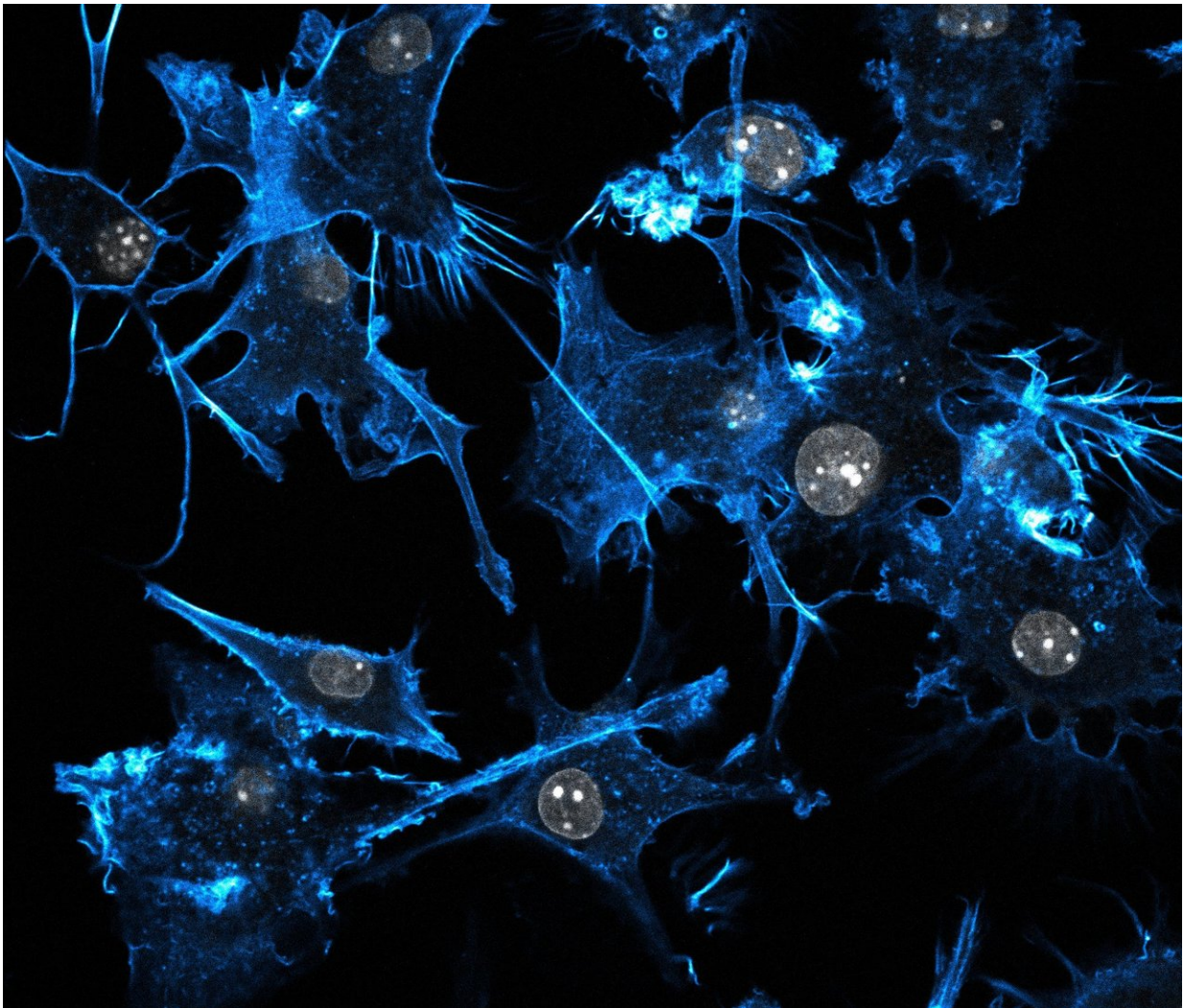


Drug combination overcomes barrier to effective melanoma immunotherapy

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Macrophages can be targeted to improve melanoma immunotherapy. Credit: M. De Palma (EPFL).

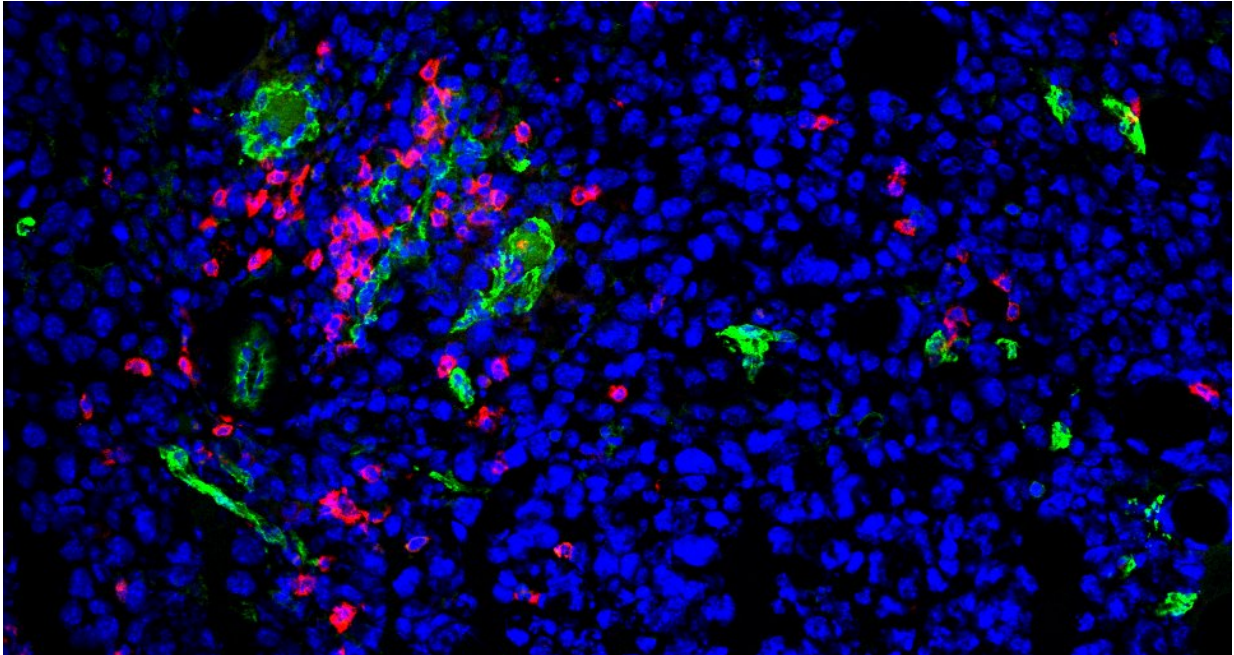
Immunotherapies are treatments that stimulate a patient's immune cells to attack tumors. They can be very effective in melanoma—a common and aggressive form of skin tumor—but nonetheless fail in the majority of patients. To address this, researchers are trying to identify the factors that enable successful immunotherapy, as well as those that may limit it. The ultimate goal is to open new avenues for immunotherapies that are more broadly effective in melanoma and potentially other cancer types.

Certain immune cells, called CD8 T cells (or cytotoxic T lymphocytes), can recognize and kill [melanoma cells](#), and thus have the potential to eradicate tumors. Immunotherapies stimulate the CD8 T cells to attack tumors more vigorously. But the activity of CD8 T cells can be suppressed by other immune cells present in tumors.

Studying a subset of [melanoma](#) patients, researchers led by Michele De Palma at EPFL and Daniel Speiser at the University of Lausanne have identified [macrophages](#) as the culprits driving resistance to a leading immunotherapy, PD-1 checkpoint blockade.

"The existence of [immune cells](#) that either execute or suppress cytotoxic immune responses is essential for limiting the potentially deleterious effects of an uncontrolled [immune response](#), a condition that may lead to autoimmunity or organ damage," says De Palma. "The problem is that tumors hijack these regulatory mechanisms to their own benefit, so that they can grow largely unchecked by the immune system."

By analyzing samples obtained from the patients' tumors, Speiser and his colleagues found that the CD8 T cells release signals that indirectly attract the macrophages to the tumors, establishing what they refer to as a "dangerous liaison" in melanoma.



CD8 T cells (red) infiltrate a melanoma. Credit: M. De Palma (EPFL)

"It is a sort of vicious cycle," says Speiser. "The good side of the coin is that the CD8 T cells get activated by certain [tumor](#) antigens and initiate a potentially beneficial immune response against the tumor. The bad side is that, when activated, the CD8 T cells also induce the production of a protein in melanoma called CSF1, which attracts the macrophages." Indeed, melanomas that attract many CD8 T cells frequently contain many macrophages, which can weaken the efficacy of PD-1 immunotherapy.

Once recruited en masse to the tumor, macrophages suppress the CD8 T cells and dampen the anti-tumoral immune response. But when the scientists used a drug to eliminate the macrophages in experimental models of melanoma, they found that the efficacy of PD-1 checkpoint blockade immunotherapy was greatly improved.

The findings support the clinical testing of agents that disrupt macrophages in combination with PD-1 immunotherapy in patients whose melanomas contain high numbers of both CD8 T cells and macrophages. "As opposed to targeted therapies that hit specific oncogenes responsible for the growth of the tumor, immunotherapies largely lack biomarkers that can predict whether a patient will respond or not to the treatment," says De Palma.

"Our study suggests that assessing the abundance of macrophages and the contextual presence of CD8 T-cells—for example by measuring genes that are specifically expressed by these [cells](#)—may serve to stratify patients who are amenable to more effective immunotherapy combinations," says Speiser.

More information: Natalie J. Neubert et al, T cell–induced CSF1 promotes melanoma resistance to PD1 blockade, *Science Translational Medicine* (2018). [DOI: 10.1126/scitranslmed.aan3311](https://doi.org/10.1126/scitranslmed.aan3311)

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