STAT

Tuesday, April 18, 2023

IN THE LAB

Novel strategy of attacking sugars on cancer cells to free immune system shows promise in early tests

By Angus Chen

ORLANDO, Fla. — Many cancer cells shroud themselves in a thicket of complex sugars called glycans that help them suppress immune cells seeking to kill them. But in most of cancer research, these glycans have been ignored because they've been exceedingly difficult to study. Stanford biochemist Carolyn Bertozzi had to invent a new field of chemistry, called bioorthogonal chemistry, just to image them — a discovery for which she won the Nobel Prize in Chemistry in 2022.

Now that work is fueling the creation of novel immunotherapy drugs through a biotech that Bertozzi helped co-found, Palleon Pharmaceuticals. At the American Association of Cancer Research annual meeting on Tuesday, researchers presented results from a Phase 1/2 clinical trial testing one of those agents, called E-602, showing preliminary signs of activity and safety. Although the trial doesn't yet show whether E-602 will be effective as a cancer medicine, experts say the data are an encouraging sign that patients may soon see therapeutics born out of an entirely new field of science.

"We need new areas and new science," said Roy Herbst, deputy director of the Yale Cancer Center, who did not work on the trial. "A lot of what you see at a meeting like this are similar things. You know, I don't need another PD1 or PDL1 inhibitor. We need new mechanisms. And now we're starting to check our tumors for glycans at Yale. It's a very emerging area."

To escape immune detection, cancer cells co-opt checkpoint markers like PD1, which will shut down immune cells when activated. Immunotherapies like Bristol Myers Squibb's nivolumab or Merck's pembrolizumab inhibit PD1, allowing the immune system to press on and destroy tumors. These kinds of drugs, called checkpoint inhibitors, have been one of the most powerful tools in medicine against cancer.

"They've had a huge impact on oncology, but they don't work for most patients," Bertozzi said. "In their best situations, maybe half of patients get benefit. So why? We think a big missing piece of the puzzle are these sugars."

All human cells are peppered with glycans, which help the cells interact and communicate with other cells in the body, and can sometimes bind directly to certain receptors on the cell surface. A group of these receptors on immune cells called siglecs bind to a sugar called sialic acid, which is typically the final sugar on a larger glycan molecule. "It turns out when those immune cell receptors bind that sialic acid, it delivers a signal to the immune cell to go to sleep," Bertozzi said. "Successful tumors have to be able to do that, otherwise the immune cell will get rid of the tumor. So, tumors evolve over time to have a lot of sialic acid."

It's possible, Bertozzi added, that some of the patients fail to respond to checkpoint therapy because of this process. Even if an anti-PD1 drug can stop cancer cells from using the pathway to shrug off immune cells, the tumor can still grow a "jungle" of sialic acid containing glycans and suppress the immune system that way.

The idea behind E-602 is to slice off that sialic acid, stopping the glycan from binding to the immune cell and suppressing it. The molecule does this by using an enzyme called sialidase, which can chew the sialic acids off glycans. "I analogize it to a lawn mower," Bertozzi said. "It literally chops these sugars off, and then they float away. Then we deprive the cancer cells of these sugars, so they can't put the immune system to sleep."

Immune cells can become inundated with sialic acids on their own surfaces, which can loop around and bind to their own siglec receptors. That also can cause suppression, and E-602 is designed to remove sialic acids on immune cells as well. "There's types of malignancies where there's so much immune suppression from sialic acids that you want to take the acids from both immune cells and cancer cells," Bertozzi said.

So far, Palleon has tested E-602 in 40 patients with a wide range of cancers including colorectal, pancreatic, non-small cell lung, and ovarian cancer. Most of these patients experienced only mild, grade 1 or 2 toxicities including fatigue, myalgia, and vomiting. The researchers also looked for signs in the blood that suggest the drug was indeed causing immune cells to turn

on more strongly. “We see certain kinds of cytokines and chemokines go up in circulation,” said David Feltquate, Palleon’s chief medical officer. Immune cells called NK cells and T cells taken from the blood also appeared to have increased levels of a certain activation marker called CD69.

That doesn’t necessarily predict that the agent will be effective, said Padmanee Sharma, the scientific director of immunotherapy platform at MD Anderson Cancer Center and who did not work on the trial. “The key pieces are going to be what they show pre- and post-treatment in a tumor biopsy,” she said. That will show if the drug is really reshaping the immune environment around the tumor, Sharma said. Palleon will need Phase 2 studies to show if the drug can be effective for patients, as well.

But the approach overall is a novel and powerful one that Sharma believes will be key to improving patient outcomes, even if E-602 does not pan out in later trials. “It gives us another entryway into how to target immune responses and eradicate tumors,” she said. “It’s definitely an important field, because sialylation plays a clear role in how immune responses are directed.”

What’s most anticipated from the science is how agents targeting sialic acids like E-602 will combine with existing checkpoint therapies. In theory, by hitting a completely different method that cancer uses to suppress the immune system, these drugs could synergize with checkpoint inhibitors, creating more powerful treatments that might benefit more patients. “It’s exciting to see the Phase 1 data because it shows a good safety profile,” Sharma said. “And it gives them the foundation to build in combination with immunotherapy like anti-CTLA4 or anti-PD1 to take advantage of what’s in the field to drive T cell responses and increase the antitumor response.”

There’s some evidence that E-602 does that from lab experiments, said Feltquate. “A goal in immunotherapy is to increase the cure fraction. We can do that by making regimens that combine therapies together,” he said. “And when tested preclinically with other modalities, E-602 makes those other therapies work better.”

Feltquate said Palleon planned to start a Phase 2 study testing E-602’s safety and efficacy later this year, as well as begin more work combining the molecule with anti-PD1 inhibitors.