A diagnosis of melanoma is very bad news. Millimeter per millimeter of tumor, it’s among the deadliest cancers. Typically first appearing as a dark, irregular skin lesion, it can spread rapidly to every organ. There are some 68,000 new cases of melanoma in the United States each year, and the incidence is growing, despite warnings to stay out of the sun or wear sunblock to minimize exposure to ultraviolet radiation, the disease’s most important risk factor. Highly curable if found early, melanoma grows aggressively if undetected. Nationwide the cancer kills almost 9,000 people a year, mostly those with fair skin, often in the prime of life and frequently within mere months of discovering that their cancer has metastasized far and wide.

The best hope is a harrowing treatment for which only the fittest patients qualify: intensive immunotherapy that uses high doses of interleukin-2 (IL-2), a potent immune hormone. IL-2 therapy requires multiple hospital stays, during which patients receive intravenous infusions several times a day. The catalogue of side effects includes a racing heart, flu-like chills, decreased blood pressure, vomiting and diarrhea, and edema, which can cause 10 to 20 pounds of weight gain.

Even then, no more than 20% of patients who get the treatment benefit, though 6% appear cured for life. Still, immunotherapy is better than the only other Food and Drug Administration-approved treatment for advanced melanoma: Chemotherapy with dacarbazine gets only a 10% response rate, and patients survive an average of just seven months.

The idea of harnessing the body’s immune system to defeat malignancies has long had appeal, and perhaps because of the dearth of other effective treatments, research on the disease has always skewed toward immunotherapy—more so than for other cancers. But beyond that, some scientists speculate that melanoma is particularly immunogenic, producing antigens that immune cells can recognize as dangerous. There have also been rumors of advanced melanoma spontaneously regressing, as if the immune system can sometimes clear the cancer on its own and just needs to be encouraged. But many physicians are skeptical about such medical miracles. “I’m still waiting to see my first case,” says Paul B. Chapman, a melanoma researcher at Memorial Sloan-Kettering Cancer Center in New York City.

Chapman thinks it’s likely that there has been more focus on immunotherapy for melanoma simply because melanoma cells, compared with those of other cancers, are easier to grow and study, so scientists have learned more about melanoma’s antigens. An added encouragement has been that researchers have witnessed more—if still very few—responses in melanoma than in other cancers to strategies that rev up the immune response of killer T cells.

Whatever the reason, the field has invested a good share of research dollars in immunotherapy. But rewards have been scant: Beyond interleukin-2’s limited effectiveness, a cancer vaccine called gp100, now in clinical trials, has so far extended survival no longer than dacarbazine does. Perhaps some of the money and effort would have been better spent on a different approach—such as developing targeted therapies that inhibit one of the mutated genetic growth signals on which cancer cells depend. Yet although that approach has worked for rare cancers driven by just one mutation, such an aggressive, invasive cancer as melanoma has seemed likely to involve many mutations.
Now, though, almost simultaneously, scientists in both the immunotherapy and the targeted therapy camps have achieved breakthroughs they describe as unprecedented. A new form of immunotherapy called ipilimumab (researchers refer to it as Ipi) targets immune cells instead of cancer cells, and it’s the first drug to prolong survival in metastatic melanoma, even if it doesn’t always shrink tumors. The other new treatment, known as PLX4032, is a targeted therapy that inhibits a particular cellular growth signal, and it has shrunk tumors more dramatically than previous approaches have.

Each therapy could receive FDA approval within a year, and there are already plans for trials testing them in combination as well as to fight other cancers. “For those of us treating a disease that we’ve had very little success against in more than 30 years,” says Steven O’Day, director of the melanoma program at the Angeles Clinic & Research Institute in Santa Monica, Calif., “the excitement is palpable.”

Very likely, each of us generates potential cancer cells every day, but they don’t amount to anything because our repertoire of immune cells contains T cells that destroy the malignant ones. “But every now and then, a cancer cell gets lucky by mutating in such a way that the immune surveillance system doesn’t see it,” Chapman says. Then the cancer cell can set up shop in a tissue and begin acquiring other malignant mutations.

Scientists are starting to understand how cancer cells hide from the immune system and also dampen its killer instincts. For one thing, tumors tone down their cells’ production of antigens, the proteins on the cell surface that act as identity tags, says Jennifer A. Wargo, a melanoma surgical oncologist at Massachusetts General Hospital. That makes cancer cells less visible to T cells, which have a complicated self-regulating system that moderates the cells’ action.

When a foreign antigen, such as a cold virus, shows up in the body, it triggers an accelerator, often a protein on the T cell membrane called CD28. Activating the protein makes T cells reproduce and become more active in eradicating the infection by producing interleukin-2. “But we don’t want to exhaust our immune system every time we get a cold, so we need to slow down the immune response after a while,” Chapman says. “Also, sometimes you want to hold your immune cells back, essentially telling them, ‘I understand you think these bacteria on my skin or in my intestine are foreign, but I don’t want you to go nuts over them, because they’re benign.’”

The discovery that led to the development of ipilimumab happened when Jim Allison, then at the University of California, Berkeley, and now chairman of the immunology program at Sloan-Kettering, found a particularly important T cell brake called CTLA-4. This protein dampens the immune response by binding to a protein called B7, which would otherwise bind to CD28. As a result, the T cell doesn’t rev up production of IL-2. This muted response helps balance other excitatory signals that could lead to an overly enthusiastic immune reaction.

Melanoma researchers in both the immunotherapy and the targeted therapy camps have achieved breakthroughs they describe as unprecedented.
The usual measurement of a cancer drug’s success considers how many participants have a tumor that shrank by at least half during treatment. In a large randomized Phase III trial published last June in The New England Journal of Medicine, in which patients with widely metastatic melanoma received infusions every three to four weeks, only 10% of patients met that benchmark. But an additional third were able to live longer, and though their tumors didn’t shrink, the tumors “also didn’t grow, for extended periods—years, not just weeks or months,” O’Day says. After a Phase II trial with similarly encouraging results, the drug was made available to other patients on a “compassionate use” basis—that is, for patients with late-stage melanoma who have no other treatment options.

“W e don’t understand why ipilimumab results in the immune system killing some tumors and just stunning others,” says Wolchok, who thinks the conventional response rate, developed to gauge the efficacy of chemotherapy, doesn’t reflect the biological activity of this immunotherapy. “W e think overall survival may be a more realistic way to understand how much benefit the drug is providing. The most important question is, How long do you live after you get treated?”

Overall, the patients who benefited from ipilimumab survived 50% longer than those on the trial’s control drug, the gp100 cancer vaccine. Some Ipi patients were still alive at the end of the 4½-year trial, and some people from an earlier trial, which began eight years ago, also continue to do well. “That’s amazing, considering that some of these patients have tumors all over their body,” O’Day says.

Still, ipilimumab didn’t help more than half of the trial participants. But a Phase III trial combining Ipi with chemotherapy was recently completed (researchers are waiting to see how subjects fare long-term), and under way is a Phase I trial for an antibody against a different T cell brake, PD-1, that also masks cancer from immune cells. Monoclonal antibodies intended to stimulate T cell accelerators are in the works as well. “Now that we’ve shown that targeting a T cell’s regulatory pathways can have a powerful effect, we’ll soon have combinations of antibodies that may provide more people with a longer benefit,” O’Day says.
Our Natural Shade //

Researchers are at work on a cream that would confer the beneficial effects of a tan yet shield us from the risks of the sun’s dangerous ultraviolet rays.

The pigment melanin, whose production is spurred by tanning, helps protect skin from the cancer-causing effects of ultraviolet radiation by spreading over the nuclei of superficial skin cells, thus shielding the DNA below. But tanning—particularly for fair-skinned Caucasians, who do not brown easily—requires significant UV exposure.

David E. Fisher, director of the melanoma program at Massachusetts General Hospital Cancer Center and the hospital’s chief of dermatology, is looking for a way around this apparent catch-22.

To conduct his research, Fisher used biologically engineered red-haired, fair-skinned mice whose bodies could generate pigmented skin cells called melanocytes. After repeated applications of a special topical cream, these ginger-furred, light-skinned creatures became progressively more bronze, and their sunless tans protected them from skin cancer when they were exposed to UV light.

The cream contained compounds acting on molecules that Fisher’s research group had found to be involved in tanning. One compound, forskolin, stimulates a chemical messenger called cyclic AMP, which triggers melanin production in melanocytes, obviating the need for sunlight to trigger that production. The second compound, rolipram, deactivates an enzyme called PDE4D3, which degrades cyclic AMP and thus curtails tanning. By disabling this brake, the melanocytes keep churning out melanin.

The tanning strategy provides a “proof of principle” for true sunless tanning, but better drugs must be identified, with the capacity to penetrate humans’ thicker skin. The approach will also need further testing to ensure that it’s safe for long-term, repetitive use. “This strategy might prevent skin cancer in two ways,” Fisher says. “The tan it produces would directly block the UV radiation that causes skin cancer, and it would also give people an alternative way to tan without sunbathing or indoor tanning.”

Though immunotherapy has long been intriguing to cancer researchers, in recent years tumor-targeting therapies have gotten most of the attention, spurred by the remarkable success of several drugs that can sometimes eliminate even widely metastasized tumors. One such compound, PLX4032, has entered a Phase III trial for treating melanoma.

In a small, early clinical trial of PLX4032 involving 32 participants whose metastatic melanoma had the BRAF mutation, the tumors of 26 patients shrank either partially or completely. That’s an 80% response rate—unheard of for a single agent against any solid tumor, let alone melanoma. Although Chapman was initially skeptical, he found the data from the trial, in his words, paradigm-changing. “I’ve been in this field a long time, and I’ve never before had a drug to give someone and expect the tumor to shrink in two weeks,” he says. The next questions, he says, are how long that effect will persist and whether patients will actually live longer.

What everyone dreads is resistance. Experience with previous targeted therapies has driven home the sobering lesson that despite initially dramatic responses, many patients relapse—because when cancer cells find one oncogenic pathway blocked, they take a detour. Indeed, melanoma cells blocked by the BRAF inhibitor seem to do just that. In the early trial, the average response lasted only six to nine months before patients’ tumors again began progressing. “That is just a little better than a death sentence,” says David E. Fisher, director of the melanoma program at the MGH Cancer Center and the hospital’s chief of dermatology. “We feel enormous excitement when the tumors shrink but incredible anguish when patients relapse.”

The next step here, as it has been for other targeted therapies, is to find additional drugs that can cut off some of the alternative routes and that could be used in combination or in
sequence. With the leukemia drug Gleevec, for example, once scientists identified the mutations that cancers use to evade that first-line therapy, they began developing second- and third-line compounds. Researchers are also testing whether a combination of drugs at the outset might prevent resistance altogether. “The fundamental question we’re addressing now in melanoma is whether resistance is from mutations upstream or downstream from BRAF, or whether the cancer is taking a different pathway,” Chapman says.

There’s much that researchers still don’t know about how these latest approaches to targeted therapy and immunotherapy have achieved their tentative successes against melanoma, but some evidence suggests their paths may intersect. For example, Wargo at MGH has observed that melanoma cells with the BRAF mutation tone down the activity of the melanoma-differentiating antigens that T cells recognize. And in the test tube, treating those cells with BRAF inhibitors doubles or triples the T cells’ ability to recognize and kill tumor cells. If PLX4032 invigorates the body’s immune response to melanoma, its action might complement immunotherapies.

The new melanoma treatments might even prove effective against other cancers. Ipilimumab, now being tested on refractory pancreatic cancer, may have a rather generic effect in rousing the body’s immune response and may enhance other targeted therapies or chemotherapies. BRAF inhibitors are likely to help fight other cancers too, because as many as 8% of all cancers have BRAF mutations—a relatively high percentage given how minutely specific other targeted therapies are.

But for now, the real buzz about both new drugs involves melanoma, and after decades of failure, researchers seem almost giddy. “We are now at the stage every cancer now curable reached shortly before those cures were discovered,” Fisher says. Childhood leukemia, Hodgkin’s disease and testicular cancer all were once untreatable, but scientists eventually learned to combine chemotherapies effectively. Now there are two distinctly different melanoma therapies, each based on a deep knowledge of the cancer’s molecular mechanisms. “We have massive scientific understanding of how the drugs work, so we’re not just taking random compounds off the shelf and trying them in combination,” Fisher says. “Melanoma is still a terribly tough fighter, but we finally have it in a corner.”

DOSSIER

1. "Inhibition of Mutated, Activated BRAF in Metastatic Melanoma," by Keith T. Flaherty et al., The New England Journal of Medicine, Aug. 26, 2010. The authors report the promising (albeit early) outcome of the first clinical trial for metastatic melanoma using a targeted therapy: a BRAF inhibitor (PLX4032) that silences an oncogenic mutation present in three-fifths of patients.
