L. Parnas, a computer scientist at McMaster University in Hamilton, Ontario. "It's very convincing and provides a lot of insight."

The traditional method of determining the reliability of a light bulb or a piece of electronic equipment involves observing the frequency of failures among a sample of test specimens operated under realistic conditions for a predetermined period of time. Using these data, engineers can estimate failure probabilities of not only individual components but also entire systems.

Unlike hardware, however, software doesn't wear out or break. "Software