

JEDD WOLCHOK

# CANCER'S GRAPHOLOGIST

WHEN IPILIMUMAB HIT THE CLINIC IN 2011, it was widely regarded a game changer. It gave years of life to many patients with metastatic melanoma, which has historically been a swiftly lethal cancer in its latter stages. Tumors disappeared entirely in some patients.

Jedd Wolchok of Ludwig MSK, who conducted pivotal clinical trials of the antibody drug before its approval by the US Food and Drug Administration, has since participated in many studies of its effects in combination with existing and experimental therapies. And with good reason. For all their promise, ipilimumab and other “checkpoint inhibitors,” when given individually, still help only about 20–40% of melanoma patients.

In 2014, Wolchok finally figured out why.

A study led by Wolchok and his MSK colleague Timothy Chan uncovered a precise set of genetic signatures borne by

tumors that are susceptible to ipilimumab treatment. Their results, published in the *New England Journal of Medicine*, could help improve outcomes for metastatic melanoma by allowing doctors to screen patients likely to respond to ipilimumab and devise other treatment strategies for those less likely to do so.

## Proffered targets

Cancer cells generate countless mutations across their genomes as they multiply. Those mutations are often expressed as subtle changes in the chains of amino acids that make protein molecules. Like all cells, cancer cells chop up and hold out tiny bits of such proteins—each about nine amino acids in length—for the immune system to assess.

The trick is to get immune cells to “see” those mutated bits and respond to the danger they betray. Checkpoint inhibitors accomplish the latter by blocking a molecule named CTLA-4, which is found on killer T cells and functions as a brake on their

activation. With the brakes lifted, immune cells that see the mutated proteins held out by cancer cells proliferate and attack them. But for that to happen, they first have to see the danger.

To explore this phenomenon, Wolchok drew on a unique Ludwig resource. Ludwig MSK has for years saved blood and biopsy tissue from cancer patients treated in

its clinical trials. “This is an international repository of biospecimens that was started by Ludwig’s former scientific director, the late Lloyd Old,” says Wolchok. “It was established to help answer unforeseeable scientific questions that might arise in the future.”

Wolchok had one of those questions. So he and his colleagues accessed samples from

25 patients treated with checkpoint inhibitors. They then compared all of the genes within the tumors and found that, as they expected, tumors with more mutations were more susceptible to CTLA-4 blockade.

But there was more to it than that. A sophisticated computational analysis of the tumor genomes revealed that, within

the bits of proteins presented by cancer cells, there is a defined set of core peptide sequences—each four amino acids long—that are unequivocally associated with response to treatment.

To test the prognostic power of these genetic signatures, the team sequenced the expressed genes of tumors from 39 other melanoma patients treated with CTLA-4

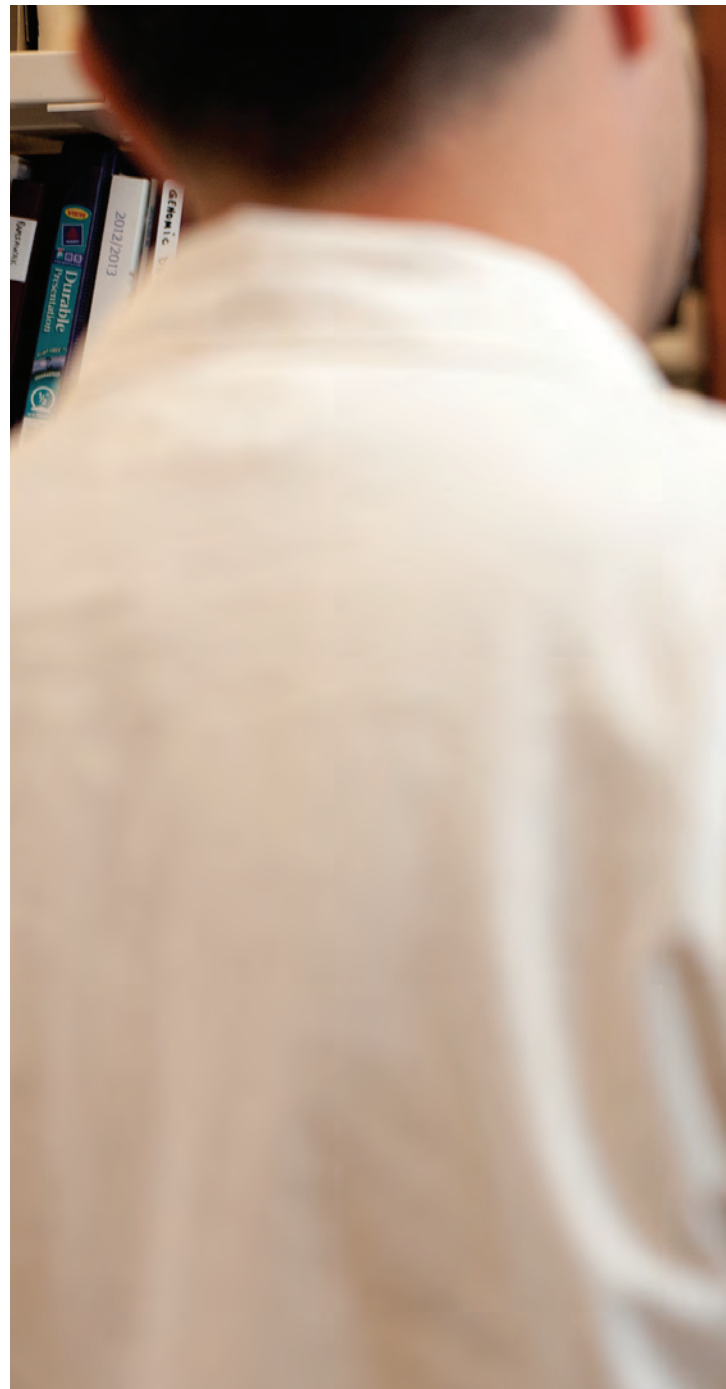
blockade. They found that all those in this set who had responded to the therapy had at least one and typically several more of the core sequences they had identified. Nonresponders did not. Importantly, their results also show that the mutant DNA sequences in those core peptides can occur anywhere in the genome—not just within ‘driver’ genes that are already known to contribute to the growth of cancer.

### **Bigger benefits**

The researchers hope this work will lead to the development of tests to screen patients before they are treated with checkpoint inhibitors. This would save precious time and money—and certainly save lives. “What do you do for those patients who do not have favorable mutations?” says Wolchok. “How do you get the immune system to notice and attack the tumor?”

Wolchok, Chan and their colleagues did notice that some of the core sequences that excite an immune attack in response to ipilimumab closely resemble those borne by known viruses and bacteria. This opens up some tantalizing opportunities for combination therapies using ipilimumab with, say, existing vaccines or even engineered bacteria and viruses (see sidebar). It also suggests that tumors with more mutations, such as those that stem from tobacco use, are likely to be more vulnerable to checkpoint blockade.

Wolchok and Chan note that the vision and long term-funding offered by Ludwig permitted the open-ended storage of tumor samples—and it paid off. “This is a very valuable resource for researchers at Ludwig and the larger biomedical research community,” says Wolchok. “It was indispensable to this study.” ■



### **REFERENCE**

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