



FEATURE STORY

Below the Surface

BY NICOLE LEBRASSEUR, PHD AND HEATHER L. VAN EPPS, PHD

New therapies for melanoma exploit biological insights to combat this dangerous skin cancer.

Retired teacher Norm Parker of California has spent much of his life in the sun. Although fair-skinned, he hadn't been particularly careful about protecting himself from the sun in his younger years. So as an adult, he decided to be cautious. For 15 years, Parker visited a dermatologist every six months in hopes of detecting any early signs of skin cancer. But when his doctor discovered an unusual-looking mole on Parker's back in 1997, it was already more serious than either would have liked. "It was an abnormal melanoma," Parker recalls. "The size suggested it was deep, not just on the surface. But it looked like it hadn't spread yet."

After Parker's melanoma was removed, his surgeon suggested regular screens as a future precaution but didn't refer him to an oncologist. Three years later, Parker's wife discovered a lump under the skin in his neck. His melanoma had spread to the lymph nodes, and scans revealed tumors in his brain, liver, arm, and hip. The brain tumors could be removed surgically, but the rest required chemotherapy.

Parker decided to do some research to find the best skin cancer experts in the United States. His search led him to Jeffrey Weber, MD, PhD, director of the Donald A. Adam Comprehensive Melanoma Research Center at H. Lee Moffitt Cancer Center in Florida, and a cutting-edge treatment that may have saved his life. Parker is one of many patients with metastatic melanoma who are benefiting from new investigational treatments that may soon improve the outlook for patients with the deadly disease.



Norm Parker, now cancer-free, received an aggressive regimen to treat his melanoma. Photo by Michael Kitada

Approximately 60,000 new cases of melanoma were diagnosed in 2007, according to data from the National Cancer Institute's Surveillance, Epidemiology, and End Results database, meaning roughly one in 70 Americans can expect to develop melanoma at some point in their lives. Several factors contribute to the development of melanoma, according to David Fisher, MD, PhD, of the Massachusetts General Hospital. Not surprisingly, sun-seeking behaviors are partly to blame. Genetics may also factor in, but most people who develop

melanoma have no known family history of the disease.

Although melanoma is one of the most aggressive types of cancer, it is easily cured if caught early, when surgical removal is an option. Simple precautionary measures, such as regular mole screening by a dermatologist, can be lifesaving.

“Because [melanoma] is on the skin, you can pick it up far earlier than almost any other type of cancer,” says Steven Rosenberg, MD, PhD, chief of surgery at the NCI. Indeed, the five-year survival rate tops 90 percent for patients whose melanomas are stage 0 or stage 1. The deeper into the skin the tumor has burrowed, however, the poorer the prognosis. Tumors with irregular borders or broken surfaces (ulcerated) are also associated with a worse prognosis.

Current Care...

In 1999, Richard Breidenbach, of Madison, Wisconsin, was diagnosed with melanoma after his wife spotted a suspicious-looking mole on his lower back. The tumor was very superficial and had not spread to other parts of his body, so it could be easily removed and the chances of it returning were slim. But Breidenbach’s battle with melanoma wasn’t over.

Three years after his initial treatment, another tumor appeared on his back, and this time the prognosis was far less optimistic. The tumor was surgically removed, but at that point, Breidenbach recalls, “the horse was out of the barn”—the cancer had already spread.

Once melanoma reaches the regional lymph nodes (stage 3) or distant organs (stage 4), treatment options are more limited and much less effective. If lymph nodes test positive for cancer during a sentinel lymph node biopsy, the nodes can be surgically removed. But once the cancer spreads beyond the regional nodes, the five-year survival rate reaches only 18 percent.

For late-stage melanoma, only three Food and Drug Administration-approved treatments are currently available. One is an intravenous chemotherapy agent called DTIC (dacarbazine), which actively destroys dividing tumor cells. DTIC is effective in no more than 20 percent of patients, and even those patients aren’t helped for long—average survival time is only about eight months. (Research suggests Temodar [temozolomide], an oral agent approved for a type of brain tumor, may be as effective as DTIC, and unlike DTIC, Temodar can penetrate the blood-brain barrier to treat melanoma that has spread to the brain.)

The other two approved agents take advantage of a different way to attack cancer, known as immunotherapy. Interleukin-2 (IL-2) and interferon are cytokines, naturally occurring proteins that stimulate the patient’s immune system to fight off tumor cells.

“High-dose IL-2 can be curative, no matter how far [the cancer] has spread,” says Dr. Rosenberg. Like DTIC, however, the caveat is that less than 20 percent of patients respond, and only about half of those successes experience lasting remissions.

Thomas Woodrow, a 58-year-old cardiologist from Florida, was one of the

successes. In the fall of 2006, a mole on his scalp that tested positive for melanoma was surgically removed. “All the tests [for metastatic disease] were negative,” says Woodrow, “but the problem was the thickness of the tumor and the fact that it was ulcerated, which are higher risk signs.” Woodrow immediately entered a melanoma vaccine trial at the University of Virginia, but was dropped from the study a month later when tumors showed up in his lungs, bone, and liver. “It was pretty depressing,” recalls Woodrow. “I thought I probably wasn’t going to survive it.”

Woodrow booked an appointment with Dr. Weber, who quickly hospitalized Woodrow and put him on a regimen of high-dose IL-2, high-dose interferon, and three different chemotherapy drugs. “It was like a bad case of the flu,” says Woodrow of the side effects of high-dose IL-2. “The first evening [of treatment] I would get fever, ache all over, and have extreme shaking chills.”

Although Woodrow weathered the IL-2 storm, the side effects of intravenous IL-2 can be severe. High doses can cause blood vessels to leak fluid, which can trigger a potentially fatal drop in blood pressure. Even mild blood vessel leaks can cause other dangerous and unpleasant side effects, including abnormal heartbeats, shortness of breath, fatigue, and weight gain. “To quote one of my old patients,” says Dr. Weber, “the last time he felt that way he was ‘on the bottom of a football pile-up.’ ”

That patient was Parker, a former football player, who was also treated with a chemotherapy cocktail that included high-dose IL-2. Parker’s inpatient treatment lasted six months, followed by three years of injections at home of low-dose IL-2. Woodrow is also now getting in-home IL-2 injections after his last scan revealed only one small tumor remaining in one lymph node—the others had disappeared. Parker also responded well to the treatment and has been tumor-free for more than six years.

...And Beyond

Other forms of immunotherapy are currently under investigation, including a slow-release variant of the immune-boosting interferon, called pegylated interferon. Although this agent has been less thoroughly tested than IL-2, early trials suggest it may work as well as high-dose IL-2 with fewer risks.

Potentially even more promising are new drugs designed to specifically activate T cells, the immune cells primarily responsible for killing tumor cells. The immune system naturally generates T cells that recognize unique proteins made by melanin-producing skin cells called melanocytes—the cells that become cancerous in melanoma. But because T cells are taught to ignore “self” cells, they do not attack skin cells. For the same reason, they also fail to attack cancerous cells in melanoma patients.

Two new drugs currently in late-phase testing, ipilimumab and tremelimumab, are designed to spur these natural T cells into attacking the tumor. The drugs work by blocking a molecule called CTLA-4 that normally suppresses T cell activity. In a recent trial of 139 stage 4 melanoma patients, 17 percent of those given ipilimumab responded positively. Three patients have now been

disease-free for several years. The drugs may cause diarrhea, abdominal pain, and skin rash, but these adverse effects are usually a good sign, as they tend to crop up when the drug is working.

View Graphic: Revving the Immune System to Fight Melanoma

Unlike IL-2 and interferon, vaccines are designed to stimulate an immune response by targeting specific antigens on melanoma cells. One promising vaccine in phase III testing contains the melanoma-associated antigen glycoprotein 100 (gp100).

Perhaps the most extreme form of experimental immunotherapy is adoptive cell transfer therapy. This treatment strategy, devised by Dr. Rosenberg and his colleagues at the NCI, involves removing the natural tumor-fighting T cells from the patient's bloodstream, expanding their numbers in culture dishes, and then re-infusing them into the patient. The cells can also be engineered to become better tumor killers while outside the body.

For the re-infused cells to take hold, however, the patient's own immune system is first wiped out using radiation, which may leave the patient temporarily vulnerable to infection. Dr. Rosenberg is hopeful about the benefits of his protocol. "Half the patients with metastatic melanoma will experience cancer regression with this therapy," he says.

It was adoptive cell transfer therapy that eventually put Breidenbach into a prolonged remission. After several surgeries and three experimental treatments, Breidenbach's cancer was still on the move. "We were getting really discouraged," he says. "My disease was progressing very rapidly. Tumors had consumed about half of my liver and half of one lung." In November 2003, his doctor estimated he had four months to live. "That was a huge wakeup call," says Breidenbach.

☑ It was a celebratory occasion. Even the doctors were blown away. ☑

—Richard Breidenbach

Then, Breidenbach got a call from Dr. Rosenberg, who had been working with T cells isolated from a tumor removed during Breidenbach's last surgery at the NCI. Dr. Rosenberg told him that his T cells were "basically jumping out of the petri dish." Breidenbach knew then that "it was either do [the experimental therapy], do chemo, or do nothing and die." He chose the new therapy, which was accompanied by eight rounds of IL-2 injections.

Just months later, his tumors were virtually gone. "It was a celebratory occasion," Breidenbach says. "Even the doctors were blown away." He has been in remission for four years.

Melanoma Mutations

Strategies for attacking melanoma may soon involve a personalized approach based on the genetic characteristics of the patient's tumor. Recently, scientists have begun to uncover genetic mutations that drive the unchecked growth of melanoma cells. By determining how the wheels have come off the cart, they hope to create drugs that better target the specific problem.

A common genetic mutation in melanoma creates an overactive version of a protein called BRAF, which instigates cell growth and division. Other mutations activate a related protein, called N-RAS, also resulting in unchecked cell division. Drugs designed to block these overactive proteins kill melanoma cells in laboratory tests, but so far they have shown little promise in patients.

Dr. Fisher is most excited by the identification of another mutated protein, called c-Kit. More than a third of metastatic melanomas found in the gastrointestinal tract or on the palms and soles have c-Kit mutations. The same mutation is commonly found in gastrointestinal stromal tumors, which can be treated with the oral drug Gleevec (imatinib). A number of clinical trials are now under way to test whether Gleevec will also be effective in patients with c-Kit-mutated melanomas.

One such trial is being held at Dana-Farber Cancer Institute and Harvard Medical School, where Dr. Fisher and his colleagues have seen promising results firsthand. "The very first treated patient had widely metastatic melanoma," Dr. Fisher says. "And her tumors just melted away. That sort of response from a single pill a day is enormously exciting and provides hope that for other tumors, there will be opportunities to have similar effects."

While new therapies work their way through clinical trials, Woodrow plans to be proactive. "Just because you have no signs of disease, it doesn't mean it's not going to come back," he says. "I don't think the long-term plan should be just wait and see." Breidenbach also champions a proactive approach. "Be your own best health advocate," he says. "Never accept no for an answer, and always look for other options. Hope is the best drug of all."