Photo by Flynn Larsen

THE IMMUNOTRANSFORMERS

Partners in science Jedd Wolchok and Taha Merghoub solved a pharmacologic puzzle, to boost a cancer immunotherapy.

Ludwig MSK's Jedd Wolchok was at a conference in 2014 when he bumped into Vito Palombella, whose lab bench Wolchok had inherited when he was working toward his doctorate as an MD/PhD student in the 1990s at New York University. Palombella was at the time chief scientific officer at a small biotechnology company named Infinity Pharmaceuticals, and he told Wolchok about an experimental drug that he thought might interest him. The molecule, IPI-549, targets an enzyme critical to a class of immune cells frequently recruited by tumors to squelch a potentially lethal immune attack. "It fit exactly into one of the lines of research in our lab—devising new ways to target these cells, which can be an obstacle to cancer immunotherapy," says Wolchok.

That encounter culminated in a Ludwig study whose results were published in *Nature* in 2016. It established that those suppressive cells, known as myeloid derived suppressor cells (MDSCs), directly mediate resistance to the effects of the immunotherapy known as checkpoint blockade in a variety of tumors. The paper also demonstrated that blocking PI3K-γ, an enzyme expressed by

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tumor-associated MDSCs and targeted by IPI-549, restores the effectiveness of the therapy. Their finding shows how selectively disrupting the noncancerous constituents of the tumor’s microenvironment, which are manipulated in a variety of ways to prevent immune attack, can boost the effects of immunotherapy. The study also opens a new door to the personalization of checkpoint blockade therapy, and to expanding its applicability to cancer types that have so far proved resistant to the treatment.

A CONSEQUENTIAL COFFEE BREAK

When Wolchok got back to New York, where he directs the Ludwig Collaborative Laboratory at Memorial Sloan Kettering Cancer Center, he shared what he had learned with lab co-director Taha Merghoub. The two decided the opportunity was worth a closer look. For all the excitement around immunotherapy, not all cancer patients respond to these treatments, which stimulate the immune system’s innate ability to kill cancer cells. Only about 40% of melanoma patients who take checkpoint blockade therapies known as PD-1 inhibitors to treat advanced melanoma, for example, see their tumors regress. Other malignancies, like breast cancer, have so far proved largely resistant to immunotherapy.

The problem in many cases is that most malignant tumors deploy a variety of defenses against immune attack. These range from biochemical tricks—depriving the foot soldiers of the immune system of vital nutrients—to manipulating the immune cells themselves, recruiting and turning them into enablers and allies of malignant growth.

Wolchok and Merghoub were particularly interested in undoing the latter type of cancerous defense and had considerable experience in probing the phenomenon. They contacted Palombella and arranged to meet up to share their ideas during the October 2014 Hallmarks of Cancer symposium (which stems from the legendary paper of the same title coauthored by Ludwig MIT Director Bob Weinberg).

During a break at the symposium, Wolchok and Merghoub met with Karen McGovern, a senior scientist at Infinity, to go over the data collected in IPI-549’s preclinical development. Infinity had done preliminary work showing that their drug could target a pathway important to the generation of MDSCs. The targeting, however, didn’t appear to have the desired effect in the tumor models being used. Wolchok and Merghoub picked up on the problem almost instantly. “When we saw the data, we had an ‘Aha!’ moment,” recalls Merghoub. “We were like, ‘Ok, you’re dealing with the wrong tumor type here. The target you need isn’t present in these tumors.’ ”

Photo by Flynn Larsen

The models Infinity was using, the Ludwig MSK researchers explained, are not typically infiltrated by MDSCs. “You could have tested this drug on five different tumor types and if none of them had MDSCs, you would have concluded that the drug is inactive,” says Wolchok. The Ludwig researchers mapped out the experiments they’d need to do to explore the immunological mechanisms of IPI-549’s effects—and help Infinity sort out its problem. Eager to tap their expertise, Infinity agreed to support studies they would lead at the Ludwig Collaborative Laboratory at MSK.

THE RESEARCHERS

The company could not have found better researchers to solve their problem. Wolchok, a clinical oncologist and leading authority on immunotherapy, has played a central role in the development of checkpoint blockade and a variety of other immunotherapies currently in clinical trials. Merghoub, an Algerian and the son of a Swiss-trained physician, grew up in a small town, deep in the Sahara, about 500 miles from the coast. After completing his undergraduate studies in genetics in Algiers and a PhD in France, where he studied the genetics of sickle cell anemia and thalassemia, he came to the US for his postdoctoral studies.

The two initially met in Alan Houghton’s laboratory at MSK in 2002, where Wolchok had once done a college internship and returned to conduct postdoctoral research with his mentor while completing his oncology fellowship. Merghoub had joined the lab after a postdoctoral stint studying gene regulation in a form of leukemia in the MSK laboratory of Pier Paolo Pandolfi, who is now an investigator at Ludwig Harvard. When Houghton’s neurological disorder—he has ALS—made it difficult for him to manage the day to day operations of his lab, Wolchok and Merghoub accepted responsibility

Photo by Stewart Marcano

for continuing the lab's operations and, eventually, oversaw its transition into the Ludwig Collaborative Laboratory.

Today they co-direct the lab's scientific investigations. The arrangement has worked out well for both. It has allowed Wolchok, a practicing clinical oncologist, to keep a foot in both the clinical and the scientific world without neglecting either. Merghoub, meanwhile, is able not only to pursue his scientific studies but to see a good share of his discoveries translated to the clinic, given the translational bent of the lab and its ties to clinical trial networks.

"Science is a full-time job and requires total commitment," Wolchok says. "Not being able to clone a human, the best solution is to have two people who scientifically see the world the same way, share a vision for the laboratory and have a track record of working together."

The pair have led several studies to devise novel immunotherapies for cancers and to explore the immunologic mechanisms of response and resistance to these treatments. For them, IPI-549 was an excellent tool to evaluate a hypothesis explaining why checkpoint blockade fails against a number of tumor types. As important, if that hypothesis passed muster in the laboratory, it could be swiftly put to the test in the clinic.

FROM HYDES TO JEKYLLS

The researchers moved quickly to explore the pharmacology of IPI-549 and use it to interrogate tumor immunology. To demonstrate that MDSCs are indeed involved in resistance to checkpoint blockade, they compared two mouse tumor models—one for breast cancer, which is typically resistant to checkpoint blockade, and another for melanoma, which is not.

They showed first that the breast cancer tumors are full of MDSCs and that their presence correlates tightly with reduced infiltration by the killer T cells, which are unleashed by checkpoint blockade to kill cancer cells. Those that do make it in are relatively defanged and ineffectual. The opposite was true in the melanoma model. Further, when they used a growth factor to boost the number of MDSCs in melanoma, it made these previously responsive tumors impervious to checkpoint blockade.

The researchers then examined the effects of IPI-549 on multiple tumor models, and showed that even treatment with this drug alone slowed the growth of tumors rich in MDSCs. Tumors with few such cells, on the other hand, hardly responded. This established that IPI-549 was not targeting the cancer cells directly but exerting its effects by compromising MDSCs in particular—in other words, by perturbing the tumor's microenvironment.

The researchers showed that it was doing so by flipping the identity of MDSCs. "By inhibiting PI3K-γ, we turned the tumor-associated MDSCs from bad guys into the good guys," says Merghoub. Instead of suppressing the immune response against tumors, treated immune cells now activated it, prompting killer T cells to turn their molecular weaponry against cancer cells.

As a consequence, IPI–549 dramatically improves responses to checkpoint blockade therapy in tumors that harbor large numbers of MDSCs, but not against those that do not. The effects appear to be multiplicative in animal models. When a combination of checkpoint inhibitors were administered to mice with MDSC-rich tumors, only 20% of the animals underwent complete remission. When the same drugs were administered with IPI–549, that portion climbed to 80%. Notably, animals whose tumors had regressed completely rejected tumors that were subsequently implanted in them, indicating that they had developed an immunological memory of the cancer that could sustain its durable control.

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The implications are exciting for other reasons as well. Several of the most common types of cancers do not respond to checkpoint blockade, and in many cases this may be due to a high infiltration of MDSCs in their tumors. Merghoub and Wolchok's findings open the door to personalizing checkpoint blockade treatments and could significantly expand the utility of this immunotherapy against a broad variety of tumor types. Best of all, their hypothesis is beginning to be tested now in a clinical trial examining the combined effects of IPI-549 and checkpoint blockade against a variety of solid tumors.