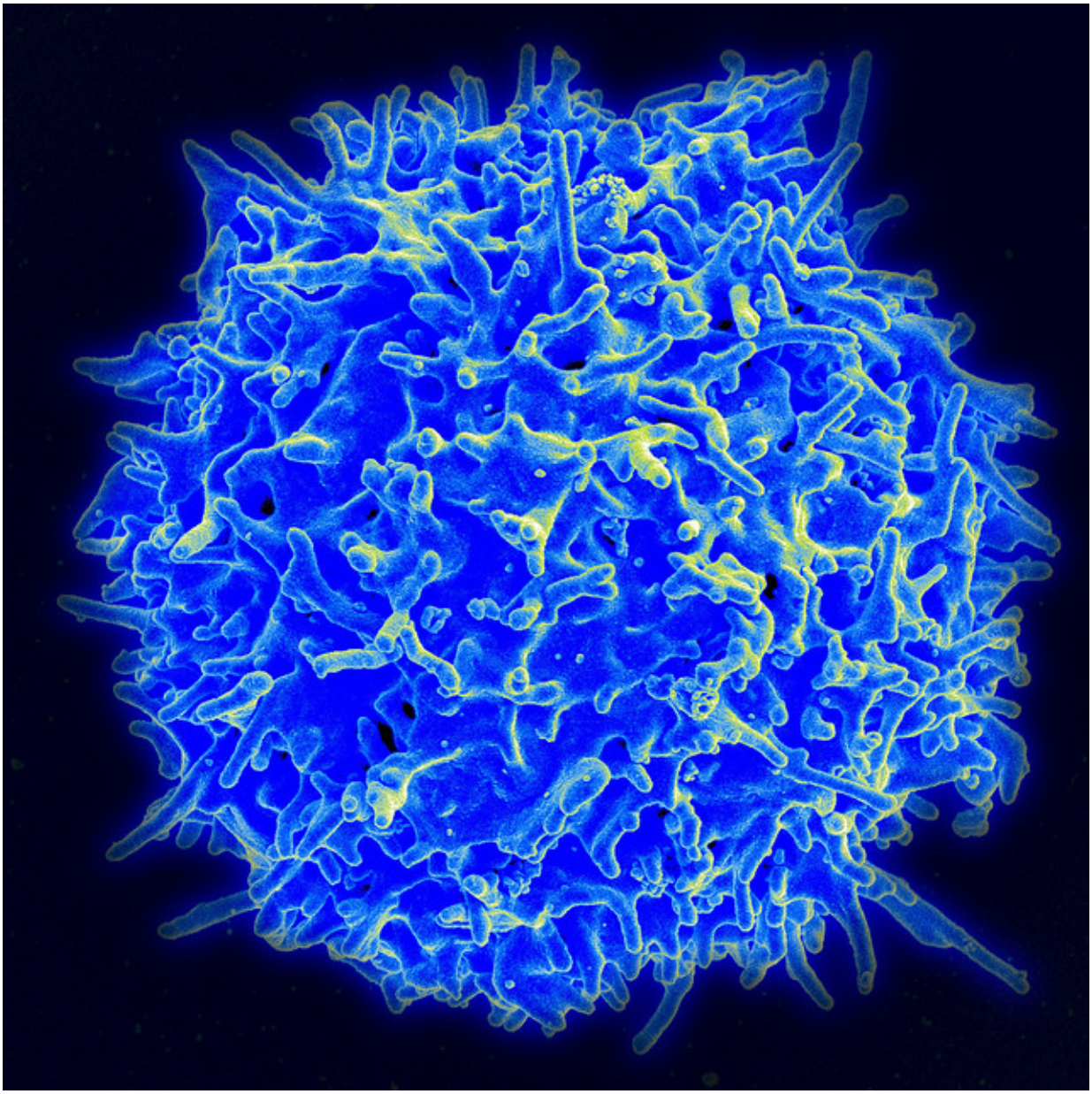
Medical Xpress

Study identifies biomarker that may help predict benefits of immunotherapy

August 25 2021



Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

In recent years, immune-based treatments for cancer have buoyed the hopes of doctors and patients alike. Drugs called immune checkpoint inhibitors have provided lifesaving benefits to a growing list of people with several types of cancer, including melanoma, lung cancer, bladder cancer, and many more.

Despite the excitement surrounding these medications, a frustrating sticking point has been the inability of doctors to predict who will benefit from them and who will not.

On August 25, 2021, a group of researchers from Memorial Sloan Kettering Cancer Center reported in the journal *Science Translational Medicine* that a specific pattern, or "signature," of markers on immune cells in the blood is a likely biomarker of response to checkpoint immunotherapy. Within this immune signature, a molecule LAG-3 provided key information identifying patients with poorer outcomes.

This link was discovered in a group of patients with metastatic melanoma and validated in a second group of patients with metastatic bladder cancer, suggesting that this potential biomarker may be broadly applicable to patients with a variety of cancers.

According to Margaret Callahan, an investigator with the Parker Institute for Cancer Immunotherapy at MSK and the physician-researcher who led the study, the large patient cohorts, robust clinical follow-up, and rigorous statistical approach of the study gives her "enthusiasm that this immune signature is telling us something important about who responds to immunotherapy and why."

The findings pave the way for prospective clinical trials designed to test whether incorporating this biomarker into patient care can improve outcomes for those who are less likely to benefit from existing therapies.

Big data, big conclusion

In making their discoveries, the researchers had data on their side. As one of the first cancer centers in the world to begin treating large numbers of patients with immunotherapy, MSK has a cache of stored blood from hundreds of patients treated over the years, efforts pioneered by MSK researchers Jedd Wolchok and Phil Wong, co-authors on the study. The investigators of this study made their discoveries using pre-treatment blood samples collected from patients enrolled on seven different clinical trials open at MSK between 2011 and 2017.

To mine the blood for clues, researchers used a technique called flow cytometry. Flow cytometry is a tool that rapidly analyzes attributes of single cells as they flow past a laser. The investigators' goal was to identify markers found on patients' immune cells that correlated with their response to immunotherapy—primarily PD-1 targeting drugs like nivolumab (Opdivo) and pembrolizumab (Keytruda). But this wasn't a job for ordinary human eyeballs.

"When you think about the fact that there are hundreds of thousands of blood cells in a single patient blood sample, and that we're mapping out the composition of nearly 100 different immune cell subsets, it's a real challenge to extract clinically relevant information effectively," says Ronglai Shen, a statistician in the Department of Epidemiology and Biostatistics at MSK who developed some of the statistical tools used in the study. "That's where we as data scientists were able to help Dr. Callahan and the other physician-researchers on the study. It was a perfect marriage of skills."

The statistical tools that Dr. Shen and fellow data scientist Katherine Panageas developed allowed the team to sort patients into three characteristic immune signatures, or immunotypes, based on unique patterns of blood markers.

The immunotype that jumped out was a group of patients who had high levels of a protein called LAG-3 expressed on various T cell subsets. Patients with this LAG+ immunotype, the team found, had a much shorter survival time compared with patients with a LAG- immunotype: For melanoma patients, there was a difference in median survival of more than four years (22.2 months compared with 75.8 months) and the difference was statistically significant.

LAG-3 as a target

LAG-3 (short for lymphocyte-activation gene 3) belongs to a family of molecules called immune checkpoints. Like the more well-known checkpoints CTLA-4 and PD-1, LAG-3 has an inhibitory effect on immune responses, meaning it tamps them down. Several drugs targeting LAG-3 are currently in clinical development, although defining who may benefit from them the most has been challenging.

When Dr. Callahan and her colleagues started this research, they did not plan to focus on LAG-3 specifically. "We let the data lead us and LAG-3 is what shook out," she says.

One strength of the study is its use of both a "discovery set" and a "validation set." What this means is that the investigators performed their initial analysis on one set of blood samples from a large group of patients—in this case, 188 patients with melanoma. Then, they asked whether the immune signature they identified in the discovery set could predict outcomes in an entirely different batch of patients—94 people with bladder cancer.

It could, and quite well.

"When we looked at our validation cohort of bladder cancer patients who received checkpoint blockade, those who had the LAG+ immunotype had a 0 percent response rate," Dr. Callahan says. "Zero. Not one of them responded. That's compared with a 49 percent response rate among people who had the LAG- immunotype."

Because of the large data set, the scientists were also able to ask how their LAG+ immunotype compares with other known biomarkers of response—specifically, PD-L1 status and tumor mutation burden. What they found was the immunotype provided new and independent information about patient outcomes, rather than just echoing these other biomarkers.

Why good biomarkers are needed

Biomarkers are important in cancer for several reasons. They may help clinicians and patients select the best treatment and may allow them to avoid unnecessary treatment or treatment that is unlikely to work.

"Immunotherapy drugs are not without potential toxicity," Dr. Panageas says. "So, if we can spare someone the potential risks of a treatment because we know they're not likely to respond, that's a big advance."

The second reason is cost. Immunotherapy drugs are expensive, so having a means to better match patients with available drugs is vital.

And, because the researchers identified this biomarker using patient blood samples, it raises the pleasing prospect that patients could be assessed for this marker using a simple blood draw. Other biomarkers currently in use rely on tumor tissue typically obtained by a biopsy.

"If I told you that you could have a simple blood draw and in a couple of days have information to make a decision about what therapy you get, I'd say it doesn't get much better than that," Dr. Callahan says. "Of course, there is still much work to be done before these research findings can be applied to patients in the clinic, but we are really enthusiastic about the potential to apply these findings."

What's next?

A limitation of the study is that it is retrospective, meaning that the data that were analyzed came from blood samples that were collected years ago and stored in freezers. To confirm that the findings have the potential to benefit patients, investigators will need to test their hypothesis in a prospective study, meaning one where patients are enrolled on a clinical trial specifically designed to test the idea that using this immunotype in treatment decisions can improve patient outcomes.

"What I'm most excited about is prospectively evaluating the idea that not only can we identify patients who won't do as well with the traditional therapies but that we can also give these patients other treatments that might help them, based on our knowledge of what LAG-3 is doing biologically," Dr. Callahan says.

More information: Ronglai Shen et al, LAG-3 expression on peripheral blood cells identifies patients with poorer outcomes after immune checkpoint blockade, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abf5107

Provided by Memorial Sloan Kettering Cancer Center