grasses and shrubs but provides marsh for herons and other species; crustaceans colonize debris from beaver dams. The Negev bacteria are also allogenic engineers.

The ecologists list six factors—including population density of an engineering species and the types of resources it controls—to help assess an engineer's importance to an ecosystem. The researchers hope that this framework can be used to make predictions about how, for instance, engineers that invade an ecosystem might alter it.

Researchers are already putting the concept to the test. Entomologist Bob Marquis and grad student John Lill of the University of Missouri, St. Louis, are studying how *Pseudotelphusa* caterpillars tie oak leaves together to form shelters. They have found that dozens of species—including spiders, weevils, and aphids—dwell in the shelters. By forcing researchers to look for those species that indirectly alter energy availability, the engineer concept "could help organize a great deal of what we're seeing in our experimental systems," says Marquis. Indeed, he says, it has prompted him and Lill to revise their research plan. Instead of merely observing engineers in action, says Marquis, "we are going to manipulate the leaves ourselves to quantify the effects of the leaf ties on the resulting ecosystems."

Others hope to put the concept to predictive use. Lawton and mathematician William Gurney of the University of Strathclyde in Glasgow, U.K., are trying to devise robust computer models that forecast how an engineer's activities could affect other species. "Experiments are now getting started," says Lawton, "but it will probably be a decade before we can really say what shape the models, and ultimately the theory, will take." Such models could someday be useful for protecting or restoring habitats. "It's hard to think about conserving ecosystems without considering the effects that engineers have on a system," says Shachak.

Experts agree that the nascent concept needs sharpening to help researchers home in on the engineers that, like keystone species, are crucial to an ecosystem's overall health. "At some level you could say that every organism is engineering its ecosystem and that this activity affects other organisms," says Alex Flecker, an ecologist at Cornell University in Ithaca, New York, who studies the ecosystem effects of fish that bulldoze sediments to find food in Andean streams. But "the important thing," Flecker says, is that the new concept has "organized the different types of engineering behavior we see in the field into a useful, testable framework."

–Joseph Alper

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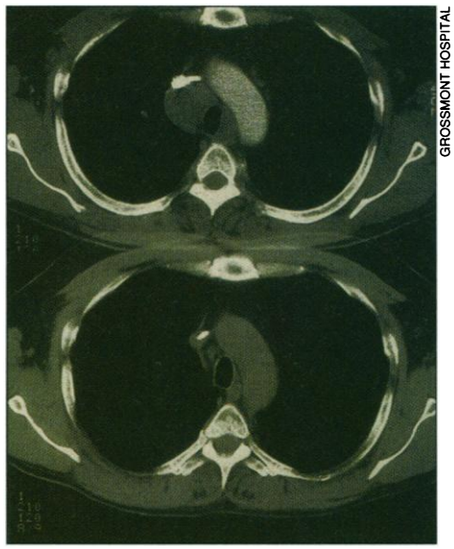
CANCER THERAPY

Antibodies Stage a Comeback In Cancer Treatment

As investors in new cancer therapies ought to know, the history of cancer research is rife with reports of cancer "cures" that all too often turn out to be ephemeral. In 1982, for example, immunologist Ron Levy of Stanford Medical Center raised the hopes of many when he reported in *The New England Journal of Medicine* that he had vanquished cancer in a patient, Philip Karr, using antibodies custom-designed to attack Karr's own lymphoma cells. In the wake of the resulting optimism, Levy co-founded IDEC Pharmaceuticals to commercialize his discovery, and other white-hot biotech companies pounced on the idea too. Expectations—and stock values—soared. "It was assumed [that antibodies] would be the final answer, that we could just produce them and the rest of cancer research could close up shop," recalls radiation oncologist Alan Lichter of the University of Michigan Medical School in Ann Arbor, who is president of the American Society of Clinical Oncology (ASCO).



GROSSMONT HOSPITAL

Antibodies attack. After treatment with IDEC's antilymphoma antibody, this patient's tumor near the heart *(top)* vanished *(above)*.

Then, in an object lesson in the dangers of hyping cancer therapies, hopes—and stock values—shriveled. Although Levy's antibody worked, the effects of other antibodies in humans didn't match those in mice, and unexpected toxicity even killed patients, bringing clinical trials to an abrupt halt. Antibodies vanished from page one, and many firms abandoned them.

But now, after a decade and a half of hard work, the tide may be turning again. Last fall, IDEC of San Diego finally received approval from the U.S. Food and Drug Administration (FDA) for an antilymphoma antibody, a cousin to Levy's original preparation. Just last week, researchers announced some success with an antibody tailored to fight recalcitrant breast cancers that is nearing regulatory approval. A handful of antibodies are in earlier stage clinical trials, with a smattering of positive results. And dozens more are in preclinical testing around the world. "We're entering a period of cautious optimism," says tumor immunologist Lloyd Old, director of the Ludwig Institute for Cancer Research in New York and co-organizer of an antibody meeting held in Manhattan last month.* Akhtar Samad, an analyst with the New York–based Mehta Partners, agrees: "We're in the early stages of renewed investor interest and confidence."

Researchers caution, though, that antibodies aren't the "magic bullets" hyped in the past, nor will they ever replace conventional cancer chemotherapy drugs. Indeed, so far results show that they may work best when combined with those drugs. "Typically in cancer treatment, you're looking at multiagent, multimodality therapy," says clinical oncologist Antonio Grillo-Lopez of IDEC.

The theory behind antibody therapy is straightforward. Antibodies are a first line of the body's defenses against infection. Each antibody grasps a specific target, or antigen, and holds on, meanwhile alerting the rest of the immune system to the intruder. Make antibodies that target antigens produced by tumors and inject them into the bloodstream, the theory went, and they would converge on a tumor and destroy it.

Some antibodies lived up to that promise—and continue to do so. For example, in the longest running clinical trial of a therapeutic cancer antibody, immunologist Gert Riethmüller of the University of Munich in Germany and colleagues report success in preventing colon cancer from spreading by giving, after surgery, a mouse antibody called Panorex, which targets a protein found in both normal and cancerous gut cells; this protein helps cells stick together and, in the case of cancerous cells, may help metastases to form. After 7 years

* Antibodies 1998, the Cancer Research Institute, New York, April 22–24.

of study, Panorex continues to be significantly more effective than control treatments, Riethmüller's team reports in the current issue of the *Journal of Clinical Oncology*. Riethmüller observed a 32% reduction in mortality—that is, 63% of 76 patients in the control group died, while only 43% of the 90 patients treated with Panorex died. There are occasional short-term side effects—severe nausea and diarrhea, presumably from the antibody's attack on normal gut cells—but such toxicity was considered manageable, particularly when only a few doses are given.

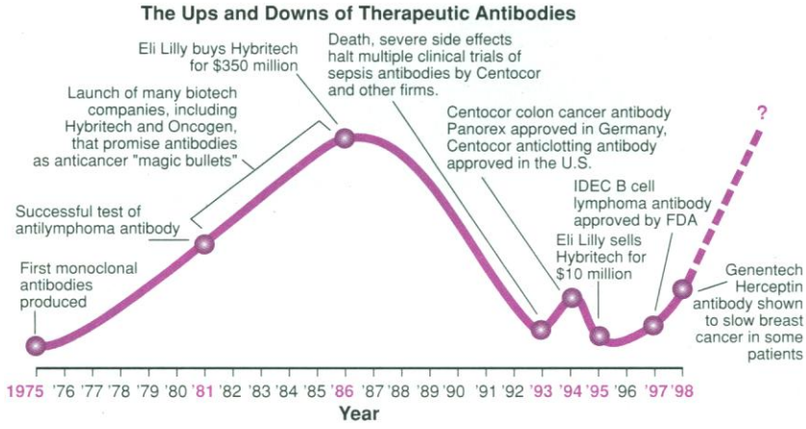
But other antibodies have been ineffective—or, worse, sparked lethal reactions. For example, in the early 1990s, several antibodies targeted against the blood infection sepsis went into late stage clinical trials—but patients who received them were found to be more likely to die than those who didn't. The trials were halted, and there is still no approved antibody treatment for sepsis. When it comes to antibody results, says oncologist Robert Cohen of Genentech, "it's hit or miss."

Some of the toxicity stems from antibodies attacking normal cells and some from the fact that most monoclonal antibodies are manufactured in mice, so human patients mount immune responses to the antibodies themselves. Researchers now have new strategies to get around that problem, by replacing varying amounts of the mouse antibody molecule with human antibody sequences. For example, IDEC's anti–B cell lymphoma antibody, Rituxan, is a half-mouse, half-human molecule. And it is aimed at a particular variant of a molecule called CD20, which is found only on B cells, especially cancerous ones. It causes only mild side effects such as fever, chills, and skin rash.

Rituxan apparently works: It matches or bests standard treatments in non-Hodgkin's lymphoma patients with poor outlooks. At the meeting, Grillo-Lopez reported that when the antibody was given together with chemotherapy, every one of 40 patients responded. Thirty-one of 38 evaluable patients were still in remission at last count. Twenty-nine months after the study, the group has already slightly exceeded the median time before relapse seen in patients who receive chemotherapy alone. Even when given alone, Rituxan caused tumors to shrink or disappear in nearly half of 166 patients who had exhausted other methods of therapy. Six percent were in complete remission, and the median survival time was 13.1 months.

Some immunologists consider lymphoma a special case, however, because cancer cells in the blood present an unusually accessible target for the injected antibodies. But recent work shows that well-designed antibodies can fight solid tumors, too.

At Genentech, researchers designed an anti–breast cancer antibody called Herceptin to attack a specific target: HER-2/neu, a growth factor receptor that is present in larger than normal amounts on some breast cancer cells. Numerous studies have shown that the unlucky 25% to 30% of breast cancer patients whose tumors produce more HER-2/neu have worse prognoses and shorter life expectancies.



Boom, bust, and boom? This representation of antibodies' fortunes illustrates how they enjoyed years of hype, fell out of favor, and are now gaining respect again.

Six years of clinical trials later, this design work has paid off. Last week at the ASCO meeting in Los Angeles, Genentech researchers announced that Herceptin can slow the progression of breast cancer in women whose cancer had already metastasized. When the antibody was combined with the chemotherapeutic drug taxol, 42% of 96 women with metastatic breast cancer responded, with tumors shrinking by half or more. That was much better than the 16% of 92 patients who improved with taxol alone. Addition of the antibody also seems to have extended the median time to relapse from 4 months to as much as 11 months. "Taxol is a pretty good drug," observes Cohen, who led the Herceptin project at Genentech. "Here, for marginal additional toxicity [to the patient], you get a huge amount of benefit."

Breast cancer patients who have exhausted other treatment options are already demanding the antibody, and the FDA has promised consideration within 6 months. "We estimate that 30,000 to 50,000 women would be eligible" to receive prescriptions for Herceptin if it is approved, says Cohen.

Still, Herceptin is not necessarily the "breakthrough" that some company representatives claim, says the University of Michigan's Lichter. For one thing, although the drug slows disease progression, it is too early to say that it prolongs women's lives. Lichter calls the response "modest" but significant in that it targets solid tumors.

And the Genentech team notes that Herceptin vindicates their strategy for reducing toxicity and humanizing antibodies. Herceptin began as a typical Y-shaped mouse monoclonal antibody. Genentech scientists replaced nearly all of it except the tiny pieces of the arms of the Y that actually contact the HER-2/neu antigen. "The antibody we're selling has about 5% original mouse sequences," says Cohen. The researchers also "fiddled with the hinge" at the base of the arms so that they could wrap around the antigen correctly.

Even so, researchers are aware that they must proceed with caution, for even "humanized" antibodies can be dangerous, as illustrated by a harrowing case study described at the meeting by oncologist Sydney Welt of the Memorial Sloan-Kettering Cancer Center in New York City. His team used a humanized version of a mouse monoclonal antibody, but the humanizing apparently hadn't gone far enough. Four out of 11 patients "developed significant anti-antibody activity," Welt reported. Worse, one late-stage cancer patient experienced stronger and stronger immune responses to each dose of antibody. Her kidneys clogged with immune complexes made of her own antibodies clinging to the therapeutic antibody. She suffered kidney failure and died. Welt's team has abandoned that antibody and is preparing others against the same target.

Still, the promising results with IDEC and Genentech antibodies, combined with new strategies for reducing toxicity, should draw new investment into the once-discredited field, predicts oncologist Lynn Schuchter of the University of Pennsylvania. "Clear-cut tumor responses" such as those in the Genentech study "will get industry interested in pursuing this again," she says. Seventeen years after his miracle cure, Philip Karr is still alive and healthy. And so is the science that saved him.

–Steven Dickman

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