

FEATURE STORY

Gaining an Edge Against Cancer

BY ELIZABETH WHITTINGTON

Cancer research pushes forward as scientists find creative ways to attack cancer.

When researcher and pediatric oncologist Judah Folkman, MD, began examining the role of angiogenesis in the early 1960s, his best hope was that it could be used to treat cancer. By developing a theory of how tumors grow by signaling blood vessel growth, Folkman gave future researchers the knowledge to attack cancer cells' environment—a novel theory at the time, and one that was not recognized for many years.

Four decades later an overly optimistic comment by fellow scientist and co-discoverer of the DNA double helix, James Watson, PhD, landed angiogenesis on the front page of *The New York Times*, claiming, “Judah is going to cure cancer in two years.”

It hasn't proven that simple.

Although Folkman's observations laid the foundation for the successful development of antiangiogenic therapies—several of which have been approved—the more researchers learn about cancer, the more they understand the complex interaction between patient and tumor, genes and treatment, and the adaptability of cancer cells to survive and multiply.

The dream of finding a single cure for cancer has been replaced with hitting cancer cells with combination therapies affecting growth pathways, DNA, environment, and other dependencies. Researchers could potentially cure specific types of cancer, prolong patients' lives, and prevent recurrence.

Past Successes Uncover New Challenges

The challenge scientists face today is the same that they have grappled with in the past—finding the best drug to kill the cancer, while allowing as little harm to the patient as possible. The increasing number not only of drugs but also entirely new classes of drugs to test in the laboratory and in human trials also means increases in research funds, the number of patients for clinical trial participation, and time to test new drugs and combinations.

Clinical trials must be designed to show sufficient safety and efficacy for an agent or it may be set aside and forgotten. Finding which patients respond, knowing when to treat them, and determining what combination of drugs to give are only some of the goals scientists are working toward, as well as tackling drug

resistance and cancer cell adaptation.

When Gleevec (imatinib) was approved in 2001 for chronic myeloid leukemia, it was considered the proverbial “magic bullet”—a drug designed to target the bcr-abl gene located on an abnormal chromosome called the Philadelphia chromosome that caused certain white blood cells to become malignant. For a proportion of patients, however, Gleevec either did not work or failed to delay the disease indefinitely. Researchers discovered that various mutations of the gene accounted for most cases of Gleevec resistance. These mutations prevent Gleevec from binding and inhibiting bcr-abl.

Soon after Gleevec’s approval, researchers started working on two second-generation bcr-abl inhibitors, Sprycel (dasatinib) and Tasisna (nilotinib), to target the mutations. These more potent drugs provided promising second-line treatment for Gleevec-resistant and Gleevec-intolerant CML. Still, some cancers failed to respond. Currently, researchers are developing and testing agents that target another mutation called T315I, the only known mutation that is not responsive to the three approved bcr-abl inhibitors.

Neil Shah, MD, PhD, assistant professor of hematology/oncology at the University of California, San Francisco, helped develop Sprycel and says it’s encouraging that the first effective therapy for Gleevec-resistant or intolerant patients was approved five years after Gleevec.

“[Sprycel] is an excellent example of not being complacent with the exciting initial responses of any particular therapy, but to really ask focused questions about why certain patients either don’t respond or lose their response.”

Scientists are also working to overcome drug resistance by blocking two or more targets with drugs like Tykerb (lapatinib), the breast cancer drug that inhibits both HER2 and the epidermal growth factor receptor (EGFR). Scientists are learning that cancer cells evolve and adapt, perhaps switching from one growth factor to another to spur proliferation, which may be why using drug combinations and targeting multiple mutations and pathways—what researchers call total receptor blockade—is often successful.

Reinventing Chemo

Oncologists have been using chemotherapy for more than 60 years, and while it carries a bad reputation for side effects, newer chemotherapies are more effective and cause less damage to healthy tissue. Reformulations of older agents have reduced life-threatening allergic reactions, and research challenging conventional treatment combinations is gaining ground. Indeed, breast cancer trials comparing the standard combination of the heart-toxic Adriamycin (doxorubicin) and Cytosan (cyclophosphamide) versus Taxotere (docetaxel) and Cytosan show the TC combination works as well or better than the AC combination, and is easier on the heart.

Advances in chemotherapy include a new class of agents called epothilones, which are similar to the taxanes Taxotere and Taxol (paclitaxel) in that they disrupt structures inside the cell called microtubules that are essential for cell division

and growth. Epothilones have shown activity in taxane-resistant cancers and don't require the pretreatment dose of steroids to ward off an allergic reaction, a common occurrence with taxanes.

Last year, the breast cancer drug Ixempra (ixabepilone) became the first epothilone to receive Food and Drug Administration approval. Another epothilone called patupilone is in early-phase testing for liver, ovarian, peritoneal, and fallopian tube cancers.

Scientists are also looking back at old drugs.

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—Louis Weiner, MD

Treanda (bendamustine) has been around since the 1960s and used in European countries for chronic lymphocytic leukemia and non-Hodgkin's lymphoma. Large-scale U.S. studies presented at the American Society of Hematology meeting in late 2007 showed Treanda outdid the standard treatment, chlorambucil, in both overall response rate and progression-free survival. Three months later the FDA approved Treanda for CLL, and it's expected to garner another indication in slow-growing non-Hodgkin's lymphoma in late 2008.

Experts realize chemotherapy isn't going away—new combinations with targeted agents and new chemotherapies still have an important role in oncology—but researchers still hold out hope that chemotherapy will be supplanted.

“It is conceivable that biologically targeted therapies will ultimately replace current standard chemotherapy, but it will be a process of evolution, not a revolution,” says Louis Weiner, MD, director of the Lombardi Comprehensive Cancer Center at Georgetown University.

Estrogen Blockers

“Chemotherapy was king back in the 1970s when I started,” remembers V. Craig Jordan, PhD, vice president and scientific director for the medical science division at Fox Chase Cancer Center in Philadelphia. Which is why it was so unusual that at the time Jordan took a failed contraceptive drug called ICI46474 and found it treated and prevented hormone-dependent breast cancer.

ICI46474, later named tamoxifen, became the first antihormonal cancer drug and a staple in treatment for about two-thirds of breast cancer patients. Tamoxifen, a selective estrogen receptor modulator (SERM), blocks the hormone by binding to its receptor in the cancer cell.

“Tamoxifen became the first targeted therapy, really targeting the tumor rather

than just killing all cells. So that was the innovation 30 years ago that really changed medicine to introduce what we have now,” says Jordan.

Researchers quickly realized about half of estrogen receptor-positive breast cancers eventually become resistant to tamoxifen—essentially the cancer cell learns to use tamoxifen instead of estrogen to stimulate growth. After running laboratory tests that flooded breast cancer cells with tamoxifen over time, researchers found that reintroducing estrogen in place of tamoxifen after several years actually killed the cells. A clinical trial involving patients with tamoxifen-resistant tumors to test the theory is imminent, says Jordan.

“There’s lots of good stuff about tamoxifen out there that everybody’s really excited about at the moment,” Jordan says. “It’s an old drug that keeps reinventing itself. And it really doesn’t go away, it just gets better year by year.” Tamoxifen can cause rare but serious side effects, including blood clots and uterine cancer.

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Newly developed SERMs, such as arzoxifene and bazedoxifene, are in late-phase testing and may soon be added to the list of chemoprevention drugs alongside tamoxifen and Evista (raloxifene), which was recently approved to prevent invasive breast cancer. Researchers hope these new compounds carry less risk of side effects.

Another class of hormonal therapies called aromatase inhibitors, which include Arimidex (anastrozole), Femara (letrozole), and Aromasin (exemestane), are effective in postmenopausal breast cancer patients and work by hindering the production of estrogen as opposed to tamoxifen’s method of blocking the estrogen receptor.

A study published in April in the *Journal of Clinical Oncology* found women with early-stage estrogen receptor-positive breast cancer had better recurrence-free survival when five years of tamoxifen was followed by five years of an aromatase inhibitor. Five years of an aromatase inhibitor is approved for use instead of tamoxifen, or for two to three years following two to three years of tamoxifen.

Targeted Tactics

Rituxan (rituximab) jump-started the era of targeted therapies when the FDA approved it in the ’90s. Approval of Herceptin (trastuzumab) for HER2-positive metastatic breast cancer soon followed, among others (see [Timeline: Milestones in Cancer Treatment](#)). Scientists are now finding more ways to target cancer cells

through survival pathways, cell structure, ability to proliferate, and the tumor environment.

A number of genes and proteins involved in the complex pathways required for cancer cell survival and growth have become an alphabet soup of moving targets, including mTOR, HIF-1, MAPK, and RAS. With this knowledge, scientists are developing agents to disrupt those survival pathways and damage cancer DNA.

“We’re right there,” says Dennis Slamon, MD, PhD, director of clinical/translational research at the University of California, Los Angeles’s Jonsson Comprehensive Cancer Center and a key player in the development of Herceptin. “We’re testing targets from a number of relevant pathways, so it’s all pretty exciting right now.”

Agents that target growth factors such as EGFR, HER2, and vascular endothelial growth factor (VEGF) have laid the groundwork for the next generation of targeted agents. Newer drugs have multiple targets or attack multiple pathways. Following the success of Herceptin, which targets HER2 overexpression by binding to its receptor on the surface of the cancer cell, Tykerb, a much smaller molecule that can be taken orally, was developed to get inside the cell and block EGFR on the inside and HER2 on the outside.

Scientists are also improving mechanisms of current drugs. Rituxan and newer drugs, such as HuMax CD20 (ofatumumab), work by attaching to antigens found on the surface of normal and malignant cells, essentially targeting the tumor cells and activating the body’s immune system to destroy the cell. HuMax CD20 appears to be more potent than its predecessor in recruiting and activating elements of the immune system, says Weiner.

[View Illustration: Cancer Therapy's Many Targets](#)

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“Rituxan is a remarkably effective antibody for the treatment of lymphoma, but it turns out that the probability of a person benefiting from single-agent Rituxan therapy is very much related to whether or not one of their critical immune system receptors is high responding or low responding,” Weiner says. People who have a high-responding version of the receptor have an 80 to 90 percent chance of responding to Rituxan treatment, while patients with low-responding receptors only have about a 40 to 50 percent chance.

“It turns out that these novel next-generation antibodies bind to the CD20 just like Rituxan,” Weiner says. “They are going to be able to so efficiently recruit the immune system to essentially eliminate the distinction between low and high responders. This should improve the treatment results for many more patients with CD20-expressing lymphomas.”

Researchers have found ways to destroy cancer cells not only by attacking the cells directly but also their environment. Avastin (bevacizumab), the first fruit of Folkman’s antiangiogenesis theory, inhibits VEGF, which is secreted by the tumor to spur new blood vessel growth. It’s also believed that Avastin helps blood vessels better carry chemotherapy to the tumor.

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Avastin, currently approved for lung, breast, and colorectal cancers with a possible indication for brain cancer on the horizon, works best in combination with other drugs. Avastin slows tumor growth by inhibiting VEGF, but it—as well as other antiangiogenic drugs—may target the cancer cell itself. Scientists hope to build the antiangiogenesis armory with other VEGF inhibitors, including Sutent (sunitinib) and Nexavar (sorafenib), both approved for kidney cancer. (Nexavar recently received a second approval in liver cancer.) Next-generation antiangiogenic drugs being examined in clinical trials for various cancers include vatalanib, VEGF Trap (aflibercept), and axitinib.

In addition to VEGF inhibitors, other agents that work against the tumor's environment, called vascular disrupting agents, include investigational agents such as cilengitide, a brain cancer therapy in mid-phase studies. Instead of halting blood vessel growth, cilengitide destroys existing blood vessels.

Vaccines Close In

“Some of the things we've discovered, which I think are very positive, are cancer patients can be immunized and they can generate immune responses against their tumors with vaccinations,” says Nora Disis, MD, director of the University of Washington's Tumor Vaccine Group in Seattle. “When I got into this business over 10 years ago we didn't know that—now we know that.”

Immunotherapy for cancer has been the hope of many researchers for years, but even with positive results seen in the laboratory, no therapeutic cancer vaccines have reached the market yet.

“I think the biggest holdup for us in terms of getting a cancer vaccine in clinical use is figuring out when to give it and what stage of disease to give it,” Disis says. “In the laboratory, things move very, very quickly, but once you hit the clinic, things move much more slowly.”

Clinical trial design may be one reason why vaccines haven't caught on because most experimental drugs are first studied in late-stage patients who have already been on several treatments. “Clearly you're trying to immunize someone who is no longer responding to treatment. To try to get that disease to go away with a vaccine is probably not realistic,” says Disis.

On the other hand, vaccines could help individuals at high risk of relapse after a complete response or those with premalignancies. People at high risk of developing cancer may also benefit, but many patients are needed to specifically answer that question in a clinical trial because only a minority of participants

would eventually develop cancer.

“There are so many interesting strategies where phase II studies have already shown some very interesting potential clinical benefit that I do think that at the end of this decade, we will have cancer vaccines that we use clinically,” says Disis, adding that large studies are ongoing and in planning.

The prostate cancer vaccine Provenge has been in limbo since last year after the FDA cited the need for more data before considering it for approval. The phase III study known as IMPACT (IMmunotherapy for Prostate AdenoCarcinoma Treat-ment) is expected to release those interim results in late 2008.

View Chart: Agents in the Pipeline

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While many experts believed Provenge would be the first therapeutic cancer vaccine approved in the United States, it may be beaten to the punch by other vaccines that show promise in clinical trials.

Researchers have developed the vaccine DCVax-Brain to teach the body’s immune system to hone in on cancer cells that express a certain protein, which could be different in each patient. By taking proteins from a patient’s tumor to create a specific marker targeting the cancer cells and combining it with immune cells called dendritic cells from the patient, technicians can design an individualized vaccine to attack only brain cancer cells. The concept is also being used for DCVax-type vaccines for prostate, ovarian, lung, and other tumors.

Vaccines using different methods are also proving successful. Stimuvax (BLP25 liposome vaccine), currently in phase III testing for lung cancer, is designed to stimulate an immune response toward cancer cells that express the protein antigen MUC1. And Disis is working on a vaccine that targets HER2, the same target of Herceptin and Tykerb. The vaccine is being tested in breast, ovarian, and lung cancers.

Several therapeutic cancer vaccines are in phase III testing, and some are close to producing final results.

“I think that a decade ago the field was defining whether you could immunize cancer patients, how you would immunize them, and what [those vaccines would] look like,” Disis says. “We’ve made tremendous progress in those areas. ... I think in the next five years, we’ll see a flurry of different strategies in different cancers using vaccines with chemotherapy, [and] using vaccines in premalignant diseases.”

Currently, more than 3,500 clinical trials are under way in the United States to test experimental agents as well as existing drugs for new indications and in new combinations. Some experts estimate the number of agents in the oncology pipeline hovers around 800.

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clinic. ❏

—Neil Spector, MD

While only a small percentage of drugs entering human testing make it to phase III trials, that percentage has doubled in the past decade, and experts predict the number of approved agents will increase by 40 percent over the next five years. But with hundreds of cancer subtypes and the growing cost of developing and testing new agents, researchers have their work cut out for them.

Neil Spector, MD, director of translational research in oncology at Duke Comprehensive Cancer Center and co-director of its Experimental Therapeutics Program, recalls the excitement surrounding Folkman's antiangiogenesis theory and the subsequent development and testing of Avastin.

"Early on, there were all these negative trials with Avastin, and people began to really sour and say this was just another magic bullet that came and went and just hasn't panned out," says Spector, who was instrumental in developing and testing Tykerb. Companies investing in Avastin-like drugs were ready to pull the plug on development until positive results in a colo-rectal cancer trial were announced. Later, the FDA commissioner called antiangiogenesis the fourth cancer treatment modality.

"The whole area was a heartbeat away from being completely terminated. You could have something that important, but if we don't know how to [test] it, you will get negative study after negative study and say it's a complete waste of time," Spector says.

"Avastin could have been shelved and that would have been the end of antiangiogenesis, and that would have been a huge mistake. Those are the dangers. We need to rapidly catch up with how to use [these targeted agents] in the clinic, and a lot of us are dedicated to solve those problems."