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To ensure that the tool would be useful to researchers working on drug design, Forbes and Harry Jubb, PhD, at Sanger partnered with Astex Pharmaceuticals (Cambridge, UK), which specializes in structure-based drug discovery.

"For small-molecule therapies, a prerequisite for drug binding is to have a concave binding pocket on a protein target, into which a small molecule can be designed to modify the protein's function," Forbes explains. To visualize the molecule's predicted drug binding sites and pockets, where known cancer mutations occur in relation to those areas, and how the mutations are likely to alter these parts of the protein, COSMIC-3D users simply need to enter the protein of interest.

Cancer researchers are beginning to explore the catalogue, which was launched in May. "I think it's great that COSMIC is expanding to think about 3-D protein structure and what this can contribute to the analysis of genetic mutations in cancer," says Rachel Karchin, PhD, a computational biologist at Johns Hopkins University in Baltimore, MD. "You can learn so much about protein function from looking at protein structure. Often, we try to interpret the functional importance of somatic mutations by their proximity to things like binding sites. What you miss when you don't look at 3-D protein structure is that things that appear to be far apart in the sequence may be very close together when the protein is folded."

Karchin notes that COSMIC-3D joins several other tools for exploring cancer mutations in 3-D, including 3D Hotspots (3dhotspots.org), Cancer3D (www.cancer3d.org), and MuPIT Interactive (mupit.icm.jhu.edu/MuPIT_Interactive), which was created by her lab. However, she says that it has been challenging to get scientists who are not structural biology experts interested in this area. For this reason, she suggests that developers who want to appeal to the broader research community ask, "Could somebody who does not know structural biology benefit from this tool?"

Forbes hopes that for COSMIC-3D, the answer is yes. "We would like to encourage cancer researchers and clinicians to explore the millions of mutations in the COSMIC database from our new perspective." *–Kristin Harper* ■

Macrophages Promote Resistance to Checkpoint Inhibitors

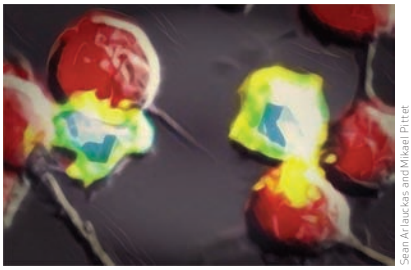
A new study identifies a surprising mechanism for resistance to checkpoint inhibitors: Macrophages prevent the drugs from working by removing them from T cells, the authors found (Sci Transl Med 2017;9:eaal3604).

Checkpoint inhibitors such as nivolumab (Opdivo; Bristol-Myers Squibb) block the PD-1 receptor on the surface of CD8+ T cells, freeing the cells to attack tumors. For reasons that aren't clear, however, no more than 30% of patients respond to the drugs.

Mikael Pittet, PhD, of Massachusetts General Hospital in Boston, and colleagues wanted to find out more about how the drugs interact with cells *in vivo*. They injected cancer cells into mice and allowed up to 8 days for tumors to become established. Then the researchers injected the animals with fluorescently labeled anti–PD-1 antibodies and used intravital microscopy to track the drug. As expected, the antibodies first stuck to T cells. "But only a few minutes later, these T cells were essentially devoid of the drug," says Pittet. The drug had started shifting to macrophages. Within 24 hours, macrophages had collected almost all of the antibodies.

The researchers found that this transfer depends on Fcγ receptors on the macrophages, which bind to IgG molecules, thus stimulating or inhibiting the cells. When Pittet and colleagues blocked these receptors *in vitro* with a different kind of antibody, macrophages captured fewer anti–PD-1 antibodies from T cells. Fcγ receptor binding is dependent on a glycan on the Fc region of the anti–PD-1 antibodies and on nivolumab, the scientists discovered.

To determine how the macrophages' removal of the drug affected the efficacy of anti–PD-1 treatment, the researchers gave mice an anti–PD-1 antibody and



Sean Arlauckas and Mikael Pittet

Macrophages (red) in the process of removing anti–PD-1 antibodies (yellow) from CD8+ T cells (blue).

an antibody that blocks the Fcγ receptor. The animals' tumors disappeared in less than 15 days. In some mice that received only the anti–PD-1 antibodies, however, tumors continued to grow.

"This mechanism is completely novel," says Bianca Santomasso, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, who wasn't connected to either study. "How broadly applicable this [mechanism] is going to be remains to be seen," she says. However, the study "opens up the potential for looking downstream to check on what effect it is having on susceptibility to checkpoint inhibitors."

If additional studies confirm that macrophages are behind resistance to checkpoint inhibitors in patients, Pittet and colleagues suggest several ways to counteract the effect. Researchers could redesign the drugs to alter the Fc domain and prevent binding to the Fcγ receptor, for example. Alternatively, treating patients with molecules that block the receptor or drugs that inhibit macrophages—several of which are already in clinical trials—might boost the effectiveness of anti–PD-1 antibodies. *–Mitch Leslie* ■

UNC Cancer Center Director to Lead NCI

President Donald Trump has selected Norman "Ned" Sharpless, MD, an accomplished cancer researcher, clinician, and administrator, to lead the NCI. Sharpless, who has directed the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center since 2014, succeeds Doug Lowy, MD, who has served as acting director for the past 2 years.

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AACR American Association for Cancer Research

CANCER DISCOVERY

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