A method to selectively grow tumor-targeting T cells for cancer therapy

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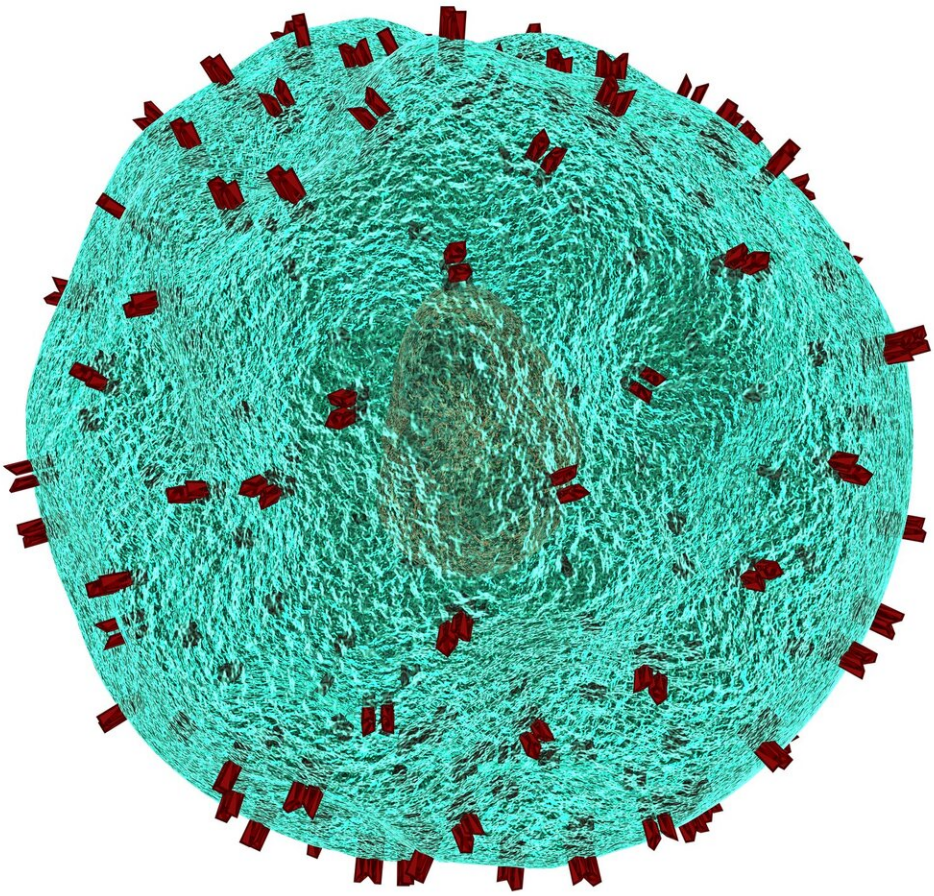

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A Ludwig Cancer Research study has devised a highly efficient method to generate large numbers of immune cells specifically engineered to recognize neoantigens—small fragments of randomly mutated proteins that are typically unique to a patient's cancer—and destroy the tumors that express them.

Developed by a team of Ludwig Lausanne researchers led by investigator Alexandre Harari and George Coukos, Director of the Lausanne Branch of the Ludwig Institute for Cancer Research, the method, named NeoScreen, significantly improves the identification of a patient's neoantigens and consequently holds considerable promise for the development of personalized immunotherapies for cancer. A paper describing NeoScreen and illustrating its utility and efficacy in a preclinical study appears in the current issue of *Nature Biotechnology*.

"We wanted to develop a better way to both identify the neoantigens uniquely expressed by a patient's tumors and efficiently isolate and expand the immune cells—tumor-infiltrating T cells, or TILs—that are spontaneously directed against them, since it is these rare cells that are considered to be best at destroying cancer cells," said Harari. "NeoScreen allows us to do all that. Better yet, it permits the identification of the specific receptors these T cells use to recognize neoantigens so that we can equip other T cells from a patient's blood with that machinery and use those cells as well for personalized immunotherapy."

To identify neoantigens and culture the T cells that detect them, researchers ordinarily isolate TILs from a tumor and grow them with that tumor's constituent cells in the presence of immune factors that

stimulate T cell proliferation. But because neoantigen-specific TILs are very rare, the wholesale stimulation of T cell growth often results in the far larger expansion of T cells that are not specifically targeted to neoantigens. This can drown out the most desirable neoantigen-targeting T cells in such cultures.

To address this limitation, Harari, Coukos and their colleagues first modified the company in which isolated TILs are cultured, adding antigen presenting cells (APCs) into the mix. APCs display antigens associated with disease to T cells and help drive the activation and proliferation of those that recognize the presented antigen. But instead of using typical APCs, like dendritic cells, the researchers engineered another type of immune cell, the B cell, to be a highly efficient antigen presenting cell. B cells were considered ideal for this role because they are far more abundant in the blood and more amenable to genetic manipulation than dendritic cells.

The researchers then used computational methods to analyze the genome of tumor cells and identify randomly mutated parts of proteins that could be presented as neoantigens. Next, they pulsed the engineered B cells with those protein fragments—or inserted DNA encoding the fragments into the B cells—to get them to present the antigens. Finally, they cultured the B cells with tumor cells and the TILs isolated from that tumor.

Because antigen recognition stimulates T cell proliferation, this co-culture had the effect of selectively and rather dramatically expanding the TILs that recognize neoantigens expressed by the tumor. The researchers isolated those TILs, identified which of the neoantigens they recognized and sequenced the genes encoding their neoantigen-detecting T cell receptors (TCRs). This approach resulted in the identification of a far greater variety of both expressed neoantigens and TCRs than did the conventional method.

The researchers showed that neoantigen-specific TCRs could be cloned and inserted into other T cells taken from blood to generate large quantities of tumor-targeting T cells.

"NeoScreen enabled the selective expansion of neoantigen-targeting TILs against melanoma as well as colon, lung and ovarian cancers," said Coukos.

Finally, the researchers tested whether NeoScreen might be useful for adoptive T cell therapy, in which T cells taken from a patient are isolated, selectively expanded and reinfused into a patient. They show that T cells engineered to express TCRs identified via NeoScreen recognized neoantigens found in tumors and could induce the regression of those same tumors after they were well established in a mouse model.

"NeoScreen could also be used to identify neoantigens for the design of personalized cancer vaccines for therapy," said Coukos. "We will be testing this and other applications of NeoScreen for cancer immunotherapy at Ludwig Lausanne."

More information: George Coukos, Sensitive identification of neoantigens and cognate TCRs in human solid tumors, *Nature Biotechnology* (2021). DOI: 10.1038/s41587-021-01072-6. www.nature.com/articles/s41587-021-01072-6

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