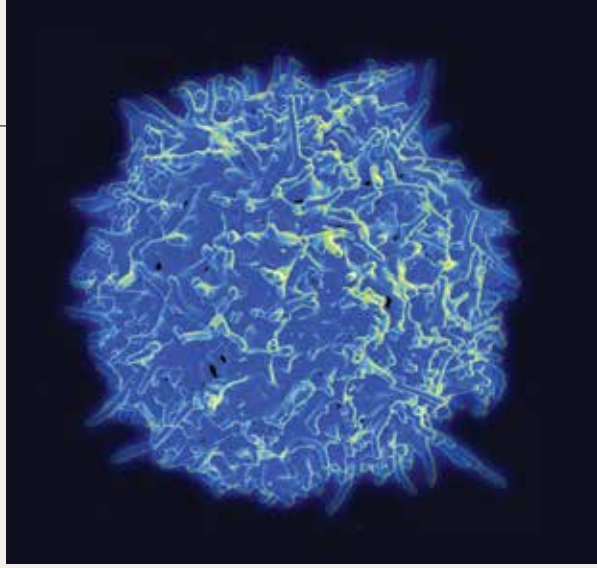


The immune system's T lymphocytes, like this one, need downtime to do their job properly.

T Cell Burnout

Some immune cells function better after taking a break.

EVERY LIVING BEING needs to rest. Even our immune cells enter a dysfunctional state called T cell exhaustion if they're overworked. In fact, this fatigue and the ensuing downtime are important parts of the immune process.

Killer T cells get their name from their function. They target sickened cells involved in chronic infections, killing them before the viruses inside can replicate and spread. But chronic infections can be lengthy, and after a few weeks of sustained action, cellular exhaustion often sets in. The T cells become less effective at slaying their targets and begin producing proteins that prevent them from recognizing infected cells.

One of these proteins is called programmed cell death protein 1, or PD-1. Susan Kaech, an HHMI early career scientist at Yale University, discovered a feedback loop by which PD-1 activation leads to an increase in a protein called FOXO1. FOXO1, in turn, produces factors that promote T cell exhaustion, including more PD-1. Kaech suspected that eliminating FOXO1 might curtail T cells' exhaustion and make them better killers.

What she found was the exact opposite. When her team created mice lacking the *FOXO1* gene, the rodents' T cells did produce less PD-1 compared to animals with the gene. But the cells weren't better at controlling the viral infection. Instead, without the rest afforded them in their exhausted state, the cells died, and viral replication increased.

Kaech concluded that T cells need this respite to function properly. "They have to turn down their response or else they'll get over-activated, and we think that causes the cells to deteriorate and die," she says. "We're starting to appreciate that exhaustion is an important process that is helping to maintain this precious pool of T cells."

The findings, published November 20, 2014, in *Immunity*, could lead to drugs that modulate FOXO1 and help reinvigorate the immune response of patients being treated for chronic viral infections or even cancer. "There may be a point where you can stop the cells from fully entering the exhausted state – where you suppress PD-1, but not so much that the cells die," Kaech says. *–Nicole Kresge*

IN BRIEF

SEEING RED

As a fish swims, nerve cells fire in its brain, sending signals racing along a neural network ending in muscles that make its fins flap and its tail swish. By using a molecule called CaMPARI to permanently mark neurons as they fire, scientists can now watch as signals light up such neural networks in live animals.

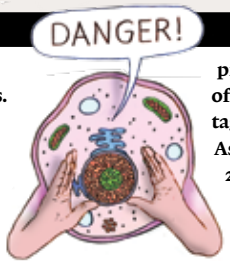
CaMPARI came out of a collaborative project spearheaded by Eric Schreiter, a senior scientist in Group Leader Loren Looger's lab at the Janelia Research Campus. The team started with a protein called Eos, which emits a green glow until it's exposed to violet light. The light changes the molecule's structure, causing it to glow red. By combining Eos with the calcium-sensitive protein calmodulin, the researchers were able to couple Eos's color change to the burst of calcium that accompanies neuronal signaling. The resulting molecule indelibly tags firing neurons with a red glow in the presence of violet light.

"Ideally, we would flip the [violet] light switch on while an animal is doing a behavior that we care about, then flip the switch off as soon as the animal stops the behavior," Schreiter explains. "So we're capturing a snapshot of neural activity that occurs only while the animal is doing that behavior."

The scientists published their results February 13, 2015, in *Science*. Although they are still tinkering with CaMPARI to make it more sensitive and reliable, they've already made it available to scientists on Addgene and the Bloomington Drosophila Stock Center. Janelia Group Leader Misha Ahrens is also distributing CaMPARI-expressing zebrafish.

IMMUNE RALLY CRY

Like a Good Samaritan, a cell that's been attacked by a virus warns neighboring cells to shore up their defenses. These alerts are sent via a family of proteins called interferons, which are produced when surveillance proteins in the infected cell detect a pathogen. Although several different surveillance proteins scout for signs of pathogens, new research shows how the proteins all activate a single molecule called IRF3 to turn on interferon production.



There are three known pathways that trigger type 1 interferon production. In each case, the individual pathway's unique surveillance protein uses its own adaptor protein to relay the message that an invader is present and interferon is needed. Siqi Liu, a graduate student in HHMI Investigator Zhijian "James" Chen's lab at the University of Texas Southwestern Medical Center, noticed that all three adaptor proteins have similar stretches of five amino acids that became tagged with phosphate groups. As the team reported March 13, 2015, in *Science*, the addition of a phosphate molecule to that stretch of amino acids causes the adaptors to activate IRF3.

Now that they know how the interferon pathways converge, Chen and his team are examining them in more detail. Eventually, they hope to develop small molecules that treat immune disorders by interfering with the pathways.

A CAT TALE

A central tenet of biology is that each amino acid in a protein is specified by a three-letter code found in messenger RNA (mRNA). That may be true most of the time, but HHMI Investigator Jonathan Weissman at the University of California, San Francisco (UCSF), along with Onn Brandman at Stanford University and UCSF

Photo: National Institute of Allergy and Infectious Diseases; Illustration: Leif Parsons