



SMART

MEDICINE

TARGETING
CANCER
INSIDE
AND
OUT



When Hubbard, Ohio, radiologist Jim Goettsch, D.O., heard ringing in his ears, he first chalked it up to aging. But at 53, it just didn't seem right. He ordered his own MRI, which came back negative. He breathed a sigh of relief and kept working. Less than a month later, however, his legs became unusually tired. As a physician, he knew the combination of ringing in his ears and leg fatigue might mean something terrible. He ordered another MRI, this time with a contrast dye that showed the difference between various internal-tissue densities. He took one look at the image and thought, "I'm dead."

The image wasn't one he had seen often in his practice. In fact, it was one of the deadliest forms of brain tumor – a glioblastoma.

Dr. Goettsch immediately underwent surgery, which removed about 80 percent of the tumor. In addition, he began chemotherapy and radiation therapy, both typical treatments for brain tumor patients. At the conclusion of his therapy the tumor hadn't grown any, but it also wasn't any smaller. The outlook remained grim: Dr. Goettsch was given less than a year to live.

Faced with that devastating news, he volunteered to take a new chemotherapy drug called Tarceva. This drug, in theory, would target specific cells within the tumor rather than kill off cells in general, the way traditional chemotherapy does. Dr. Goettsch credits Tarceva with allowing him to continue living months beyond that fatal prediction.

Modifying Chemotherapy

Cancer isn't a single disease; it is numerous diseases with one key factor in common: Somewhere in the body, the natural process of new cells dividing to replace those that have died spirals out of control. Cells proliferate at a fierce rate, causing an unnatural growth. If that growth continues, other organs and body processes are affected and possibly shut down.

To stop the unwanted growth, patients typically undergo chemotherapy. While it

can be effective, traditional chemotherapy uses too broad of a brush. Good cells die along with the bad, often causing terrible, debilitating side effects and weakening a person's immune system. Scientists are looking to modify this approach – to make chemotherapy "smarter" and more effective in killing cancer while having little-to-no negative side effects on the patient.

Genetics and Cell Growth

Some researchers refer to the emerging field of targeted medicine as "personalized" medicine. While one person may beat cancer, another may die – even if the two tumors look exactly the same. Why? What makes the individual difference?

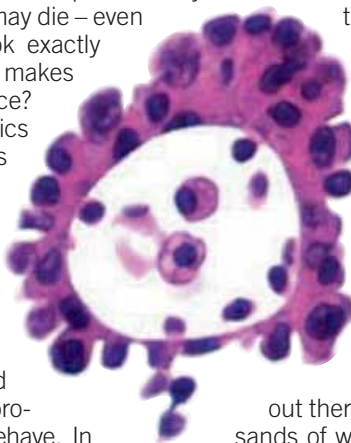
That's where genetics comes in. Genetics control the way cells behave and function. Fifty years ago the discovery of DNA set scientists on the journey to uncover more details about how cells – and the molecules and proteins within them – behave. In 2003, the finished mapping of the human genome gave researchers even more information about finding ways to attack cancer at the cellular level.

Joseph Crowe, M.D., director of the Cleveland Clinic's Breast Center, calls the sequencing of the human genome "huge." "Over the past 50 years, major steps have been made in understanding how DNA governs the growth of cells, the behavior of cells," he explains. "In many respects, we're way ahead of the ballgame because we know a lot about the structure of what makes us human. Our job now is to figure out, of all the DNA that we have, what is the important DNA and what does it do?"

Is it the person's genetics, meaning the wiring he or she was born with, that can predict the likelihood of who will get – or who will recover from – cancer? Or does recovery depend on the genetic make-up of the tumor itself? Likely, it is both.

Currently, one of the best examples of a genetic cause of cancer is in patients who carry the genes for breast cancer, called BRCA-1 and BRCA-2. But of all the types of breast cancer

out there that impact the lives of thousands of women each year, only an estimated five percent of women carry either of those genes. However, that information is critical to those five percent: If a woman carries even one of those genes, she has up to an 85 percent chance of developing the disease.



A DNA strand (image, left), and an epithelial cancer cell (image, right) called an adenocarcinoma.

Research is being done, as well, on who might recover from cancer. Once a person develops cancer, how he or she responds to drugs might be estimated by a look at the individual's genetic make-up. "An area of interest is the side effects of chemotherapy," says Ronald Bukowski, M.D., director of Experimental Therapeutics in the Cleveland Clinic Taussig Cancer Center. "We're just starting to learn the kinds of genes people carry that can predict for slow metabolism of the drugs, and therefore, greater side effects for so many medicines."

But predicting a person's responsiveness through genetics has to take into account other variables. "There's a certain amount of basic genetic instability that's present in all living organisms," says Michael Vogelbaum, M.D., Ph.D., associate director of Neurosurgical Oncology at the Clinic's Brain Tumor Institute. "Much of this instability is environmentally influenced. And much of it is random."

Still, many scientists believe that since most cancers occur randomly, caused by something triggering the cells to grow out of control, it's best to focus on the genetic make-up of the tumor, rather than the person.

"The nature of cancer is such that it's a process where you lose growth control in some part of the body," says Derek

Raghavan, M.D., Ph.D., chairman and director of the Taussig Cancer Center. "Our understanding of the human genome has allowed us to get a better handle on what controls growth. In some cases, activation of certain genes allows stimulation of unwanted growth, turning normal tissue cancerous. If we can identify those genes, the trick then becomes to block them and therefore block the growth."

Adds Dr. Bukowski: "You identify something in the tumor that you think is a critical determinant of that cancer cell and how it functions. Then you develop a drug that can interfere with it, bind to it. That something can be on the surface of the cell or it can be inside the cell. It also could be something outside of the tumor cell that the cell then takes inside and is consequently destroyed."

Missing Puzzle Pieces

Traditionally, cancer doctors have given patients an estimate of how they'll do based on what life-cycle stage the cancer is at and how far the cancer has spread to other organs. Now tumor genomics, which looks at the genetic make-up of a tumor, is playing a role in assessing the treatment protocol and projected outcome for the patient.

Physicians are using genomics to help decide the course of treatment for patients with a type of primary brain tumor called an oligodendroglioma.

Researchers have known for many years that genetic alterations are present in a wide variety of brain tumors. But only within the last five years have physicians been able to use this information as a tool to decide the treatment regimen for a patient.

It turns out that some oligodendrogliomas are missing pieces of two different chromosomes, called 1p and 19q. Like two jigsaw puzzle pieces whose interlocking knobs are missing, they do not fit together. The genetic information in these tumors is incomplete.

"In a study conducted five years ago, researchers showed that the subset of patients who responded to chemotherapy were the patients who were missing these chromosomes," says Susan Staugaitis, M.D., Ph.D., a researcher in the department of Neurosciences and Anatomic Pathology at the Clinic's Lerner Research Institute. "That was a big splash because it was one of the first times in brain tumors where there was a molecular predictor of prognosis." In other words, patients who had both incomplete puzzle pieces in their brain tumors got better with chemotherapy. Patients who had oligodendrogliomas that still had all their chromosomes intact didn't do as well.

Today, each patient who has a brain tumor gets a biopsy of that tumor. The physicians can send the biopsy to an



"If we can identify those genes, the trick then becomes to block them and therefore block the [tumor] growth."

Derek Raghavan, M.D., Ph.D., Chairman and Director, Cleveland Clinic Taussig Cancer Center

Small cell carcinoma

"You identify something in the tumor that you think is a critical determinant of that cancer cell and how it functions. Then you develop a drug that can interfere with it, bind to it."

Ronald Bukowski, M.D.

approved reference laboratory that uses a specialized process to specifically look for the absence of 1p and 19q. In general, if the patient is missing these chromosomes, he or she will probably be given chemotherapy before radiation.

In another example, breast cancer researchers have discovered "gene patterns" within breast cancer tumors that may play a bigger role than previously thought in determining a woman's outcome in treatment.

"If we look at a car, we can tell what make it is, and we know a lot about it just by looking at it because of the exterior appearance. Or, we think we do," explains Dr. Crowe. "But what we really don't know is what the performance of that car is going to be. Does it run? Can you even turn it on? If you turn it on, how fast is it going to go?" In this analogy, it's as if the tumor genes are the engine. Looking for gene patterns or biomarkers may be the future of predicting outcome.

"We've always done things the same way for everybody," says Dr. Crowe. "What I'd like to see is to take cancerous tissue and do a biochemical analysis. Rather than subject a breast cancer patient to a large operation, radiation and chemotherapy, we would be able to begin a tailored systemic medical treatment that would be easy for the patient to tolerate and would be something she would take for a long time. While it's hard to think about this as an aspirin a day, it may not be that far from the truth."

Targeted Drugs

The key in getting to that point, however, is the development of smart drugs, which is well on its way. "What used to be an occasional trial is now turning into the

predominance of trials of targeted agents," says Dr. Vogelbaum.

Although targeted therapy is growing rapidly, it's actually been around since the 1970s. One of the first smart drugs was tamoxifen, used to treat breast cancer. Discovered in the 1970s, Dr. Crowe holds it up today as still "the single most important drug for breast cancer ever."

Tamoxifen targets a part of the cell called the estrogen receptor protein. This protein attracts estrogen to it, allowing cancer growth. Tamoxifen blocks the interaction of the estrogen on the estrogen receptor protein, stopping this process.

In addition to treating breast cancer, tamoxifen also is given to women who are at high risk of developing this disease. This way the process can be blocked before it has even started. But, because estrogen receptors aren't present in all breast cancers, tamoxifen won't work for all women.

A different receptor, called epidermal growth factor receptor or EGFR, appears to be a key area in glioblastomas, the type of brain tumor Dr. Goettsch has. In 2002, the Clinic was one of the first medical centers to start clinical trials of the drug Tarceva in patients with glioblastomas. The drug also is being tested for treatment in other types of cancer, including lung cancer.

"Tarceva is designed to be a smart drug," explains Dr. Vogelbaum. "High levels of EGFR are seen only in a tumor. In the rest of the body there are normal levels of EGFR. If the receptor is there, the drug affects it. If the receptor isn't there, it should not affect that cell."

So, in theory, the Tarceva would be drawn to the tumor cells by sheer numbers, and wouldn't cause many side effects in the rest of the body. The Clinic's initial study showed an astounding 40 percent response rate.

Like Tarceva, a new, targeted drug called Avastin also has been approved by the FDA. Avastin binds to a different receptor, this one called the vascular endothelial growth factor or VEGF. This growth factor, however, deals with the vascular element of cancer so, rather than acting like a barrier to block the receptor from getting what it needs to interact and create the cancer, the drug works more like a rubber band, choking off the blood vessels that feed the tumors. It is the first drug of its kind to work this way on a tumor, starving the blood vessel production to the tumor, medically termed "angiogenesis."

Unfortunately, Avastin doesn't work across the board. It had little effect on breast or lung cancer, but great effect shrinking colon cancer tumors. "Avastin was tried in colon cancer patients, along with chemotherapy, and there was a definite improvement in how the patient did," says Dr. Bukowski. "Patients lived longer. The tumors were smaller. It was a very significant difference." In fact, Dr. Bukowski says, the research strongly supports using a combination of Tarceva and Avastin, especially for kidney cancer.

The area of targeted drug development has evolved from targeting receptors to also targeting critical enzymes within the cancer cell. Sometimes, it's even a dozen enzymes that all function together. Two enzyme-targeting drugs, as yet unnamed, are in trials right now for kidney cancer. But Dr. Bukowski likes what he sees so far. "These drugs will change how we treat the disease," he says. "This is an example of medicine where the target is not just one molecule, one receptor. It's multiple targets in the cell."

(Continued on next page)

“[W]hen we know that a certain group of patients have their cancers behaving because of a certain biochemical or molecular pathway, we can develop for those patients a very specific, not very toxic treatment.”

Joseph Crowe, M.D.

Attacking From The Inside Out

In the ancient Greek story of the Trojan horse, soldiers hid inside a large wooden horse, which was then placed outside the impenetrable walls of the city of Troy. Thinking it a gift, the citizens of Troy wheeled the horse inside the city. Once inside, the soldiers sneaked out and overtook the city.

Now think of that strategy in terms of battling cancer. What if something could hide until it has made its way deep inside the tumor, then suddenly become active and kill off all the cancer cells from the inside out? The Trojan horse anecdote is one that Joseph Bauer, Ph.D., a research scientist with the Taussig Cancer Center, uses to illustrate how his approach to chemotherapy works.

One day, while in graduate school and reading a biochemistry book about vitamin B-12, it hit him. Why not get the vitamin to secretly carry a deadly chemotherapy agent into the tumor? Dr. Bauer's invention uses B-12 to deliver the anti-cancer drug, nitric oxide, to the tumor. Cancer cells love B-12 and even have receptors to draw it into the tumor. But in this case, they're completely fooled because they have no idea that a deadly agent lurks inside.

“The nitric oxide that's released inside the tumor cell has a half-life outside the cell on the order of milliseconds. It doesn't have time to kill the surrounding cells, so it just kills the tumor cell,” Dr. Bauer explains. Then, with the cancer cells dead and the nitric oxide no longer active, the vitamin B-12 can get out into the blood stream and help the body heal (*see sidebar, right*).

Dr. Bauer's “biological Trojan Horse” may be one of the best things to happen in cancer research in recent years. Preliminary independent testing by the National Cancer Institute noted that it had anti-cancer effects – showing inhibition of the growth of human tumor cells – on 60 different types of cancer. It did best among blood cancers, breast cancer and ovarian cancer. In fact, it destroyed the breast cancer 100 percent. However, while it had some impact, it was less effective on prostate cancer and melanoma. Those results make sense to Dr. Bauer. It turns out that some cancers have more vitamin B-12 receptors than others. The more receptors, the more the drug gets into that cell.

Unfortunately, the drug hasn't made it into trials in human patients yet – and it may be well beyond a year before such tightly regulated trials get underway. In the meantime, Dr. Bauer has expanded his research – and has made even more powerful discoveries. He found that if he adds interferon to the mix, then the interferon stimulates the tumor cell to develop more B-12 receptors – and that means more drug can get into the tumor. Dr. Bauer cautions that while he's very excited about his work, strict FDA protocols mean that this therapy is years away from hitting the general market. It must first go through numerous trials to assert its effectiveness and safety.

The Right Direction

Researchers agree that a cure is a long way off – and that traditional chemotherapy probably won't disappear in the near future. But, they also agree that the direction of the research is having a profound impact on the treatment for cancer.

“It's unlikely we're going to find one key that unlocks the answers for everyone who develops cancer,” admits Dr. Crowe.

One tough hurdle researchers and drug developers face in creating targeted therapies is a phenomenon that's common in antibiotic usage: drug resistance. That is, as more potent antibiotics are used, viruses find ways around those drugs. They become stronger and more resistant.

It appears that cancer does the same thing. A few years ago, one drug was hailed as a cure for a type of leukemia. Patients immediately got better. But then the cancer got smarter. It returned in some patients and part way through the treatment, the drug was no longer effective.

“Cancer cells are pretty smart, so when you give them these drugs, they start to recognize that there's a medicine around. They mutate themselves to create resistance to that medicine,” says Dr. Bukowski. “Does that happen in all instances? Thankfully, it doesn't. But it's just another problem that you face when you start to bring up a cure for cancer.”

Still, the future of targeted medicine is very bright. “We're going to be able to group individuals by knowing their genetic and molecular make-up as well as the genetic and molecular make-up of their cancers,” says Dr. Crowe. “Then, when we know that a certain group of patients have their cancers behaving because of a certain biochemical or molecular pathway, we can develop for those patients a very specific, not very toxic treatment. One that doesn't affect other, healthy cells. That's what targeted therapy is all about.” ■

To read more about targeted medicine, go to www.clevelandclinic.org/clevelandclinicmagazine

A Biological Trojan Horse

1 Nitric oxide is bound to vitamin B12 and is picked up by protein “shuttles,” or transports.

2 The nitric oxide and B-12 are delivered to B-12 receptors that reside on the surface of the tumor cell.

3 The cell takes in the whole package, combining it with a mildly acidic lysosome.

4 The acid inside the lysosome causes the molecular bond to break and release deadly amounts of nitric oxide, killing the cancer cell from the inside.

Lysosome