Chasing Cancer
New directions in research may finally break the stalemate.
By David H. Freedman
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Sept. 19, 2006 issue - You've probably never heard of Theodor Boveri, but his insight into cancer might save your life someday. It certainly has scientists buzzing. "Everyone cites Boveri in their papers, and he gets talked about at a lot at conferences," says Peter Sorger, an MIT biologist who studies cancer. The acclaim comes a little late for Boveri; he died in 1915. But a year before that he noted that tumor cells under a microscope showed mix-ups in their chromosomes. These X-shaped blobs of DNA, found in almost every human cell, contain the 25,000 or so genes that form the blueprint for a human being. A cancerous tumor, Boveri reasoned, begins with a single cell in which the stuff of chromosomes accidentally gets scrambled, misdirecting the cell to divide uncontrollably.

For most of the following century that notion received little more than a shrug from biologists, who saw genetic scrambling as a symptom, and not a cause, of cancer. But over the last five years a growing number of researchers, many of them at the top of the field, have come to believe that Boveri may have been right. They argue that focusing on his chromosome-scrambling idea (or a modified version of it) may finally enable scientists to unlock the disease's most elusive secrets. "This is the mechanism by which all other bad stuff happens," says Prasad Jallepalli, a researcher at Memorial Sloan-Kettering Cancer Center in New York.

Not everyone is converting to the new approach. Since the late 1980s, researchers have focused on the theory that cancer emerges when a specific handful of genes in a single cell are faulty, through some combination of inheritance and "random mutation"—that is, when the cell divides and creates two copies of its genes, giving one of the new cells a bad copy. Ever since then the cancer-research community has focused intensely on finding the six to 10 specific faulty oncogenes believed to be involved in each form of cancer. Once the oncogenes are identified, goes the theory, it will be possible to develop drugs that counteract the effect of one or more of them. The vast majority of funding continues to back oncogene research. Only a dozen or so labs focus on Boveri's large-scale gene scrambling as a key to understanding cancer.

Yet the traditional method has had mixed results. Over the last two decades, researchers around the world have been breeding mutant mice with faulty oncogenes that readily grow tumors. In many cases, to be sure, researchers have found chemicals that shrank or prevented the tumors. But the result has been hundreds of drugs that cure cancer in mutant mice—and don't do much for human cancer victims. Meanwhile, cancer is still killing about 7 million people worldwide every year. Although more people are surviving cancer because it is typically detected earlier on, when it comes to treating adult cancers caught after the earliest stages, survival rates for adults grouped by age have barely budged since 1950. And that's despite the fact that in the United States alone, some $6 billion a year is sunk into cancer research. A few new drugs like Gleevec and Iressa have had good results—but only for a tiny fraction of patients with highly specific forms of cancer, and even in these patients the disease often becomes resistant to the treatment.

Ever since the late 1990s some scientists, mulling over the meager results of the consuming hunt for oncogenes, have gravitated instead to a theory put forth by Lawrence Loeb, now at the University of Washington in Seattle. Given the low rate at which normal cells create copies with bad genes, Loeb pointed out, the chances of a cell's being hit with the exact set of oncogenes needed to trigger cancer should be so low that cancer would hardly ever turn up in anyone, never mind strike almost half the population. The best explanation, he theorized, was that cancer emerges only when something happens to a cell to make it "genetically unstable"—that is, to keep it from doing an accurate job of copying its genes. Once a cell and its offspring start messing up large numbers of their genes on a regular basis, the chances of one of these unstable cells' hitting a gene sequence...
needed to become cancerous might become pretty good. "If getting the right combinations of mutations for cancer in a cell is like winning the lottery, then instability is a way to buy many, many lottery tickets," says Jallepalli.

A random shuffling or modification of at least part of a chromosome—and thus of the genes that compose it—is now seen by some top researchers not only as a potential trigger for cancerous growth, but also as the key to how a tumor acquires the ability to invade surrounding tissue, spread through the body and resist treatment. They argue that focusing on this genetic instability offers the best hope of besting many, if not most, forms of cancer in a decade or two—and possibly of making real headway in treatment far sooner than that. "If we could figure out how to use existing drugs to exploit newly understood chinks in the armor of cancer cells, we might be able to get striking responses from some patients in two or three years' time," says Robert Weinberg, a scientist at MIT's Whitehead Institute who is considered a pioneer in modern cancer research.

Cancer's dependence on genetic instability could help explain why drugs that work on lab mice don't work on people: the genetically engineered mouse tumors are relatively stable, which makes them easy to knock out. A naturally occurring cancer tumor, by contrast, is a continuously evolving crazy quilt of cancerous cells—a moving target capable of building up resistance to any drug that comes close to working. "This means that chemotherapy that targets oncogenes is not going to be effective," says Loeb. A large study, published last week, of the mutant genes in breast and colorectal tumors underscores how flawed the handful-of-oncogenes approach is: the study found that 189 different genes are frequently mutated in these tumors, and that any given tumor cell has an average of 90 mutated genes.

Proponents of the new approach hold out hope for more effective strategies for besting cancer. They also point out that because genetic instability appears to be a fundamental characteristic of most tumor cells, any instability-based technique that proves effective on one type of cancer might well work on most types. That could theoretically mean a near-universal treatment for cancer, perhaps even a cure. "Instability may be an obstacle that prevents us from coming up with a great therapy," says Bert Vogelstein, a biologist at Johns Hopkins University. "But it may prove to be cancer's Achilles' heel." If conventional cancer researchers are like mechanics trying to fix broken cars by catching everything that could go wrong with every component of every car, then instability researchers are like quality-control engineers focusing on the factory line that's causing all the problems.

Vogelstein, widely considered one of the leading cancer researchers in the world, heads one of several groups searching for "master genes"—genes that, if randomly mutated, may destabilize the rest of the genes by interfering with a cell's ability to make accurate copies of its chromosomes. Master genes would be fertile targets for a drug that could stabilize the genes in a tumor's cells, slowing down their wild evolution and possibly cutting off their ability to become increasingly virulent and drug-resistant. About an eighth of all cancers have already been linked to specific genes that cause instability, Vogelstein says. His group will soon report on new genes that will add more types of cancer to the list. In theory, these destabilizing genes could point the way to new drugs. But this approach would be more effective, says Loeb, if instability could be pinned down to a mere handful of genes, so that drugs can hit them all. "There may be a hundred genes involved in instabilities," he says. "That would be disappointing."

Treatment wouldn't necessarily be dependent on countering the genes that cause instability, says Loeb. Instead, a drug could aim to help cells repair errors made during genetic copying, which might have much the same effect. Such drugs are already in the pipeline, he says, and could be available in about five years. Yet another, more radical approach would be to perform a sort of jujitsu-style attack on cancer cells through a drug that increases cellular instability in a patient. The idea is that healthy cells would cope with a little extra instability via normal repair mechanisms, but tumor cells would be pushed over the edge into a chaotic process of gene replication resulting in so many genetic errors that the cells wouldn't survive. "That's the stinger in the tail with instability," says Ashok Venkitaraman, a Cambridge University researcher who heads a group dedicated to finding treatments based on instability. "A genetically unstable cell is usually less able to survive and grow. We've
reached the point where we understand enough about these sorts of mechanisms so that we can start to convert them into cancer treatments that have the potential to change people's lives.

If treatments based on instability prove elusive, researchers may still be able to enlist genetic instability to identify cancers earlier and more accurately than ever before, so that they can be cured via surgical removal. Vogelstein notes that cells with genetic scrambling can already be picked up in the blood of cancer patients, which suggests that catching cancer early may end up a matter of a routine blood test. That in itself is a hurdle for researchers, though. "Early diagnosis is undervalued in the research community, because prevention isn't as dramatic as curing," says Vogelstein. "Pharmaceutical companies are more interested in treatment, because they make drugs, and they account for a large part of the cancer-research budget." And so much time, money and expectation have been staked on the oncogene approach that abandoning it would be a demoralizing admission of defeat and, in many cases, a career sinker. "The way science works is, when you end up backing a theory you can't afford to be wrong or your grant will suffer," says UCLA researcher Jeffrey H. Miller.

Then there's the problem of Peter Duesberg. Up until the 1980s Duesberg, a researcher at the University of California, Berkeley, was one of the most respected research biologists in the world—he was one of the founding fathers of the oncogene effort. But he attracted the disdain of many medical researchers by questioning whether HIV causes AIDS long after that relationship had been widely accepted as fact. Duesberg has since put his energy behind backing the theory that cancer is caused by a mix-up in chromosomes. Even though many esteemed researchers now say much the same (albeit with more qualifications), Duesberg's prominent backing has given the new approach a black eye, some scientists suggest. "When other scientists evaluate his ideas about cancer, they seem to be thinking about his AIDS theory," says one scientist, who spoke on the condition of anonymity because the research community tends to frown on anybody who cuts Duesberg some slack.

Many scientists and funding administrators often simply choose to ignore a promising avenue of research until pressured to do so; careers are more easily advanced by sticking with accepted paths even when they may be wrong. That places the ball squarely in the public's court, says Benjamin Djulbegovic, a researcher at the University of South Florida who studies clinical trials of new cancer therapies. "There's dissonance between what researchers study and what patients need," he says. "When there are competing research agendas, there needs to be public discourse on who should control those agendas." Given cancer's toll, maybe it is time for the public to have more of a say in how cancer-research dollars are spent. And if the public does speak up, it probably wouldn't defend the status quo. Call it Boveri's revenge.


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