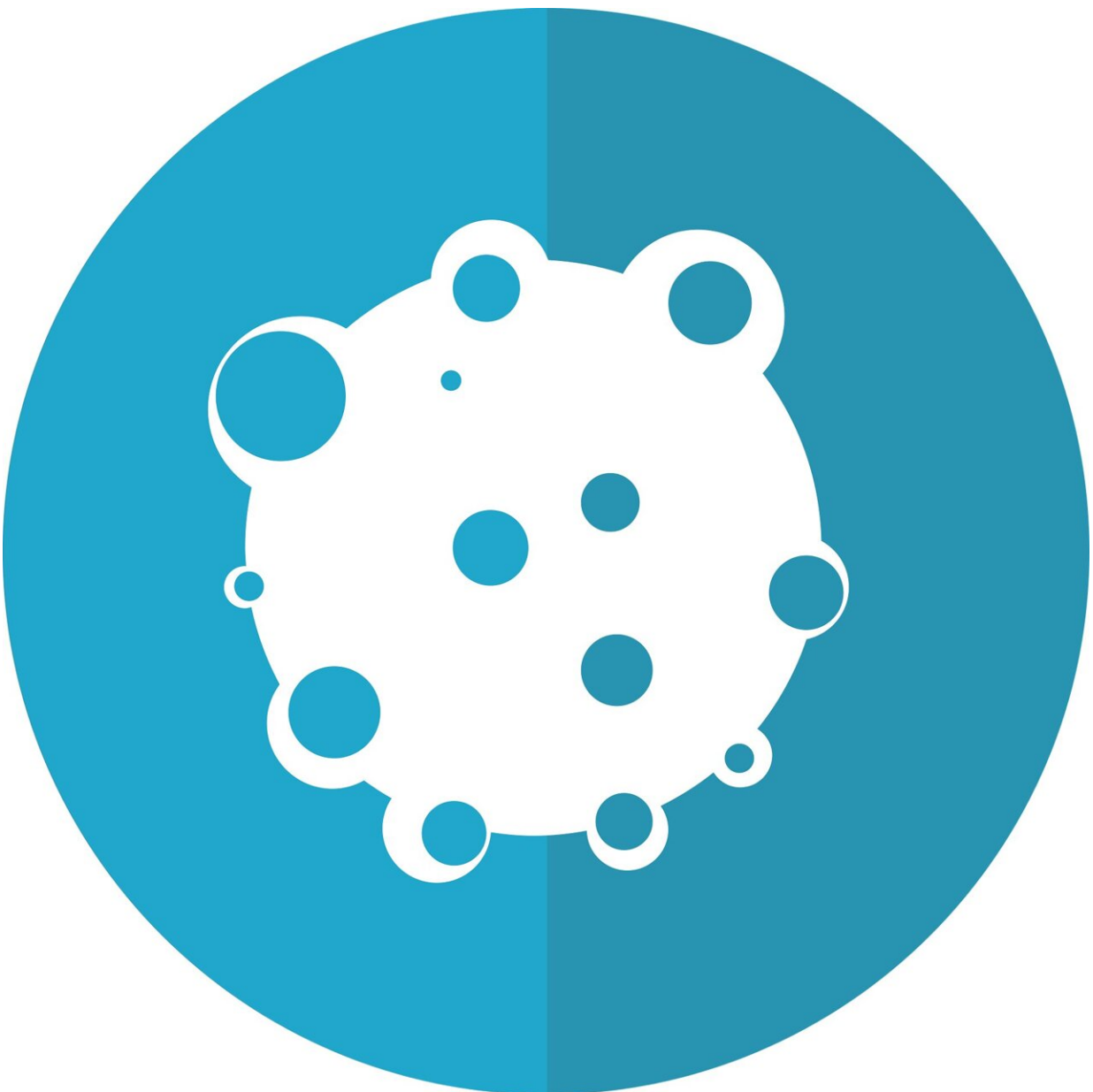


Sequential-combinatorial regimens can make treatment more effective for people with aggressive cancers

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A new preclinical study led by researchers at the UCLA Jonsson Comprehensive Cancer Center suggests that treating people who have aggressive cancers, including melanoma, pancreatic and colorectal cancers, with immune checkpoint inhibitors, quickly followed with mutation-targeted therapy, can help overcome treatment resistance and help people live longer.

Immune checkpoint inhibitors, which work by re-energizing tumor-killing immune or T cells, and mutation-targeted therapies, which kill tumors that harbor specific mutations that turn on [cancer](#)-driving pathways, have revolutionized the way people with advanced cancers are treated. However, [therapy resistance](#) to each type of [therapy](#) is a common problem—especially when resistance develops in the brain—limiting the effectiveness of these newer therapies.

Recent studies suggest that combining immune checkpoint inhibitor targeting PD-1/L1 with MAPK-targeted therapy—which are typically used separately to treat people with cancer—may help overcome treatment resistance. In their new work, a UCLA team, however, found that simply initiating the therapies together is not optimal. Instead, starting with two doses of anti-PD-1/L1 therapy, then adding MAPK-targeted therapy, is much more effective in prolonging tumor shrinkage and preventing resistance development.

"We already have powerful drugs in our arsenal against advanced cancers," said co-senior author Roger S. Lo, MD, Ph.D., a professor of medicine at the David Geffen School of Medicine at UCLA and

member of the UCLA Jonsson Comprehensive Cancer Center.

"Knowing how to rationally dose, sequence, and combine them offers physicians realistic and near-term chances to improve patient survival."

In the study, published in *Cancer Cell*, the researchers tested different sequential-combinatorial regimens in multiple animal models of human melanoma, pancreatic and [colorectal cancers](#) driven by common mutations in genes such as *BRAF*, *NF1*, *NRAS*, and *KRAS*.

They found consistently that only one regimen far out-performed the rest and uncovered molecular and cellular mechanisms to explain why sequencing on top of combination maximizes treatment efficacy. They also analyzed their own clinical trial data and found that patients who unintentionally received immune checkpoint therapies, compared to those who had not, responded better subsequently to MAPK-targeted therapy.

"The optimal regimen led to the highest level of both the 'good macrophages' in the tumor and the clonal expansion of T cells responsible for killing the tumor," said co-senior author Gatien Moriceau, Ph.D., assistant adjunct professor at the David Geffen School of Medicine at UCLA. "Retrospective analysis of clinical data supports our finding, but we need to prospectively test our proposed rapid-fire regimen in clinical trials designed specifically based on our animal studies."

The team also demonstrated that rational sequencing of anti-PD-1/L1 therapy before adding MAPK inhibitors suppresses melanoma brain metastasis and improves the survival of mice.

Researchers detected robust T-cell clonal expansion in all body sites the cancer spread to, including the brain. The team discovered that lead-in with two types of immune checkpoint therapy—anti-PD-1/L1 plus anti-

CTLA-4—further eliminated cancer spread, including spread to the brain and prolong survival in mice.

In the sequential-combinatorial regimen, the team was able to make the tumors more visible to the body's cancer-fighting T cells and the T cells' environment more hospitable for their growth and tumor-killing activity.

"In melanoma in particular, we were surprised by how well this regimen suppresses [treatment resistance](#)," Lo said. "In a metastatic model where the majority of animals with metastatic melanoma die within a couple of weeks with brain metastases, the regimen we proposed afforded survival with complete responses that extends routinely to 10 months, which is currently our longest follow-up."

This study was inspired by observations in the clinic, which generated hypotheses this team tested in the laboratory. Based on these laboratory findings, the team has begun to test rational sequencing in a [clinical trial](#) at UCLA.

More information: Anti-PD-1/L1 lead-In before MAPK inhibitor combination maximizes antitumor immunity and efficacy, *Cancer Cell* (2021). [DOI: 10.1016/j.ccell.2021.07.023](https://doi.org/10.1016/j.ccell.2021.07.023) , [www.cell.com/cancer-cell/fullt ... 1535-6108\(21\)00402-5](http://www.cell.com/cancer-cell/fullt...1535-6108(21)00402-5)

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