

QUELLING MELANOMA WITH IMMUNOTHERAPY

When Ludwig scientist Jedd Wolchok looked at the radiographs of his patient, a 42-year-old woman with advanced, recurrent metastatic melanoma, he was stunned. Where there should have been tumors, there were none.

His patient, a single mother of three, had already gone through several rounds of treatment. After her chemotherapy failed, she took the melanoma drug ipilimumab, which powers up the immune response to cancer. While she was on the drug, her tumors continued to grow, albeit more slowly than before, and new ones began to appear in other organs. Then she received palliative radiation to quell the pain from a tumor pressing on nerves exiting her spine. Three months later, her radiographs showed that the treatment had not only shrunk the tumor near the spine, as expected, but also minimized or eliminated many of the other tumors in her body.

“I had never witnessed this phenomenon,” recalls [Wolchok](#). But he knew what it was. There were several reports in the scientific literature describing similar but extremely rare events. In what is called the “abscopal effect,” radiation directed at one tumor in the body affects tumors far from the site of the treatment. “This was the most important scientific surprise of the year for us,” says Wolchok.

Wolchok and his colleagues went back to the patient’s blood samples to try and piece together what had happened. Could ipilimumab, a new drug on the market, have had something to do with the patient’s response to radiation?

The blood workup revealed the outlines of an explanation. Before she was treated with ipilimumab, the patient had an immune response to a protein dubbed NY-ESO-1. It is a tumor antigen that is almost exclusively associated with tumor cells. Ipilimumab seems to work better in patients, such as this one, with pre-existing immunity to NY-ESO-1. Previous studies had shown



Jedd Wolchok

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Nivolumab plus ipilimumab in advanced melanoma.

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that the drug increases the immune response to this tumor antigen and other cancer-associated molecules. But in this case the radiation multiplied the effect. Radiation seems to have caused dying melanoma cells to release new target antigens, as well as changes in the tumor microenvironment that fostered tumor destruction. “The immune system’s cancer-fighting response was turned up,” says Wolchok.

Ten months after radiation treatment, the patient was stable and her remaining tumors, if any, were still tiny.

The findings, published in the *New England Journal of Medicine*, have led to several clinical trials to test ipilimumab in combination with various radiation regimens. One of these trials, led by Wolchok and managed by Ludwig clinical trials experts in New York, will soon begin in collaboration with Ludwig researchers at Memorial Sloan-Kettering Cancer Center, the University of Chicago and Stanford. Throughout the trial, subjects’ immune systems will be closely monitored so the researchers can better understand how these two treatments synergize. The data could lead to more effective ways to combine immune agents like ipilimumab with therapies such as radiation or chemotherapy.

Wolchok’s studies highlight a major theme of cancer research – the power of combination treatments. In addition to pairing radiation with an immune-boosting agent, many other

combinations are under investigation, such as combining two or more “targeted” drugs directed against specific molecules associated with cancer cells.

“Two of medicine’s most vexing problems, tuberculosis and HIV, were only satisfactorily controlled when combinations were used,” says Wolchok. “In cancer we are at that same point,” he adds, explaining that combination therapies in this clinical trial and others still being investigated in the laboratory could make a big difference in the lives of patients. This theme has been embraced by Wolchok and other scientists at Ludwig and was a particularly fruitful avenue in 2012.

Wolchok’s laboratory, for instance, is involved in clinical trials combining ipilimumab with a vaccine to bolster the immune response to NY-ESO-1. The group hopes that this will increase the effectiveness of ipilimumab. They are also combining ipilimumab with nivolumab, a new immune modulator. Nivolumab neutralizes the programmed death 1 protein, which cancer cells can exploit to escape destruction by the immune system. Promising results from this study were unveiled in June 2013 at the Annual Meeting of the American Society of Clinical Oncology and in the *New England Journal of Medicine*. The findings from the phase 1 trial showed that a regimen of the two antibody therapies led to strong and durable tumor regression in

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patients with inoperable, metastatic melanoma. The researchers have also gone back to the laboratory bench to find new ways to combine immunotherapy treatments to destroy tumors.

In one such study, published in the *Journal of Experimental Medicine*, Wolchok and his colleagues combined conventional chemotherapy with two experimental immunotherapies, a drug-like antibody and a cell-based treatment called T cell transfer. The antibody activates OX40, a molecule on the surface of immune cells, including cells that shield tumors from destruction called regulatory T cells. “When OX40 is activated on regulatory T cells in the tumor, they get so stimulated that they actually die,” explains Wolchok. The researchers then explored whether adding T cell transfer to the mix would improve the outcome. This cell-based treatment involves removing T cells from the bloodstream and engineering them to target a molecule on tumor cells, flagging the tumor cells for destruction. The tumor-fighting T cells are then infused back into the bloodstream. The researchers tested this approach in a mouse model of melanoma, and observed a swift response. The treatment eradicated the tumors, even when it was administered several weeks after the tumors began to grow.

Ludwig plans to take this research forward to test a similar approach in people. They are aided in this effort by the Cancer Research Institute, a nonprofit organization devoted to research and development of immune-based cancer therapies, and a long-standing Ludwig partner. Ludwig and the Cancer Research Institute are collaborating with the biotechnology company MedImmune to obtain an OX40 antibody and other agents to use in human trials.

Meanwhile, immunologists at Ludwig are seeking out new ways to turn the immune system against tumors, and other biologists are developing ways to put a wrench in the cellular machinery that drives the proliferation of cancer. These avenues of research could lead to new therapies that may pack a punch in combination with other treatments.

The clinical and laboratory research of Wolchok and other Ludwig researchers is buoyed by Ludwig’s rich, decades long tradition of support for basic research and unwavering commitment to the field of immunotherapy. For example, the NY-ESO-1 molecule, which is critical to the immune analysis of the powerful anticancer response in Wolchok’s 42-year-old patient, was first described by Ludwig investigators more than a decade ago.

Says Wolchok, “Because of the high quality of science that has been done at Ludwig for many years, we are in a position to do the kind of work we’re doing now.”

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NEW APPROACHES EMERGE FROM WITHIN A TUMOR



New ideas for immunotherapy emerge from Ludwig research labs throughout the world. The development of these ideas is bolstered by infrastructure Ludwig has fostered for decades, such as a Brussels-based tissue bank containing valuable material obtained with consent from patients with melanoma.

Last year, Ludwig Brussels researcher Nicolas van Baren tapped into this infrastructure to uncover a curious facet of melanoma immunobiology. He and his colleagues found that immune structures could develop in metastatic tumors in people with melanoma. These structures, akin to those that develop in lymph nodes, may be a source of immune cells that keep the tumor in check, preventing it from growing or metastasizing further.

Van Baren hopes to learn how to manipulate these structures to prompt their growth or strengthen their immune activity against a tumor. His research could lead to a new way to bump up immune activity against a tumor and add to the pipeline of treatments entering preclinical and clinical testing.

Van Baren's study, which was published in *Cancer Research*, probes the intersection of two long-standing spheres of Ludwig research, melanoma and immunotherapy. Van Baren collaborates with researchers in Oxford, Lausanne and Melbourne as part of the melanoma initiative to study many shared melanoma cell lines and tumors. Says van Baren, "At Ludwig there are many people working on similar topics. This leads to serendipitous interactions that in turn elevate the level of science."