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Drug profiling and gene scissors open new avenues in immunotherapy

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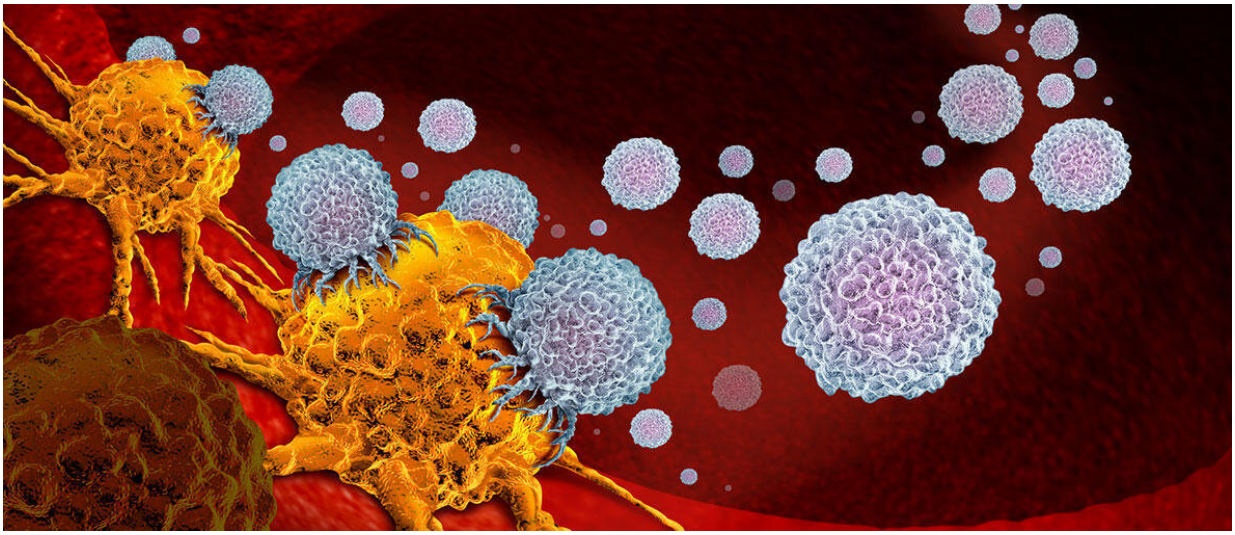

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Researchers have discovered ways to boost CAR T-cell therapy. According to a study published in the *Blood* journal, drug profiling and the CRISPR-Cas9 gene editing method have opened new avenues in the development of CAR T-cell therapy, used to treat leukemia and lymphoma.

The study, carried out collaboratively by the University of Helsinki and the Finnish Red Cross Blood Service, surveyed the effect of more than 500 cancer drugs on the function of CAR T cells.

CAR T-cell therapy has yielded excellent results in the case of certain blood cancers and lymphomas resistant to other forms of treatment. In CAR T-cell therapy, patient's own T cells (immune cells) are extracted from blood stream, after which they are engineered to express chimeric antigen receptors (CAR), which activate the cells to destroy cancer cells after identification.

"In spite of good treatment outcomes, the therapy is not effective in all patients. CAR T-cell therapy can also have adverse effects," says Professor Satu Mustjoki from the University of Helsinki.

The drug profiling highlighted a class of drugs known as SMAC mimetics, which in laboratory tests sensitized cancer cells to CAR T cells. At the same time, drugs that inhibit the function of CAR T cells were found, which have potential in the treatment of adverse effects.

By employing the CRISPR gene editing method, the researchers investigated which mechanisms impact the sensitivity of cancer cells to CAR T cells. A process known as death receptor signaling and the FADD gene required to initiate this process were found to be vital for CAR T-cell function. The CRISPR method also revealed that the mechanism of SMAC mimetics is based on the initiation of death receptor signaling.

Based on the test results, SMAC mimetics could potentially be used to further sensitize cancer cells to cell death caused by CAR T cells. If the promise of the drugs identified in the preliminary profiling is upheld by further research, SMAC mimetics could be utilized in improving the outcome of CAR T-cell therapy.

"The study provides an extensive dataset on the effect of cancer drugs on the function of T cells, which are essential to immunotherapies. This data can be put to use when planning the combination of cancer drugs

with therapies activating the immune system," says doctoral candidate Olli Dufva from the University of Helsinki.

More information: Olli Dufva et al. Integrated drug profiling and CRISPR screening identify essential pathways for CAR T cell cytotoxicity, *Blood* (2019). DOI: 10.1182/blood.2019002121

Provided by University of Helsinki