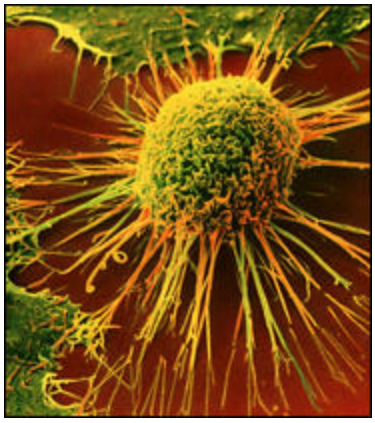
The New York Times
ON THE WEB
Health

PREVENTING CANCER

Slowly, Cancer Genes Tender Their Secrets

By GINA KOLATA

Jay Weinstein found out that he had chronic myelogenous leukemia in 1996, two weeks before his marriage.



Quest/Photo Researchers Inc.

A cervical carcinoma cell with cytoplasmic projections, as seen through an electron microscope.

He was a New York City firefighter, and he thought his health was great.

He learned that there was little hope for a cure. The one treatment that could save him was a bone marrow transplant, but that required a donor, and he did not have one. By 1999, his disease was nearing its final, fatal phase. He might have just weeks to live.

Then, Mr. Weinstein had a stroke of luck. He managed to become one of the last patients to enroll in a preliminary study at the Oregon Health & Science University, testing an experimental drug.

Mr. Weinstein is alive today and still taking the drug, now on the market as Gleevec. Its maker, Novartis, supplies it to him free because he participated in the clinical trial.

Dr. Brian Druker, a Howard Hughes investigator at the university's Cancer Institute, who led the Gleevec study, sees Mr. Weinstein as a pioneer in a new frontier of science. His treatment was based not on blasting cancer cells with harsh chemotherapy or radiation but instead on using a sort of molecular razor to cut them out.

That, Dr. Druker and others say, is the first fruit of a new understanding of cancer as a genetic disease. But if cancer is a genetic disease, it is like no other in medicine.

With cancer, a person may inherit a predisposition that helps set the process off, but it can take decades - even a lifetime - to accumulate the additional mutations needed to establish a tumor. That is why, scientists say, cancer usually strikes older people and requires an element of bad luck.

"You have to get mutations in the wrong place at the wrong time," Dr. Druker says.

Other genetic diseases may involve one or two genetic changes. In cancer, scores of genes are mutated or duplicated and huge chunks of genetic material are rearranged. With cancer cells, said Dr. William Hahn, an assistant professor of medicine at Harvard Medical School, "it looks like someone has thrown a bomb in the nucleus."

In other genetic diseases, gene alterations disable cells. In cancer, genetic changes give cells a sort of superpower.

Phil Marino for The New York Times

Jay Weinstein with the drug Gleevec, which has helped him battle his myelogenous leukemia.

At first, as scientists grew to appreciate the complexity of cancer genetics, they despaired. "If there are 100 genetic abnormalities, that's 100 things you need to fix to cure cancer," said Dr. Todd Golub, the director of the Cancer Program at the Broad Institute of Harvard and M.I.T. in Cambridge, Mass., and an oncologist at the Dana-Farber Cancer Institute in Boston. "That's a horrifying thought."

Making matters more complicated, scientists discovered that the genetic changes in one patient's tumor were different from those in another patient with the same type of cancer. That led to new questioning. Was every patient going to be a unique case? Would researchers need to discover new drugs for every single patient?

"People said, 'It's hopelessly intractable and too complicated a problem to ever figure out,' " Dr. Golub recalled.

But to their own amazement, scientists are now finding that untangling the genetics of cancer is not impossible. In fact, they say, what looked like an impenetrable shield protecting cancer cells turns out to be flimsy. And those seemingly impervious cancer cells, Dr. Golub said, "are very much poised to die."

The story of genes and cancer, like most in science, involves many discoveries over many years. But in a sense, it has its roots in the 1980's, with a bold decision by Dr. Bert Vogelstein of Johns Hopkins University to piece together the molecular pathways that lead to cancer.

It was a time when the problem looked utterly complicated. Scientists thought that cancer cells were so abnormal that they were, as Dr. Vogelstein put it, "a total black box."

But Dr. Vogelstein had an idea: what if he started with colon cancer, which had some unusual features that made it more approachable?

Colon cancer progresses through recognizable phases. It changes from a tiny polyp, or adenoma - a benign overgrowth of cells on the wall of the colon - to a larger polyp, a pre-cancerous growth that, Dr. Vogelstein said, looks "mean," and then to a cancer that

pushes through the wall of the colon. The final stage is metastasis, when the cancer travels through the body.

"This series of changes is thought to occur in most cancers, but there aren't many cancers where you can get specimens that represent all these stages," Dr. Vogelstein said.

With colon cancer, pathologists could get tissue by removing polyps and adenomas in colonoscopies and taking cancerous tumors in surgery.

Colon cancer was even more appealing for such a study because there are families with strong inherited predispositions to develop the disease, indicating that they have cancer genes that may be discovered.

So Dr. Vogelstein and his colleagues set out to search for genes "any way we could," Dr. Vogelstein said. Other labs found genes, too, and by the mid-1990's, scientists had a rough outline of what was going on.

Although there were scores of mutations and widespread gene deletions and rearrangements, it turned out that the crucial changes that turned a colon cell cancerous involved just five pathways. There were dozens of ways of disabling those pathways, but they were merely multiple means to the same end.

People with inherited predispositions to colon cancer started out with a gene mutation that put their cells on one of those pathways. A few more random mutations and the cells could become cancerous.

The colon cancer story, Dr. Druker said, "is exactly the paradigm we need for every single cancer at every single stage."

But scientists were stymied. Where should they go from there? How did what happens in colon cancer apply to other cancers? If they had to repeat the colon cancer story every time, discovering genetic alterations in each case, it would take decades to make any progress.

The turning point came only recently, with the advent of new technology. Using microarrays, or gene chips - small slivers of glass or nylon that can be coated with all known human genes - scientists can now discover every gene that is active in a cancer cell and learn what portions of the genes are amplified or deleted.

With another method, called RNA interference, investigators can turn off any gene and see what happens to a cell. And new methods of DNA sequencing make it feasible to start asking what changes have taken place in what gene.

The National Cancer Institute and the National Human Genome Research Institute recently announced a three-year pilot project to map genetic aberrations in cancer cells.

The project, Dr. Druker said, is "the first step to identifying all the Achilles' heels in cancers."

Solving the problem of cancer will not be trivial, Dr. Golub said. But, he added, "For the first time, we have the tools needed to attack the problem, and if we as a research community come together to work out the genetic basis of cancer, I think it will forever change how we think about the disease."

Already, the principles are in place, scientists say. What is left are the specifics: the gene alterations that could be targets for drugs.

"We're close to being able to put our arms around the whole cancer problem," said Robert Weinberg, a biology professor at the Massachusetts Institute of Technology and a member of the Whitehead Institute. "We've completed the list of all cancer cells needed to create a malignancy," Dr. Weinberg said. "And I wouldn't have said that five years ago."

The list includes roughly 10 pathways that cells use to become cancerous and that involve a variety of crucial genetic alterations. There are genetic changes that end up spurring cell growth and others that result in the jettisoning of genes that normally slow growth. There are changes that allow cells to keep dividing, immortalizing them, and ones that allow cells to live on when they are deranged; ordinarily, a deranged cell kills itself.

Still other changes let cancer cells recruit normal tissue to support and to nourish them. And with some changes, Dr. Weinberg said, cancer cells block the immune system from destroying them.

In metastasis, he added, when cancers spread, the cells activate genes that normally are used only in embryo development, when cells migrate, and in wound healing.

But so many genetic changes give rise to a question: how does a cell acquire them?

In any cell division, there is a one-in-a-million chance that a mutation will accidentally occur, Dr. Weinberg notes. The chance of two mutations is one in a million million and the chance of three is one in a million million million million.

This slow mutation rate results from the fact that healthy cells quickly repair damage to their DNA.

"DNA repair stands as the dike between us and the inundation of mutations," Dr. Weinberg said.

But one of the first things a cell does when it starts down a road to cancer is to disable repair mechanisms. In fact, BRCA1 and 2, the gene mutations that predispose people to breast and ovarian cancer, as well as some other inherited cancer genes, disable these repair systems.

Once the mutations start, there is "a kind of snowball effect, like a chain reaction," Dr. Vogelstein said.

With the first mutations, cells multiply, producing clusters of cells with genetic changes. As some randomly acquire additional mutations, they grow even more.

In the end, all those altered genes may end up being the downfall of cancer cells, researchers say.

"Cancer cells have many Achilles' heels," Dr. Golub says. "It may take a couple of dozen mutations to cause a cancer, all of which are required for the maintenance and survival of the cancer cell."

Gleevec, researchers say, was the first test of this idea. The drug knocks out a gene product, abl kinase, that is overly abundant in chronic myelogenous leukemia. The first clinical trial, which began seven years ago, seemed like a long shot.

"The idea that this would lead to therapy was something you wrote in your grant application," said Dr. Charles Sawyers, a Howard Hughes investigator at the University of California, Los Angeles. "It wasn't anything you believed would happen soon."

But the clinical trial of Gleevec, conducted at the Oregon Health & Science University, U.C.L.A. and M. D. Anderson Cancer Center in Houston, was a spectacular success. Patients' cancer cells were beaten back to such an extent that the old tests to look for them in bone marrow were too insensitive, Dr. Sawyers said.

Gleevec is not perfect. It is expensive, costing about $25,000 a year. It is not a cure: some cancer cells remain lurking, quiescent and ready to spring if the drug is stopped, so patients must take it every day for the rest of their lives. And some patients are now developing resistance to Gleevec.

Still, Dr. Sawyers says, "Seven years later, most of our patients are still doing well." Without Gleevec, he added, most would be dead.

As for the future of cancer therapy, Dr. Golub and others say that Gleevec offers a taste of the possible.

Dr. Golub said he expected that new drugs would strike the Achilles' heels of particular cancers. The treatment will not depend on where the cancer started - breast, colon, lung - but rather which pathway is deranged.

"It's starting to come into focus how one might target the problem," Dr. Golub said. "Individual cancers are going to fall one by one by targeting the molecular abnormalities that underlie them."

And some cancer therapies may have to be taken for a lifetime, turning cancer into a chronic disease.

"Seeing cancer become more like what has happened with AIDS would not be shocking," Dr. Golub says. "Does that mean cure? Not necessarily. We may see patients treated until they die of something else."

That is what Mr. Weinstein hopes will happen with him. The cancer is still there: new, exquisitely sensitive tests still find a few cells lurking in his bone marrow. And Gleevec

has caused side effects. Mr. Weinstein says his fingers and toes sometimes freeze for a few seconds, and sometimes he gets diarrhea.

But, he said, "Certain things you put out of your mind because life is so good."