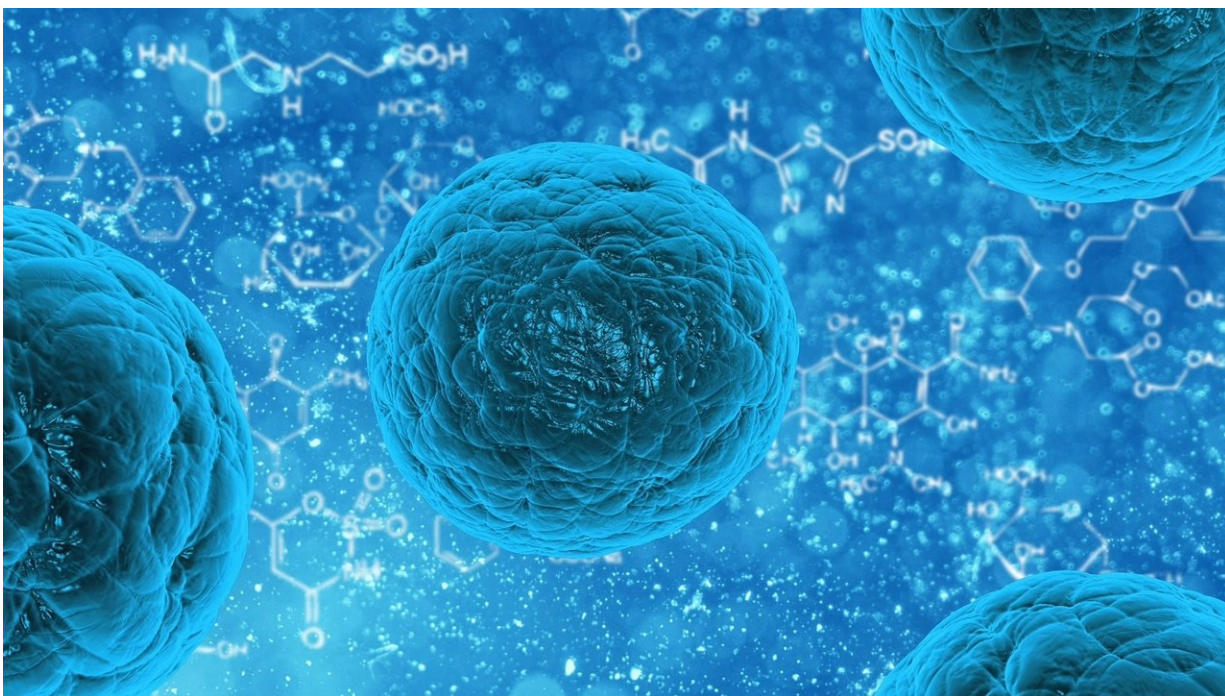


# New screening method identifies potential anticancer compounds that reawaken T cells

December 4 2019

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Scientists at Scripps Research have developed a method for rapidly discovering potential cancer-treating compounds that work by resurrecting anti-tumor activity in immune cells called T cells.

Cancerous tumors often thrive because they render T [cells](#) dysfunctional or "exhausted." The new method uncovers medicinal compounds that

can restore the function of these T cells, making cancers vulnerable to them again.

The approach, described in a study published in *Cell Reports*, may also help restore T-cell responses to persistent infections from viruses or other pathogens. It therefore should speed the development of new cancer and infectious-disease immunotherapies, including those that can be combined with existing immunotherapy drugs to enhance their effects. The scientists demonstrated the potential utility of the approach by using it to rapidly screen a collection of more than 12,000 drug compounds—uncovering 19 that can reawaken exhausted T cells.

"This new screening method should be particularly useful because we can use it not only to identify compounds that restore needed function to exhausted T cells, but also to quickly analyze these T cells to determine how these compounds work on them," says senior author Michael Oldstone, MD, Professor Emeritus in the Department of Immunology and Microbiology at Scripps Research.

The new screening system—and to some extent, the wider field of cancer immunotherapy—is based in part on research over the past several decades by Oldstone's laboratory and several former lab members including Rafi Ahmed, David Brooks, and John Teijaro, along with other scientists that have conducted animal-based research on how the [immune system](#) responds to lymphocytic choriomeningitis virus (LCMV).

A unique variant of LCMV known as "clone 13" establishes a persistent infection by exhausting the virus-specific T cells that are required to clear the infection. It does this by boosting signals through T-cell receptors such as PD-1 and IL-10. The discovery that LCMV clone 13 can survive by switching off anti-LCMV T cells was quickly followed by the recognition that cancers often persist using the same trick.

Immunotherapies that block signaling from PD-1 or similarly acting receptors to restore T cells' anti-cancer responses are among the most powerful [cancer](#) medicines available today. These therapies save many patients who in the past had seemingly untreatable tumors. But because treatment with these drugs typically works well for only a few cancers, including melanoma—and less often on other cancers—scientists suspect that cancers usually hijack multiple inhibitory T-cell pathways. This suggests that a combination of immunotherapies directed to different molecular pathways could be more effective than the current therapy.

"The idea now is to develop more immunotherapy drugs and find the best combinations of them," Oldstone says.

## **A promising hit**

The new screening system is designed to enable scientists to swiftly find such drugs—in this case, pharmacologically active small-molecule compounds that might work better than, or augment, the current injectable antibody immunotherapies now available.

The system uses T cells that have been exhausted by LCMV clone 13 and detects signs of renewed activity in these cells when a tested compound works to reawaken them. An advantage of the new screening system is that it is specific and highly automated; thus, thousands of compounds can be tested within days, with the "hits" verified in experiments involving mice.

Oldstone and colleagues applied the new screening system to a drug repurposing library of more than 12,000 compounds that either are FDA-approved or have been tested as potential drugs. They quickly identified 19 hits—compounds that, at modest doses, can effectively resurrect the activity of exhausted T cells.

One of these compounds, ingenol mebutate, is a plant-derived molecule that is already used in gel form (Picato) to treat actinic keratosis, a pre-cancerous skin condition. The researchers employed elements of their screening system to study the reactivated T cells and determined that ingenol mebutate restores function for these cells largely by activating signaling enzymes called protein kinase C enzymes, a known pathway of activity for this compound.

Co-first authors of the study, postdoctoral fellows Brett Marro, Ph.D. and Jaroslav Zak, Ph.D., in the Department of Immunology and Microbiology, are currently collecting and exploring the therapeutic potential of other reported hits that may work in combination with treatments that block PD-1- and another T-cell-inhibitory receptor, CTLA-4. Indeed, one such hit in combination with antibody to PD-L1 is already undergoing evaluation in patients.

Oldstone notes that the new screening approach is flexible enough to adapt for finding [compounds](#) that have other effects on T-cells, such as reducing T-cell activity to treat autoimmune conditions.

**More information:** Brett S. Marro et al, Discovery of Small Molecules for the Reversal of T Cell Exhaustion, *Cell Reports* (2019). [DOI: 10.1016/j.celrep.2019.10.119](#)

Provided by The Scripps Research Institute

Citation: New screening method identifies potential anticancer compounds that reawaken T cells (2019, December 4) retrieved 25 April 2024 from <https://medicalxpress.com/news/2019-12-screening-method-potential-anticancer-compounds.html>

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