Diverse Strategies to Vanquish Cancer

Researchers take aim at malignancy

By KATHLEEN FACKELMANN

During World War II, scientists realized that the chemical weapon known as mustard gas, used in World War I, could inhibit the growth of cells. A similar substance was found to be an effective treatment for cancer, a disease in which cells aggressively divide and invade other tissues.

Thus began modern medicine's reliance upon chemotherapy.

Many chemotherapeutic agents kill cancer cells by blocking their growth. However, drugs that kill a rapidly dividing malignant cell will also destroy rapidly dividing healthy cells, such as some of those in the intestinal lining, hair follicles, or blood. Thus a treatment that shrinks the tumor may also cause vomiting, hair loss, and a dangerous drop in white blood cells.

Most people would be willing to endure such ill effects if they could count on chemotherapy for a cure. Unfortunately, cancer has proved a vicious competitor.

For many people with a diagnosis of cancer, the first line of defense is surgery to remove the primary tumor. Then, to kill malignant cells that have made their way into the bloodstream, cancer specialists give a regimen of chemotherapy. This strategy generally succeeds for a while, but some cancer cells survive the chemical blast. Such cells are generally resistant to another round of chemotherapy. If they go on to form a second tumor, the cancer almost always proves lethal.

Many researchers now believe that indiscriminately blasting the body with chemotherapy is an outdated approach.

"The old way of thinking about tumor therapy is really the blitzkrieg idea—you blow out the tumor cells, and hopefully you don't take the patient with it," says Howard A. Fine of the Dana-Farber Cancer Institute in Boston.

Fine and others are focusing instead on key abnormalities that set a malignancy apart. This approach, they hope, will yield a guided missile that homes in on cancerous cells. In one such attempt, scientists are tailoring a drug to kill tumor cells that harbor a certain cancer-causing gene, or oncogene. In another, researchers have harnessed a virus to destroy cells having a certain genetic defect. In a third approach, Fine's team is blocking the tumor's voracious appetite for blood.

Although the three groups have taken different approaches, each is looking for a chink in cancer's armor.

The first group's work began with *Ras* genes, which are abnormal in half of all colon cancers, about 90 percent of pancreatic cancers, and smaller fractions of other human cancers. Like other oncogenes, *Ras* is a normal gene that, when damaged or mutated, directs the cell's machinery to manufacture a flawed protein. That abnormal protein then tells the cell to divide aggressively. Cancer can be the result.

Drugs designed to block that proliferation may prove effective against human cancer, according to a team working at the Merck Research Laboratories in West Point, Pa. These researchers searched fruitlessly for an antidote to the Ras protein for almost a decade, recalls Allen Oliff, executive director for cancer research at Merck. The company was poised to shut down the entire project in 1989, he recalls.

Then, Patrick J. Casey of Duke University Medical Center in Durham, N.C., and his colleagues showed that the cell modifies mutant Ras proteins before they send the signal to begin dividing wildly. The next year, Casey's team and several others showed that a cell enzyme called farnesyltransferase is at the heart of this malignant process. Without the enzyme, the mutant Ras protein can't instruct a cell to embark on a path of explosive growth.

The Merck team began testing a series of compounds that block farnesyltransferase. In theory, such chemicals would block abnormal cellular growth caused by mutant *Ras* genes.

To explore this possibility, the researchers first applied one of the chemicals to human cancer cells that carried a mutant *Ras* gene. The compound halted proliferation of those cells.

The researchers followed up with an animal study. Under the skin of nude (hairless) mice, which are especially susceptible to cancer, they implanted cancer cells containing damaged *Ras* genes and allowed growths to form. The treatment slowed the development of these cancers, Oliff says.

Another formulation of the same compound does more than block the growth of such tumors. The researchers relied on a line of mice genetically engineered to carry a mutant *Ras* gene. Such mice develop many breast and salivary gland

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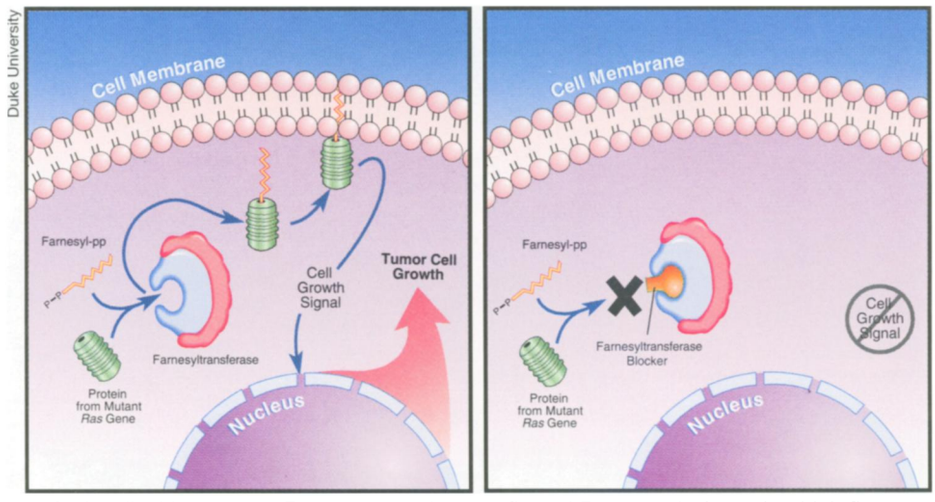

Left: A cell with a mutant Ras *gene produces a flawed Ras protein (green), which fits into the active site of the enzyme farnesyltransferase. The enzyme attaches a fat molecule called farnesyl-pp (yellow) to the protein, which allows the whole unit to move to the cell membrane. There, the Ras protein signals the cell's nucleus to start dividing. The process can lead to cancer. Right: An experimental drug (orange) blocks the enzyme's active site. The flawed Ras protein cannot get to the cell membrane, thus its malignant message never reaches the nucleus.*

cancers. The Merck team allowed tumors to develop and then injected the experimental drug.

The treated tumors "melt away" but return if the drug is discontinued, Oliff says. His team published that work in the August 1995 NATURE MEDICINE.

The company has yet to test such compounds on people with cancer, and Merck researchers don't make any promises about whether the drugs could get rid of a human cancer. If they could keep the tumor's growth in check, then a person with cancer might take a pill every day to prevent runaway cell growth.

Such compounds "ought to give a significant beneficial effect, assuming that human tumors behave like these model systems," Oliff says. He reviewed his team's findings March 25 at the American Cancer Society's 39th Science Writers' Seminar in Reston, Va.

When will such drugs reach the trial phase in humans? Oliff says that, after several wrong guesses, he has stopped making predictions. However, Casey and his colleagues have published a report that may speed up the development of drugs that block farnesyltransferase.

In the March 21 SCIENCE, Casey, Lorena S. Beese, also at Duke, and their colleagues nailed down the three-dimensional structure of farnesyltransferase. The precise configuration of the enzyme's active site (see cover) may help researchers at Merck and elsewhere tailor a drug that fits snugly and is thus more effective at stopping cancer, Casey says.

While Merck has placed its bet on the *Ras* gene, another company has focused on a different molecular aspect of cancer—abnormalities in a tumor-suppressor gene called *p53*. When working properly, the gene encodes a protein that regulates cell growth. For example, if something injures a cell's DNA, the p53 protein tells the cell to stop dividing until the damage has been repaired. When the *p53* gene is mutated, its protein product doesn't work properly, and the cell with the injured DNA keeps on dividing.

Mutated *p53* genes are found in about 50 percent of most human cancers. Frank McCormick, founder of ONYX Pharmaceuticals in Richmond, Calif., and his colleagues decided to zero in on cancer cells with a *p53* flaw. They have employed a virus, one that causes mild respiratory symptoms, as a novel cancer killer.

The California researchers altered an adenovirus so that it would replicate only in cells lacking a functional *p53* gene. In theory, the adenovirus would kill only cancer cells that had a flawed *p53*. When it encountered healthy cells, the virus couldn't replicate or kill, the researchers speculated.

Last year, they published evidence of this virus' tumor-killing abilities (SN: 11/30/96, p. 348). McCormick and his coauthors injected a solution of altered adenovirus into human cervical tumors growing in nude mice. The injections led to "significant reductions" in tumor size, the researchers noted in the Oct. 18, 1996 SCIENCE.

In some cases, the treatment annihilated the cancer. "There's no sign of any tumor," McCormick says.

Since that time, the drug company has teamed with clinical investigators to administer the altered virus to 23 people who have head and neck cancer. That trial is almost complete.

"The agent has been very well tolerated," ONYX's Christopher A. Maack told science writers at the cancer meeting. "We're up to very high doses now, and we see no toxicity at all," adds McCormick, now a consultant to ONYX and director of the University of California, San Francisco Cancer Center.

How well does the cancer therapy work in humans? Neither Maack nor McCormick will say. "We're trying to be very cautious about interpreting what's being seen," McCormick says. "We don't want to raise any false hopes." Maack says the company does plan to continue testing the treatment.

The company is already initiating trials with people who have tumors of the pancreas and ovaries. Those experiments are still in the very early stages, McCormick adds.

If killing cancer cells with a drug or a virus doesn't work, there's another approach: Starve the tumor.

Fine and his colleagues take advantage of another characteristic of malignant tumors—their need for a steady blood supply.

The researchers knew that tumors secrete substances, called growth factors, that entice new blood vessels to set up shop near the tumor. This blood vessel growth, called angiogenesis, brings in nutrients and oxygen, enabling the malignant cells to continue dividing.

The blood vessels surrounding a tumor also provide malignant cells with a path to the bloodstream. The cancerous cells can travel to distant parts of the body, a process that causes widespread, or metastatic, disease.

Fine and his colleagues have been exploring whether drugs that stop angiogenesis will slow down the growth and spread of human cancers. The scientists have focused on a lethal brain tumor known as glioblastoma. They implant human glioblastoma cells into the brains of nude mice, where the malignant cells become tumors.

Instead of injecting powerful drugs that act throughout the body, Fine's group is trying a more refined approach to inhibiting angiogenesis.

"It's a strategy we call targeted anti-angiogenesis," Fine says.

The strategy relies on an adenovirus to carry their active agent. The researchers insert into the virus the gene for platelet factor 4 (PF4), a substance that stops the growth of blood vessels. Next, they inject the altered adenovirus into the tumor-containing region of the animals' brains.

The researchers discovered that the tumors of mice treated with the altered adenovirus had fewer blood vessels than the tumors of the control mice, which received adenovirus without the gene. Moreover, the tumors in the treated mice were significantly smaller. Finally, the treated mice lived significantly longer than the controls.

The researchers believe that once injected into the tumor, the adenovirus infects many types of cells and makes each one crank out the *PF4* gene's protein. The blood vessels surrounding the tumor are thus bathed in the substance, which stops their proliferation, Fine says.

More recently, the researchers inserted a different gene, one that codes for a more powerful inhibitor of blood vessels, into the adenovirus. When they injected this virus into human tumors growing in mice, the tumors became smaller. Fine's team presented its results last month at the American Association for Cancer Research annual meeting in San Diego.

This strategy may turn cancer into a chronic disease, much like diabetes or hypertension, Fine says. Cancer patients would need to keep taking injections in order to keep their tumors in check. If they did so, the cancer would never expand beyond its boundaries. Stripped of its potential to spread, the cancer couldn't kill the patient, Fine speculates.

None of these three methods has met the ultimate test of a new cancer therapy—a large-scale human trial. Indeed, Merck's Ras-blocking drugs and the anti-angiogenesis method engineered by Fine and his coworkers have yet to be tested in people.

There's no doubt that all three will face challenges in the uncertain journey from the laboratory to federal approval. The Merck team's approach would kill metastatic cancer—if it can overcome the tendency of cancer cells to become resistant to the drug that blocks farnesyltransferase. Both Fine's team and the ONYX researchers may be limited to treating local tumors unless they can figure out a way to get the virus to spread to distant parts of the body.

Although they're not ready for a prime-time appearance, these novel methods of fighting cancer represent a tangible payoff from the recent explosion of knowledge about the molecular biology of cancer. Researchers may have more solid rewards within the decade. □