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For infection-fighting cells, a guideline for expanding the troops

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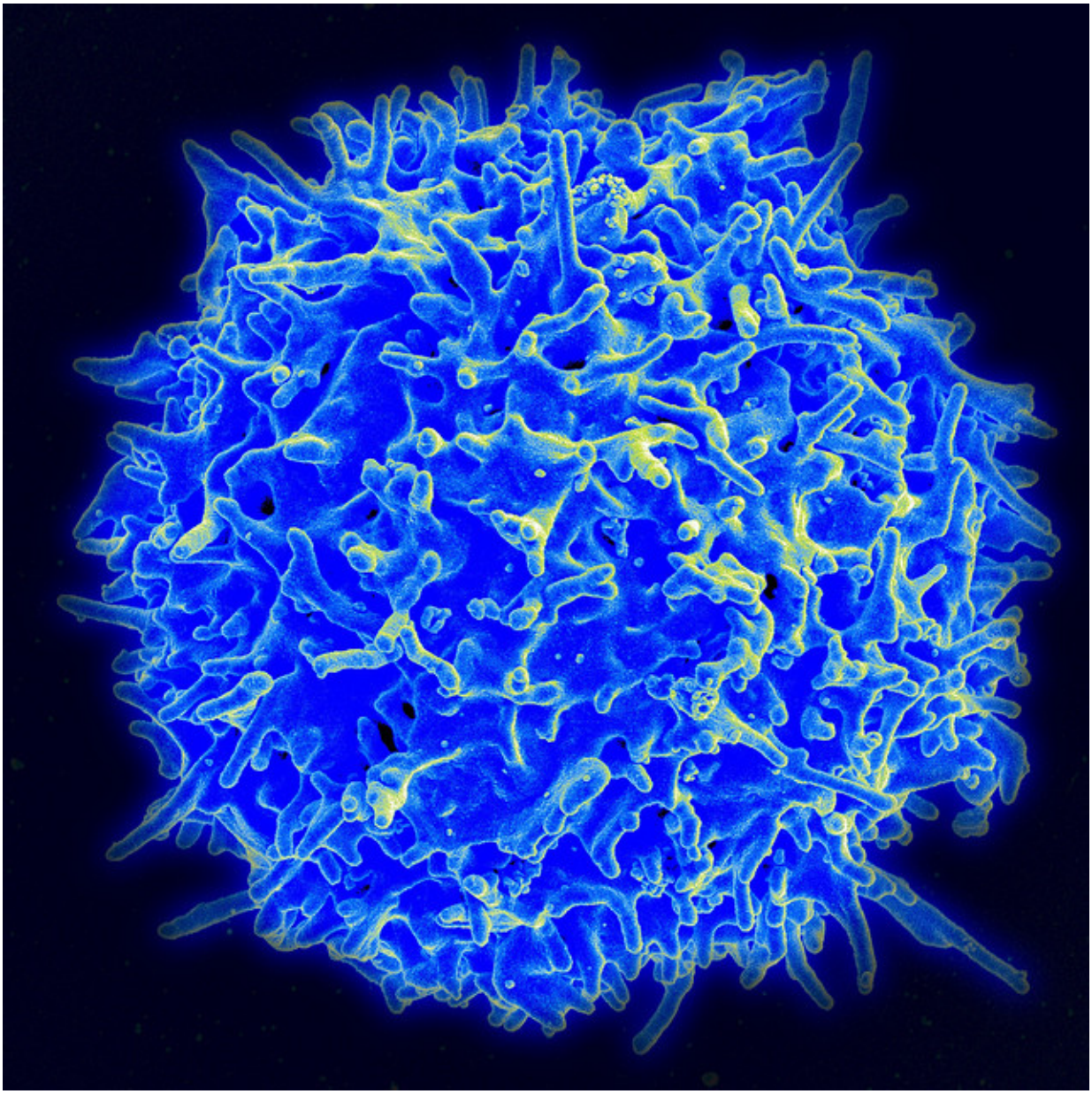

Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

T cells are like the special ops forces of the immune system, detecting and killing infected cells. When a new threat is detected, the cells ramp up from just a few sentry cells to a full platoon. But how does the immune system make just the right amount of T cells, when the starting populations of T cells vary?

Now a team from Princeton has provided insight into this question using mathematical modeling. The team found that the most important factors in how T cells expand were the starting amount of infectious agent and the affinity of the cells for that agent. The research, which could help optimize vaccine strategies, was published online last week in the journal *Proceedings of the National Academy of Sciences*.

The Princeton team became intrigued by this question after a recent study by another team (Quiel, *et al.*) found that this ramp-up follows a predictable pattern: If the initial number of T cells is small, the ramp-up is large, but if beginning number of T cells is large, the ramp-up is small. This relationship follows a mathematical "power law," which states that the amount of T cell expansion depends inversely as a power of the initial number of T cells.

"The significance of this observed relationship is that even though the immune system is very complicated and has all sorts of feedback mechanisms, you see a kind of regularity, meaning there is likely to be some sort of simple underlying mechanism at work," said Ned Wingreen, the Howard A. Prior Professor in the Life Sciences, a professor of molecular biology and the Lewis-Sigler Institute for Integrative Genomics, and senior author on the study. "Whether you start

with 50 or 50,000 cells, the process that is governing their amplification is the same."

The upshot of this relationship is that, whether there were few or many T cells to begin with, the final number ready to fight infection is neither too large nor too small. This makes sense for the organism fighting the infection, but the Princeton team wondered what is happening in the immune system to make this selective ramp-up possible.

First author Andreas Mayer, associate research scholar in Princeton's Lewis-Sigler Institute for Integrative Genomics, and the team used mathematical modeling to explore how T cells respond when an infection occurs.

T cells are dotted with receptors capable of detecting bits of infectious agents, known as antigens, on the surface of infected cells. When the T-cell receptors stick to antigens on the surface of these cells, the T cells are spurred to clone themselves to make an infection-fighting army.

Early in a new infection, antigen-presenting cells display lots of antigens on their surfaces, but this presentation wanes over time, especially if the infection is being successfully fought by the immune system.

The team found that these waning levels of antigen provide a simple mechanism which can explain the power-law relationship.

The idea is that T cells amplify at their maximum rate until the decreasing number of antigens means that the T cells are no longer able to find antigens.

"If you start off with a low number of T cells, you get to expand for longer until you reach the decreasing level of antigens," Mayer said. "But if you start off with a larger number of T cells, then relatively quickly

you run out of antigens." T cells that cannot find antigens eventually stop dividing.

This relationship makes evolutionary sense, Wingreen said, because when the infection is gone, the T cells stop expanding, keeping the immune system from becoming overactive.

The team also looked at another facet of the relationship between T cells and antigen-presenting cells: how strongly the two interact. Their model predicted that cells that stick strongly to the antigen will proliferate for longer: the higher the affinity for the antigen, the larger the final number of cells. The researchers were able to check this prediction by reanalyzing data from another previously published study (Zehn, *et al*.).

"We are particularly excited that our model can explain multiple phenomenological laws of how T cells expand," Mayer said. "When we started, we did not expect such a simple mechanism to explain so many disparate observations."

These relationships suggest lessons for vaccine developers, Wingreen said. Vaccines involve the use of antigens to stimulate the production of immune system cells. Mathematical models may help researchers figure out how much antigen is needed to achieve an optimal immune response.

The study, "Regulation of T cell expansion by antigen presentation dynamics," by Andreas Mayer, Yaojun Zhang, an associate research scholar in physics at the Princeton Center for Theoretical Science, Alan S. Perelson of Los Alamos National Laboratory, and Ned S. Wingreen, was published online on March 8, 2019, in the journal *Proceedings of the National Academy of Sciences*.

More information: Andreas Mayer et al, Regulation of T cell expansion by antigen presentation dynamics, *Proceedings of the National*

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