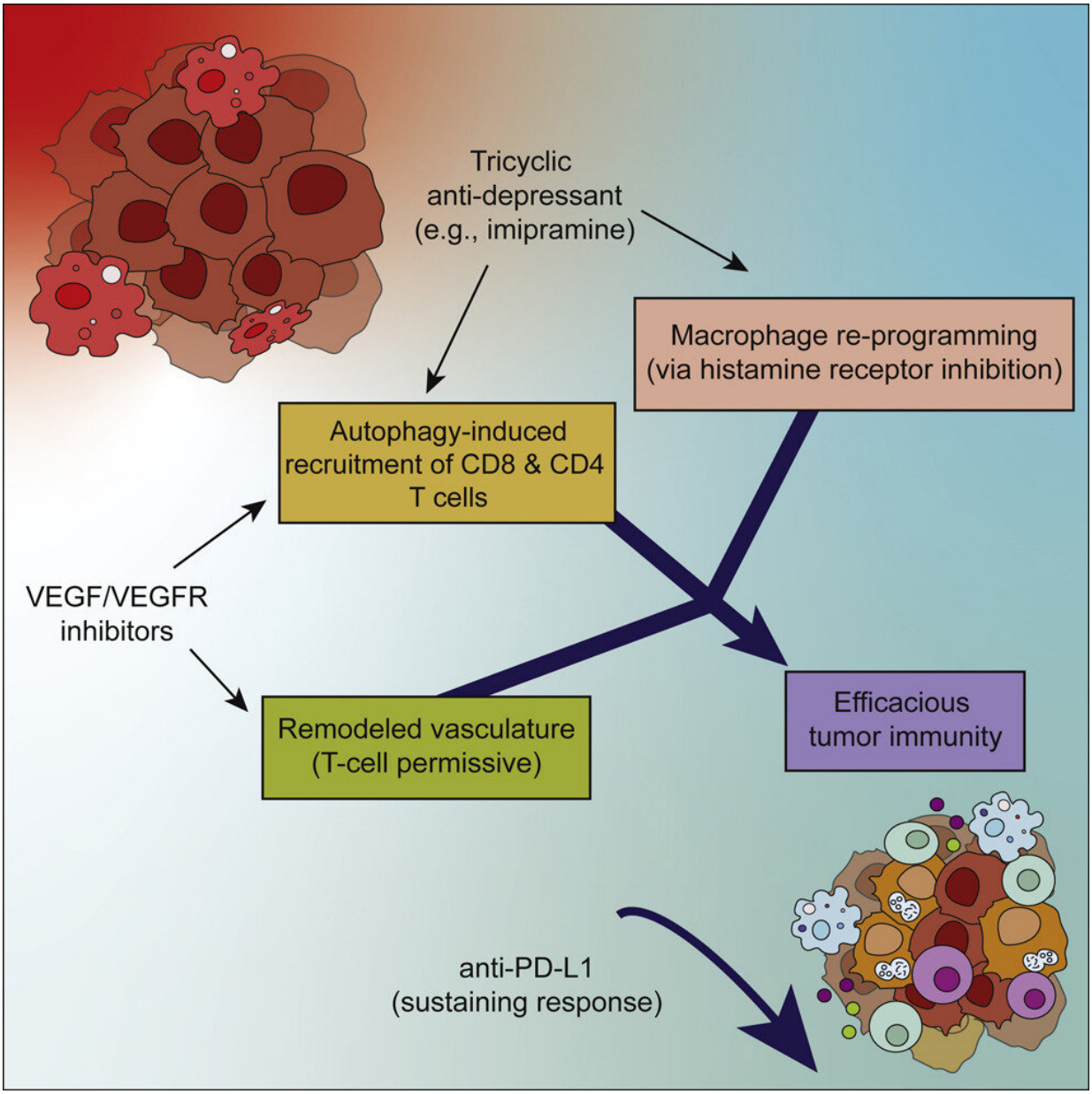
Study identifies potential combination therapy for testing in deadly brain cancer

September 20 2022



Graphical abstract. Credit: *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.08.014

A Ludwig Cancer Research study has identified a combination of three existing drugs that significantly extends survival in mouse models of the lethal brain cancer glioblastoma multiforme (GBM).

Researchers led by Ludwig Lausanne's Douglas Hanahan report in the current issue of *Cancer Cell* how the drugs used in the combination—an antidepressant, an immune checkpoint blockade antibody and a mouse analog of a cancer therapy that by themselves provide no survival benefit against GBM—synergize to unleash potently therapeutic immune responses against the tumor.

"Our investigation illustrates the great potential of drug repurposing for cancer therapy," said Hanahan, distinguished scholar at the Ludwig Institute for Cancer Research Lausanne Branch. "We've shown here that three extensively characterized drugs already in use in the clinic can be newly combined to lift the tumor's immunosuppressive barrier and induce a therapeutic immune response that significantly extends survival in mouse models of GBM, a cancer that has so far evaded every therapy used to treat it."

Hanahan and his colleagues have been exploring in preclinical studies whether drug combinations that target distinct growth-promoting properties of tumors might work synergistically to stall or reverse disease progression. Previous studies in Hanahan's lab had shown that a generic "tricyclic" antidepressant, imipramine, could be used in combination with an anticoagulant drug to hyperactivate a process known as autophagy, in which cells cannibalize their own proteins and organelles for the nutrients required to sustain their growth. Hyperactivation of autophagy by these drugs modestly extended survival of mice with

GBM.

In this study, the researchers tested whether a drug aimed at an unrelated phenomenon, the abnormal blood vessels of tumors, used in combination with imipramine might further improve outcomes. They used a mouse analog of the human anti-VEGF antibody bevacizumab, which has been approved as a second line treatment for GBM, though not so much to extend survival as to provide relief to patients by alleviating the edema caused by the aberrant vasculature. Bevacizumab is known to quasi-normalize leaky tumor blood vessels, whose abnormalities also compromise both chemotherapy and immunotherapy.

The researchers found that combining imipramine and the VEGF-blocking antibody significantly delayed tumor progression and increased survival times in mice with GBM. The combination, they discovered, disrupts the immune defenses of the tumor via multiple mechanisms, unleashing a powerful anti-tumor immune response characterized by the recruitment of both helper and cytotoxic T cells, which are critical to anti-tumor immunity.

An analog of human-specific bevacizumab that targets the VEGF angiogenic factor in mice proved to remodel the tumor blood vessels in ways that are known to promote the infiltration of T cells. At the same time, imipramine's hyperactivation of autophagy stimulated anti-tumor immunity.

But that wasn't all. Hanahan and his team found that the antidepressant also has a separate and unanticipated effect on a type of immune cell known as the macrophage, which is found in large numbers in GBM tumors. Imipramine, it turns out, also targets a biochemical signaling pathway that helps maintain macrophages in a so-called "M2" state, in which they support tumor growth. Blocking that signal with the antidepressant reprogrammed them into an "M1" state that supports

infiltration and killing of cancer cells by T cells.

Yet though this drug combination extended survival, its effects were not very durable. Hanahan and his team, however, saw an opportunity in its reconditioning of the tumor's immune microenvironment. To capitalize on that opportunity, they added to the mix a checkpoint blockade antibody that amplifies anti-tumor immune responses.

Such treatments have so far failed dismally against GBM in humans. But when added to the bevacizumab-imipramine combination, an ant-PD-L1 antibody drug significantly extended the survival of the mice.

"Because each of these therapies are already in clinical use," said Hanahan, "they wouldn't have to go through the time-consuming pharmacological development and safety testing required of novel drugs. For this reason, we are hopeful that the combination therapy we've identified in this study can be tested relatively soon in human clinical trials for GBM, a fiercely aggressive cancer for which there is a desperate need for new treatment strategies."

More information: Agnieszka Chryplewicz et al, Cancer cell autophagy, reprogrammed macrophages, and remodeled vasculature in glioblastoma triggers tumor immunity, *Cancer Cell* (2022). DOI: 10.1016/j.ccell.2022.08.014

Provided by Ludwig Cancer Research