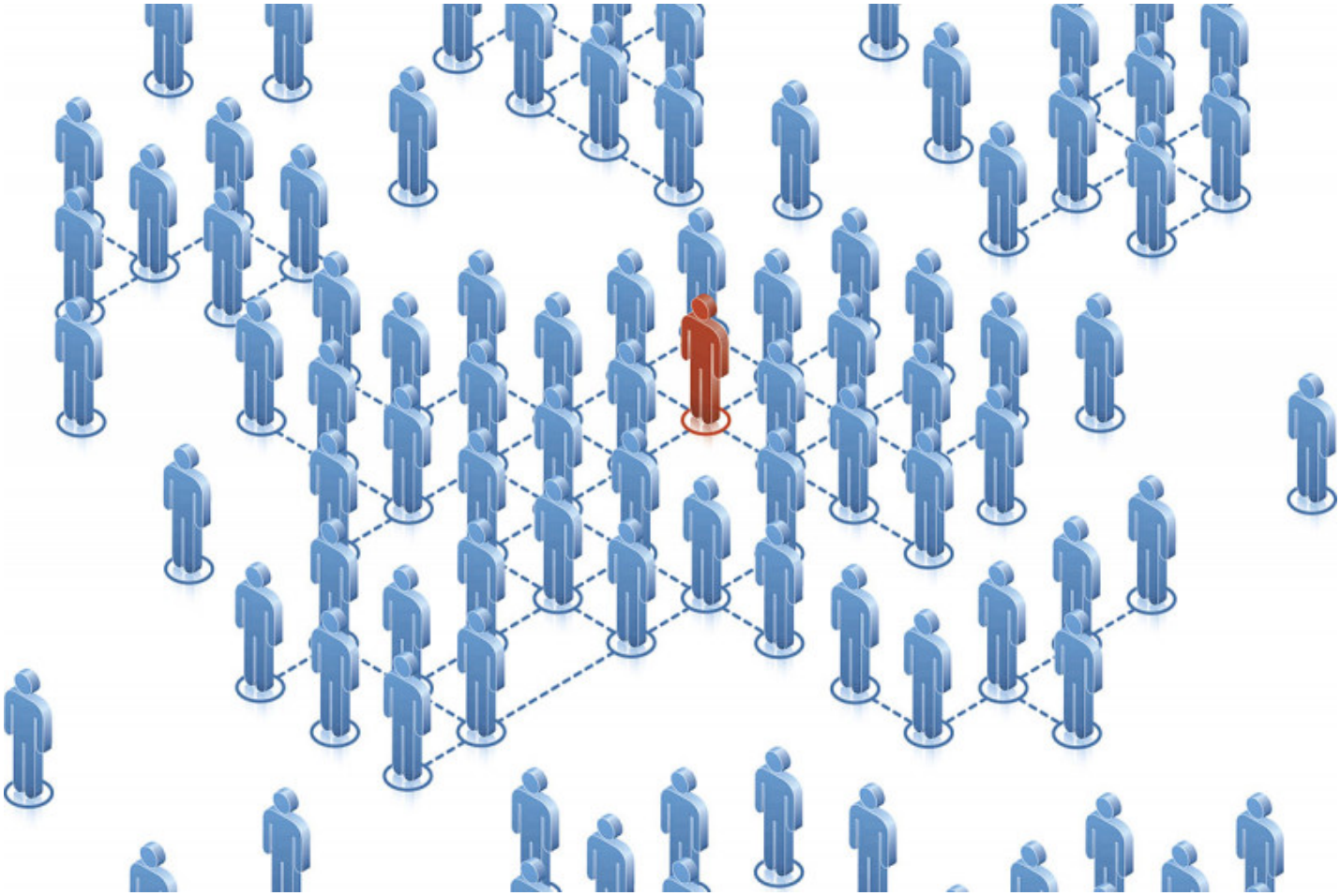
On Cancer

One Patient's Exceptional Response Leads to a Surprising Discovery about Immunotherapy

By Julie Grisham, **Tuesday, April 30, 2019**



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Summary

> Research suggests that a type of genetic change called a gene fusion can send signals that the immune system can recognize.

Findings from a single person with cancer can kick-start a major scientific breakthrough. When one person benefits from treatment in an uncommon way, doctors call it an exceptional response. In this era of personalized medicine, exceptional responses offer clues about how a drug or class of drugs works.

In a **study published** online on April 22 by *Nature Medicine*, a group of Memorial Sloan Kettering doctors and scientists describes one such exceptional response. The research suggests that in some cancers, genetic changes called gene fusions can occasionally send signals that the immune system can recognize. These signals can boost the effectiveness of **immunotherapy drugs called checkpoint inhibitors**. Checkpoint inhibitors take the brakes off the immune system and allow it to attack tumor cells.

"This is a great reminder that despite what we know about how immunotherapy and other cancer drugs work, we're far from understanding all the rules," says physician-scientist **Timothy Chan**, one of the paper's two senior authors.

Checkpoint Inhibitors

Checkpoint inhibitors work by releasing a natural brake on your immune system so that immune cells called T cells recognize and attack tumors.

Learn more

"What we've learned from this one patient has opened a new door," adds surgeon-scientist **Luc Morris**, the paper's other senior author. "Our findings suggest a new way that the immune system can recognize and attack certain types of tumors. But we're really just at the beginning of knowing how to apply this discovery and target these alterations. We are working on the next steps in the laboratory."

An Unexpected Outcome

The exceptional response described in the paper was in a teenage girl with a **head and neck cancer** that had spread to her lungs. She initially saw Dr. Morris, a head and neck cancer surgeon, who began tests to genetically profile the tumor, saving

samples in the hopes of learning more about her cancer in the future. She was then treated by MSK pediatric oncologist **Leonard Wexler** with chemotherapy, which kept the disease stable. When the cancer started growing again, Dr. Wexler decided to try the immunotherapy drug **pembrolizumab (Keytruda®)**.

"Further chemotherapy was unappealing because of the side effects and the limited chance that it would be effective," Dr. Wexler says. "We also knew that the tumor had some unusual features for a head and neck cancer. We decided to think outside the box about how to treat the patient."

Only about 12 to 15% of head and neck cancers respond to drugs like pembrolizumab. An initial analysis of this patient's tumor suggested that she was not likely to be one of them.

There were two reasons for this belief. For one, her tumor had very few mutations. It's known that the more mutations a tumor has, the more likely it is to respond to checkpoint inhibitors. That's because having a lot of mutations means a tumor is more likely to produce proteins called neoantigens, which the immune system recognizes as foreign. **This discovery** was first reported in 2014 by Dr. Chan and his colleagues.

Additionally, her tumor was "cold," meaning it had little immune activity around the tumor cells. By contrast, tumors described as "hot" — with many immune cells interspersed among the tumor cells — are more susceptible to checkpoint inhibitors. Immune cells can more easily find and attack a cancer when they're already in the vicinity.

Despite these factors, the girl's cancer had begun to shrink within five months. After three more months, it had completely disappeared. The MSK team decided to take a deeper dive, studying the tumor in greater detail to figure out why.

> "What we've learned from this one patient has opened a new door."

Luc G. T. Morris
surgeon-scientist

A Focus on Neoantigens

After sequencing the entire genome of the patient's tumor, the MSK team discovered it had a kind of alteration called a gene fusion. Gene fusions occur when a gene from one chromosome breaks off during cell division and attaches to a gene on another chromosome. This new combined gene can make a protein that drives cancer growth.

"The fusion that this patient had was totally unheard of, something that has not been seen before," Dr. Morris says. "But this gene fusion is probably what caused her cancer."

The researchers discovered that the protein created by the gene was a neoantigen. "Neoantigens are seen as foreign by the immune system. They're something that doesn't belong in the body," says Dr. Chan, who is Director of MSK's **Immunogenomics and Precision Oncology Platform**. "In this case, the neoantigen resulting from the gene fusion made the patient's cancer susceptible to immunotherapy."

Looking for Potential Benefit in More Cancer Types

Although this patient's particular gene fusion was rare, other fusions are more common in certain cancer types. The investigators analyzed tumors from other people treated at MSK for a type of head and neck cancer with common fusions. They found that immune cells in these people were able to recognize tumor cells with these gene fusions.

"One of the things that our team is doing now is systematically going through every single gene fusion across human cancers and predicting which ones may result in neoantigens that can be seen by the immune system," Dr. Chan says. "We expect these findings are going to apply broadly to many different types of cancer."

The original patient completed treatment with pembrolizumab and has remained free of cancer. It has been more than 30 months from when she started immunotherapy.

This research was funded by National Institutes Health grants P30 CA008748, K08 DE024774, R01 DE027738, R01 CA205426, and NIH R35 CA232097. It was also supported by **Cycle for Survival**, the Frederick Adler Chair at MSK, the Jayme Flowers Fund, the Sebastian Nativo Fund, the Damon Runyon Cancer Research Foundation, the Adenoid Cystic Carcinoma Cancer

Research Foundation, the Geoffrey Beene Junior Faculty Chair at MSK, the Pershing Square Sohn Cancer Research Alliance, the STARR Cancer Consortium, and the PaineWebber Chair at MSK.

Dr. Chan and Dr. Morris are inventors on a provisional patent application filed by MSK relating to the use of tumor mutational burden (TMB) in cancer immunotherapy. Dr. Chan is also an inventor on a Patent Cooperation Treaty patent application filed by MSK relating to the use of TMB in cancer immunotherapy. MSK and the inventors may receive a share of commercialization revenue from license agreements relating to these patent applications. Dr. Chan is a co-founder of Gritstone Oncology and holds equity. He acknowledges grant funding from Bristol-Myers Squibb, AstraZeneca, Illumina, Pfizer, An2H, and Eisai, and has served as an advisor for Bristol-Myers Squibb, Illumina, Eisai, and An2H. Dr. Morris has received consulting fees from Rakuten Aspyrian and speaker fees from Physician Educational Resources.

Comments

> Commenting is disabled for this blog post.

Gexin Tang

Apr 30, 2019 • 12:52 PM

I am an an anesthesiologist practicing in Orange County , Ca. My sister , who is 64 years old, diagnosed metastatic rectal cancer. The cancer has metastasized to liver and Lungs. She is doing very well considering the metastasis. She just received her first Chemo on April 18 th and tolerated very well. She is ready for next Chemo this Thursday. She had rectal site biopsy NGS done by Foundation One. Also liquid genetic analysis done in City of Hope in Ca. She just had first treatment, so we do not know if she is responding to the chemo. But her clinic symptoms improved significantly, much less cough, no more chest congestion, and much easier bowel movement. I am wondering if I should ask her oncologist to look into gene fusion if she does not respond or stop response to current Chemo therapy? Please advise. Thank you very much.

Gexin Tang, MD

Memorial Sloan Kettering

May 1, 2019 • 3:23 PM

Dear Gexin, we’re sorry to hear about your sister’s diagnosis. She may want to discuss with her medical team whether the testing she had looked for fusion genes, or whether they would recommend additional testing to look for this. This was a study of one patient and it’s too soon to know how broadly these findings will apply,