STAT REPORTS

TARGETING CANCER

The new frontier of immunotherapy and precision oncology

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The rise of a tumor is the product of two things: the sum of genetic aberrations that warp cells into malignancy, and a failure of the immune system to detect and destroy those cells. Some cancers cause this immune system failure by cloaking themselves from the body's defenses. Other cancers do it by taking advantage of immunosuppressive compounds or by cajoling other cells to build a fortress of connective tissue around themselves. Once a tumor has taken root, the immune system by itself cannot overcome the disease.

Over the last decade scientists, using novel technologies, have been devising strategies to give the immune system the upper hand. In this report, you'll learn about these methods, which rely on biological targets — or biomarkers — that make it possible for the immune system to distinguish cancer cells from healthy ones or to remove tools that tumors use to fend the immune system off. The biomarkers could be DNA, peptides, RNA, proteins, or other features of cells. Scientists design drugs or therapies that interact with these targets to attack cancers.

The report focuses on five cancer targets that are the subject of active research by pharmaceutical or biotech companies, and that have recently shown promise in clinical or preclinical research among the countless potential targets that exist. They are: LAG-3, TGF-beta, CLDN6, mesothelin, and KRAS. We'll outline the biology of these targets, as well as the strategies that researchers are using to attack them.

Some strategies the companies are deploying aim to manipulate the machinery of the immune cells known as T cells and unleash their destructive potential. Others involve taking T cells out of patients and

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using genetic engineering to provide the cells with additional weapons to recognize and kill cancer. You'll read in this report about some combinations of immunotherapies that might work together to create a synergistic therapeutic effect.

You'll also learn about the limitations of each target, some of those unique to the target and others common for immunotherapy as a whole. Cancers are vastly diverse, and a target that works for one cancer may not for another — or may not even work for another part of the same tumor. In many cases, tumors evolve resistance to the therapy, as well, rendering it obsolete before the patient has a chance to fully recover.

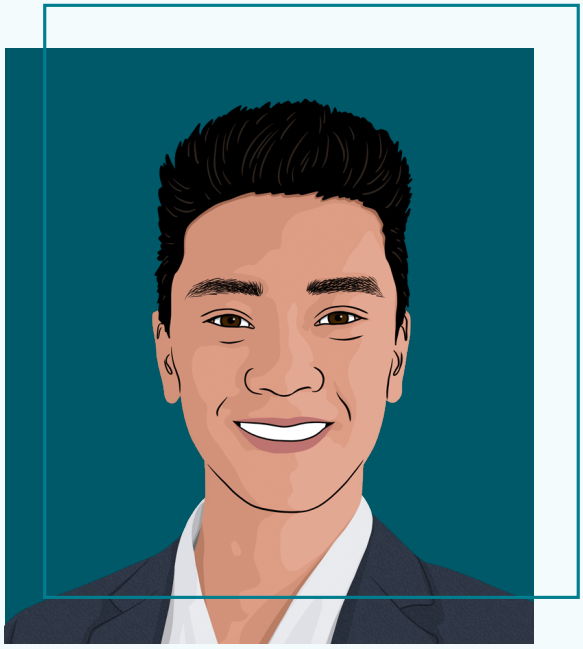
We hope you'll come away from this report with a thorough grounding in the science of these exciting new approaches, and a good sense of which companies are pursuing cancer targets and how that work is proceeding. Therapies for one target alone cannot cure all cancers. But with more targeted therapies, clinicians get more options for more patients, and more chances to eliminate tumors before they can adapt to the therapy. If they prove safe and effective, these new treatments would provide clinicians with more tools to treat cancer, even as it wriggles out from under the existing treatments doctors try. With that comes the vast potential to cure many patients — or at least to offer some of them more precious time.

Angus Chen, STAT cancer reporter

Companies pursuing different cancer targets

CANCER TARGETS	COMPANIES
LAG-3 Short for lymphocyte activation gene, the protein naturally slows the immune system down.	Merck Immutep Novartis Bristol Myers Squibb Agenus/Incyte F-Star MacroGenics EpimAb Roche Xencor GlaxoSmithKline Regeneron Symphogen
CLDN6 Claudin-6 is a gene found on several types of solid tumors.	NovaRock Xencor Context Therapeutics I-MAB Amgen BioNTech Daiichi Sankyo
KRAS TCR KRAS mutations are carried by roughly a third of all human cancers.	Anocca Affini-T Neogene Alaunos Immunocore Gristone Bio T-knife
TGF-beta An inflammatory cytokine that helps cancer cells disable the immune system and metastasize.	Oncotelic Bristol Myers Squibb Genentech Tilos Therapeutics Sirnaomics Thirona Bio
Mesothelin A protein highly expressed on the surface of some cancer cells, but also found in healthy tissue.	Atara Harpoon Cellectis Lonza

THE AUTHOR



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Angus is a cancer reporter at STAT. He was previously a reporter at WBUR and NPR, covering health and science. His work has also appeared in Scientific American, Hidden Brain, 99% Invisible, and other publications and podcasts.