

# UNLEASHING CELLULAR SOLDIERS

Switching on tumor-targeting T cells and turning off their suppressive siblings to kill cancers

**A**s a clinical oncologist, Jedd Wolchok routinely sees patients with advanced melanoma, an aggressive and often lethal cancer. But Wolchok is also an accomplished researcher. Some of his patients are alive thanks mainly to drugs and therapeutic strategies he has helped develop. They include a recent headline-grabbing, two-drug combination tested against advanced melanoma in a phase 1 clinical trial. But even that relatively potent regimen, which is now being assessed against a variety of cancers in large trials, worked only in some of the patients.

To help the others, Wolchok, who leads Ludwig MSK's Collaborative Laboratory, is probing further into his particular field of research—immunotherapy, which harnesses the immune system to attack tumors. In that effort, he must work closely with basic researchers who specialize in immunology.

He doesn't have to go too far to do that. A small stretch of carpet separates Wolchok's office from that of Alexander Rudensky, director of the Ludwig MSK Center and one of the world's leading immunologists. "We seek each other out," says Wolchok of his collaboration with Rudensky. "We have a very nice confluence of complementary interests, from the level of basic science extending to the early stages of clinical investigation."

In 2013, some of the most promising new therapeutic strategies grew out of this meeting of minds.

## TARGETING T CELLS

Rudensky's research focuses on the regulatory T cell, a key agent of the immune system that puts the brakes on immune responses before they do too much collateral damage to healthy tissue. But regulatory T cells also tend to infiltrate tumors, where they perversely quell critical antitumor responses.

In a recent study, Rudensky took a close look at these cells in breast cancer. "This is a type of cancer that has long been thought not to be amenable to immunological means of treatment," he notes. Rudensky and his colleagues asked what would happen when they eliminated regulatory T cells from such tumors: Would other immune cells launch an attack?

That, in fact, is precisely what happens—at least in mice. When the researchers transiently removed regulatory T cells through gene manipulation, they found that tumor cells succumbed quickly to immune attack, and the progression of even well-established and metastatic tumors was slowed.

What's more, when they also treated the regulatory T cell-depleted mice with radiation,



Jedd Wolchok, left, and Alexander Rudensky, Ludwig MSK

the animals suppressed their tumors even more efficiently, and lived considerably longer.

“We were surprised by the magnitude of the effect,” says Rudensky, who credits Wolchok with sparking his interest in clinically relevant research. “Without Jedd, I don’t think we would have gone into this.”

The researchers have shown that an antibody that binds a molecule known as GITR on regulatory T cells can shut down their suppressive activity. They are now testing it in a phase 1 clinical trial in patients with many different types of cancer. This trial is overseen by Ludwig’s clinical trials management team

and is being conducted in collaboration with Ludwig’s longstanding partner, the Cancer Research Institute, and the two institutions’ joint CVC Trials Network.

#### **KILLER COMBINATION**

In addition to paving the way for a new type of immunotherapy, Rudensky’s findings on radiation and T cell ablation illustrate the value of combining distinct types of cancer therapy. And that is a salient theme of Wolchok’s work.

In the phase 1 melanoma trial completed last year, Wolchok combined two immunotherapies: ipilimumab, which has been used since 2011 to treat melanoma, and an experimental drug,

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nivolumab. Each drug targets a specific molecule on the surface of immune cells that functions as a ‘checkpoint’ to dampen their activity. Blocking each of these checkpoints with antibody drugs lifts the brakes on the cellular immune response.

When melanoma patients receive ipilimumab alone, about 20% achieve long-term remission extending over three years, which is a notable achievement. The median survival time for this disease before this and other modern medicines became available was just seven months. Wolchok’s study suggests that combining it with nivolumab has the potential to dramatically improve outcomes. His small trial found that a concurrent regimen of the two drugs significantly shrank tumors in 21 of 52 patients, with 90% of those who responded to the therapy continuing to benefit after more than a year of follow-up.

“We were very pleased by the speed and sheer depth of the response in so many patients,” says Wolchok.

The findings helped convince *Science*, a prestigious journal, to choose cancer immunotherapy as its “breakthrough of the year.” Several pharmaceutical firms are vigorously pursuing agents with activity similar to that of nivolumab. They and a host of smaller biotechnology firms in the immunotherapy field are also looking closely at combined immunotherapies of this kind as a new approach to cancer therapy.

#### FAST FORWARD

Wolchok and others are now testing the combination of ipilimumab and nivolumab in larger clinical trials for melanoma and a variety of other cancers. “It is important to recognize that none of this would have been possible without many decades of basic science,” says Rudensky.

Wolchok notes that Ludwig’s translational support is allowing his team to move its basic research findings quickly into early clinical trials. Just as invaluable, he notes, is the instant access to other top-notch Ludwig researchers, like Rudensky, who are just a stone’s throw from his laboratory.

“It is a pleasure to have such remarkable expertise right next door,” says Wolchok. “This collaboration will endure and I believe it will ultimately be of benefit to people diagnosed with a wide variety of cancers.”

#### REFERENCES

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