# Researchers chart pathway to 'rejuvenating' immune cells to fight cancers and infections

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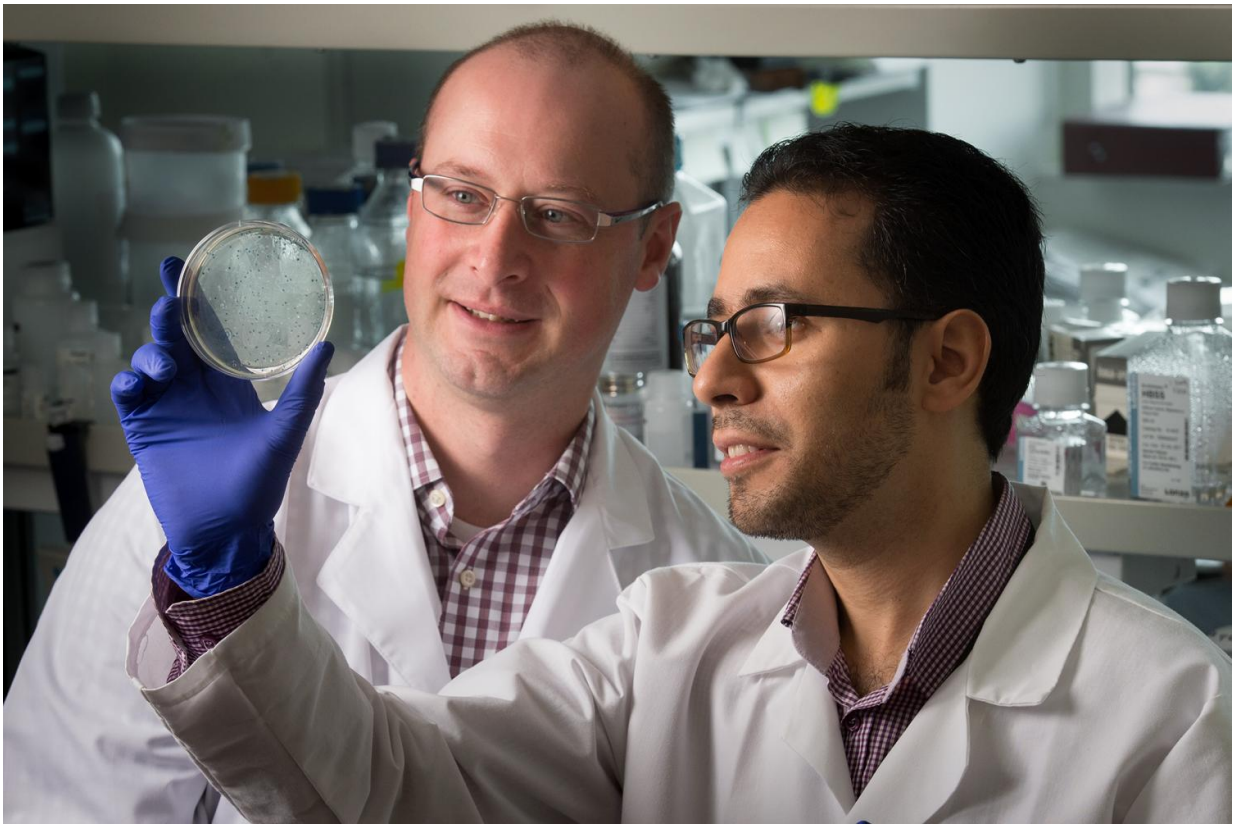

(from left) Corresponding author Benjamin Youngblood, Ph.D., is with first author Hazem Ghoneim. Credit: Seth Dixon / St. Jude Children's Research Hospital

St. Jude Children's Research Hospital immunologists have discovered

how immune cells called T cells become "exhausted"—unable to do their jobs of attacking invaders such as cancer cells or viruses. The finding is important because patients treated with immunotherapies against cancers are often non-responsive or experience a relapse of their disease, and it has been suggested that these challenges may be due to T cell exhaustion. In preclinical model systems studying viral infections or tumors, the researchers found that a chemotherapy drug already in use can reverse that exhaustion.

The finding offers a new pathway to more powerful and durable immunotherapies, as well as immune therapies for viruses such as HIV that would marshal the immune system to kill the virus, researchers said.

In a paper appearing in the June 29 edition of *Cell*, researchers led by Ben Youngblood, Ph.D., an assistant member of the St. Jude Department of Immunology, reported findings that explain the failure of a form of immunotherapy called immune checkpoint blockade. In this treatment, patients receive a drug that releases the brakes on their T cells allowing them to kill virally infected or tumor cells. The tumor-fighting T cells detect a protein called an antigen on the cancer cells' surface that triggers the attack. Youngblood said T cell exhaustion in such immunotherapies is a major roadblock to successful treatment.

"The clinical significance of T cell exhaustion is huge, because when a person comes into the clinic with a tumor, it is likely they have had it for many months," he said. "And their T cells, which would be responding to that tumor, have been exposed to the tumor antigen for a long time. This may likely be why immunotherapy fails in many patients, because their T cells are already exhausted or stably repressed."

In preclinical studies, the researchers explored the mechanism by which both viral infection and a tumor caused T cell exhaustion. They found the culprit was a so-called "epigenetic program" that repressed the T

cells' ability to respond to tumor antigens.

Epigenetic controls are molecular switches that turn genes on or off to control the cell's machinery. While the genome of thousands of individual genes is like data stored on a computer disk, the epigenome is like a set of computer programs that control how stored data are read.

In their experiments, the researchers found that the exhaustion program was passed on to successive generations of T cells. Specifically, they found that the epigenetic program involved a process called DNA methylation, which is a key epigenetic off-switch. They also found that the exhaustion program persisted, even after the T cells were not exposed to the triggering antigen.

"We thought there should be epigenetic changes that affected the biology of the T cells, but it was a real surprise how much impact the changes had on their biology," Youngblood said.

He and his colleagues discovered the exhaustion process was intrinsic to the T cells. This finding has important implications for immunotherapies in which a patient's T cells are engineered outside the body to supercharge them to fight a cancer and then are reintroduced into the body.

"Now that we have shown this is an intrinsic property of T cells, it means you can pull out the T cells, treat them, and reintroduce them to attack the cancer," Youngblood said. "With such approaches, you limit toxicity to the patient."

The researchers found that treating the T cells with a widely used immune-checkpoint inhibitor called PD-1 did not erase the epigenetic exhaustion finding. "This finding shows that, at least for this particular therapy, the therapeutic effect may be inherently transient and prone to

relapse," Youngblood said.

However, when researchers treated mice that had tumors with the chemotherapy drug decitabine, their T cells showed properties indicating enhancement. Decitabine acts to thwart the epigenetic DNA methylation off-switch.

"We found this treatment reversed the exhausted state," Youngblood said. "When we treated the mice with PD-1, their T cells proliferated actively and had the properties of rejuvenated T cells." The researchers found the enhanced T cell proliferation was coupled with significant control of tumor growth. The findings suggest that combining epigenetic reprogramming with immune-checkpoint blockade could enhance treatment efficacy.

Youngblood said the findings have important implications for treating chronic viral infections, notably HIV.

"We know the T cells in patients with HIV become exhausted," he said. "Although there are very effective drugs that reduce the viral load to undetectable levels, that therapy is costly and is not a cure. I'm optimistic that the immune system holds the ultimate promise of a cure for HIV infection, and basic findings such as ours represent one step toward that cure."

Youngblood emphasized the findings reported in *Cell* were made using viral and tumor models in mice, not humans. So he and his St. Jude colleagues are now exploring the epigenetic exhaustion programs in human cancers to determine whether they are similar to the one they identified in mice.

The researchers are also seeking to understand differences and similarities between the T cell exhaustion programs in cancers and viral

infections. Such basic understanding will aid the application of immunotherapy to chronic viral infections such as HIV, Youngblood said.

**More information:** Hazem E. Ghoneim et al, De Novo Epigenetic Programs Inhibit PD-1 Blockade-Mediated T Cell Rejuvenation, *Cell* (2017). DOI: 10.1016/j.cell.2017.06.007

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