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 errors are the product of improper human reasoning," Butler says.

Unless they are caught, software errors persist throughout a system's lifetime. That makes conventional methods of risk assessment difficult to apply.

The problem is further compounded by the high degree of reliability required for life-critical applications. Historically, manufacturers of aircraft and other systems in which faults could threaten human lives have accepted a reliability level that corresponds to a failure rate of about 1 in a billion for every hour of operation.

Butler and Finelli demonstrate that techniques often used by computer scientists and programmers to quantify software risk take too long to be practical when used to assess systems that require such high reliability. For example, software design often involves a repetitive cycle of testing and repair, in which the program is tested until it fails. Testing resumes after the cause of failure is determined and the fault repaired.

But it generally takes longer and longer to find and remove each successive fault. To establish that a complicated computer program presents minimal risk would require years, if not decades, of testing on the fastest computers available, Butler says.

In an attempt to reduce the risk of failure, computer-system designers sometimes use multiple versions of a program, written by different teams, to perform certain functions. The idea is that although each version may contain flaws, it's highly unlikely that all or even a majority of the programs would contain the same error. However, experiments have shown that computer programs independently written to do the same thing often contain surprisingly similar mistakes.

Many computer experts at last week's meeting pointed to these findings as evidence that limits should be placed on the complexity of computer programs that go into life-critical applications. "Do we want to run with systems that are not as demonstrably safe as we say they are ... when we cannot demonstrate ultra-reliability before deployment?" asks Martyn Thomas of Praxis plc, in Bath, England.

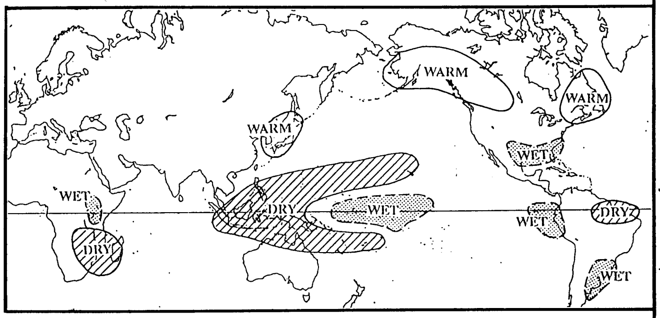
"We should build only those systems that rely on software to a degree that can be assessed," contends Bev Littlewood of City University in London, England. That means accepting a higher risk or building simpler computer systems.

A few remain optimistic. "Maybe we're being a lot more demanding than we need to be," says John D. Musa of AT&T Bell Laboratories in Murray Hill, N.J. "There are risks in everything we do in engineering."

He adds that software developers have a variety of tools and techniques that can help them deliver — if not assess — highly reliable systems. *— I. Peterson*

'Tis the season for an El Niño warming

After more than a year of perplexing signals, the Pacific Ocean has generated an El Niño warming that promises major changes in the world's weather through much of 1992, bringing floods to some regions and droughts to others. The emergence of this temporary oceanic fever signals a success for computer models that predicted when the event would occur and, perhaps more important, when it would not.



Typical temperature and precipitation patterns for November through March when El Niño warmings occur in the central Pacific.

Climate Analysis Center/NMC

In the past month, meteorologists have observed a number of El Niño traits that did not exist earlier in the year. In particular, a large region of the central equatorial Pacific has warmed enough to generate thunderstorms, which carry ocean heat into the atmosphere, warping the jet stream's flow.

"From the observations, it looks as though we're in the middle of a warm event," Chester Ropelewski said this week at the American Geophysical Union meeting in San Francisco. "These things are important for [altering] rainfall patterns around the world, and they're also important for temperature," explains Ropelewski, a researcher at the National Meteorological Center (NMC) in Camp Springs, Md.

Generated by a complex interplay between the Pacific Ocean and the atmosphere, El Niños recur at irregular intervals of four to seven years. They are associated with a pattern of atmospheric pressure called the Southern Oscillation. The name El Niño (Spanish for "the child") refers to the warm water's tendency to appear off South America's coast around Christmastime, ruining the region's anchovy harvest.

Although these coastal waters have yet to warm, scientists say the most important traits of the El Niño have already developed. The National Weather Service has factored the new evidence into its winter forecast for the United States. For instance, it calls for above-normal precipitation in the Southeast, in part because that region tends to receive increased rainfall during El Niños, says Gerald Bell of the NMC.

Other countries can also use the El Niño in predicting weather. In certain dry areas of Peru, Ropelewski says, farmers might plant crops that would survive the heavy rains that drench the coast during these warmings.

Scientists have theorized that El Niños originate because the size and shape of the Pacific basin provide just the right conditions for water and air masses to slosh from west to east and back again, creating a natural engine that generates the warmings.

The last El Niño ran from late 1986 through 1987. Warm water began appearing in the central Pacific early in 1990, leading some meteorologists to expect a full-fledged El Niño later that year. While nature fooled those forecasters, some machines fared better. One computer model at the Lamont-Doherty Geological Observatory in Palisades, N.Y., has forecast for two years that an El Niño would develop now rather than in 1990, says Stephen Zebiak, who developed the model with Mark Cane. Zebiak discussed the prediction at this week's meeting.

"That's really amazing. Even that far back, it was calling for the event to be now," he told SCIENCE NEWS. The Lamont-Doherty model resembles a simplified version of the atmospheric general-circulation models used for short-term weather forecasting. Unlike the weather models, however, this version includes an ocean that interacts with the atmosphere.

A statistical model run at the NMC also predicted an El Niño for late 1991, but that forecast did not emerge until early this summer. The NMC model, derived from one created at the Scripps Institution of Oceanography in La Jolla, Calif., uses past patterns to predict how the weather will evolve.

The modest success of these and other El Niño models offers hope that scientists can develop versions with even more predictive power. "Ten years ago, if anyone said we would have climate models that would give a handle on what will happen six months, nine months or a year ahead, people would have dismissed it," Ropelewski says. "We're really on the brink of a new era." *— R. Monastersky*