

A T cell (left) attacks a tumor cell. MAURIZIO DE ANGELIS/SCIENCE SOURCE

An old antidepressant helps the immune system fight tumors in mice

By [Jocelyn Kaiser](#) | May. 14, 2021, 2:00 PM

Drugs that unleash the body's immune system to attack tumors, known as checkpoint inhibitors, have put some cancer patients into remission for years. But many others don't benefit from the treatments. Now, researchers have found that an old type of antidepressant boosts the power of these inhibitors in mice—and they suspect it could do the same in people.

It's the "first study" to suggest such a role for the antidepressant, called a monoamine oxidase inhibitor (MAOI), says biochemist Jean Chen Shih of the University of Southern California, who was not involved with the study but has long studied the MAO-A enzyme in the brain and, more recently, its role in cancer. She adds that the new combination therapy could benefit cancer patients who don't respond to a widely used type of checkpoint inhibitor known as anti-PD-1 drugs.

Anti-PD-1 drugs block a molecule on the surface of T cells that tumors use to hide from these immune system soldiers. Using a surface protein that binds this PD-1 receptor, cancer cells can put a "brake" on signals that would otherwise cause the T cells to attack. But simply lifting this brake, known as a checkpoint, with anti-PD-1 drugs isn't always enough.

In search of other molecules that might boost T cell responses, cancer immunologist Lili Yang and her lab members at the University of California, Los Angeles, studied gene expression in T cells that had infiltrated mouse melanoma tumors. To their surprise, the researchers found the tumor-infiltrating T cells had unusually high activity of the gene for MAO-A, which breaks down mood-lifting neurotransmitters such as dopamine and serotonin in the brain. The MAOA gene got labeled many years ago [the "warrior gene"](#) because low levels of MAO-A activity in some men have been tied to aggressive behavior. But high MAO-A levels are linked to depression, hence the development of MAOI antidepressants in the 1950s.

Although they aren't used much today because new drugs for depression have fewer side effects, MAOIs are still an approved drug—something that excited the researchers because they could quickly be tested in cancer patients. That "made us jump into studying this molecule," Yang says.

Yang's team found that, compared with normal mice, tumors grew more slowly in mice engineered to lack the MAO-A protein in immune tissues and T cells were less exhausted, producing more molecules toxic to cancer cells. Giving three types of MAOIs to normal mice implanted with mouse melanoma or colon cancer cells caused the tumors to grow more slowly. And combining an MAOI with an anti-PD-1 drug worked better than either drug alone, [wiping out tumors in some mice within 1 month](#), Yang's team reports today in *Science Immunology*.

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produce their own serotonin that helps activate the cells to attack tumor cells, and without it, they lose power. Yang hopes the study will inspire clinical researchers to test cheap, readily available MOAIs in combination with anti-PD-1 drugs. Adding MAOIs to cancer treatment regimens may also ease depression, her team notes.

The new paper's findings are "really interesting results grounded in good science," says Harvard University's Gordon Freeman, a molecular immunologist who co-discovered the PD-1 pathway. He notes that drugs inhibiting various other checkpoints have been combined with anti-PD-1 drugs in clinical trials, but these expensive treatments haven't been "a home run." If an anti-PD-1 drug could be combined with an inexpensive MAOI drug, he adds, "that's a real advantage."

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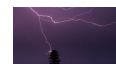
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