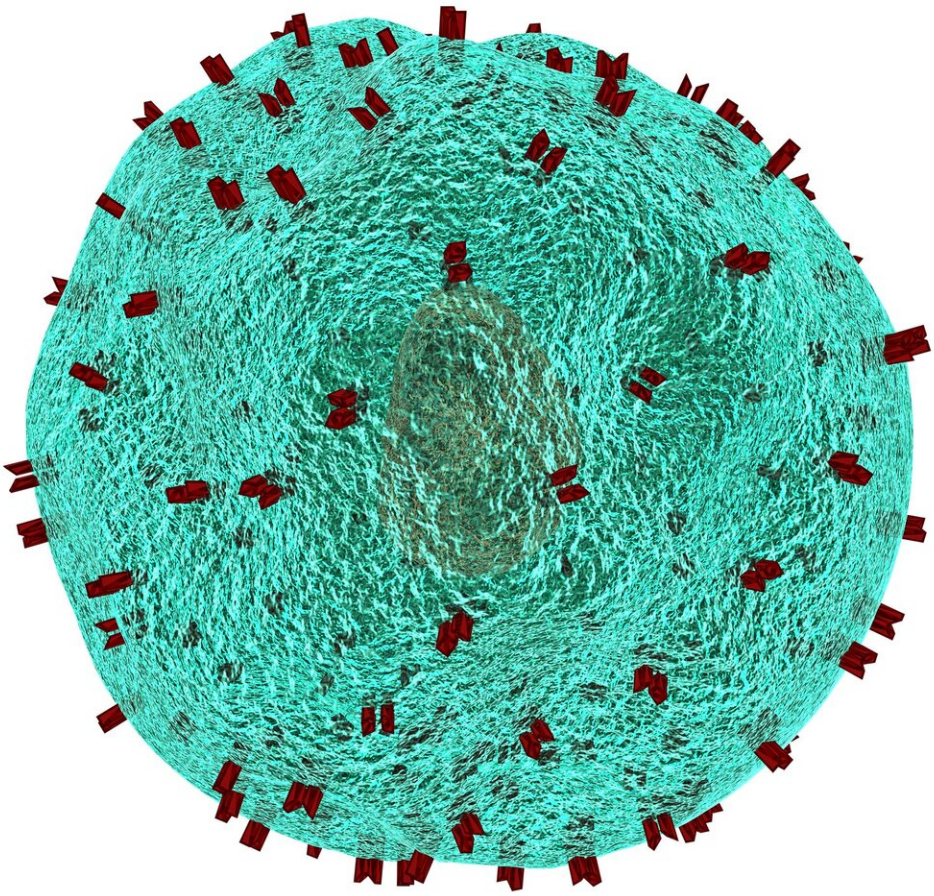
Mode-of-action of T-cell immunotherapies in focus

July 25 2022



Credit: CC0 Public Domain

A new 3D imaging technique brings the working mode of T-cell immunotherapies into live view. T-cell immunotherapy is already leading to promising results in some children with leukemia. Researchers plan to use the new imaging technique to improve T-cell therapies for solid tumors.

T-cell therapies, such as CAR-T cells, are a promising type of immunotherapy that is already showing results in treating children with leukemia. These kind of therapies use the own immune system. T-cells, a type of white blood cell, which have been modified in the lab are administered and subsequently attack the tumor in a targeted manner. Effective T-cell therapies are also being sought for solid tumors, such as neuroblastoma, sarcoma and kidney tumors. However, to improve their clinical efficacy, we need to better understand the solid tumor-targeting behavior of T-cells. That's why the lab of Dr. Anne Rios, specialized in 3D imaging at the Princess Máxima Center and Oncode investigator, teamed up with Dr. Zsolt Sebestyén and Prof. Dr. Jürgen Kuball, T-cell therapy experts and group leaders at UMC Utrecht, and the group of Prof. Dr. Hans Clevers, organoid specialist and visiting researcher at the Máxima and the Hubrecht Institute. The results of this collaborative research endeavor were published today in *Nature Biotechnology*.

A wealth of fundamental knowledge

Lead authors of the publication Dr. Florijn Dekkers and Dr. Maria Alieva from the Rios group developed an imaging and analysis technology, BEHAV3D, that allows to analyze the interaction between T-cell therapies and solid mini tumors, also known as tumor organoids, live and three-dimensionally. Florijn Dekkers says that what's "unique about

this approach is that we are looking at cell therapy efficacy by studying the behavior of the T-cells. In total, we studied the behavior of over 150,000 engineered T cells. This revealed a huge variety in behavior, like very potent behaviors, such as killing of multiple tumor cells in sequence, but also ineffective behaviors, with cells just sitting around and doing nothing. This suggested to us that there is room to improve clinical efficacy by promoting the most potent tumor-targeting behaviors."

Maria Alieva adds that "to be able to stir T-cell therapies towards their most effective behaviors, we need to know the underlying mechanisms that dictate this behavior. Therefore, I developed a method that for the first time links the behavior of the cell to the genes that cause this behavior. With it, we were able to identify the specific gene signature of highly potent T cells that are able to kill many tumor cells in a row. Thanks to BEHAV3D and the use of mini-tumors grown from tumor tissue of children and adults, we can now gather a wealth of fundamental knowledge about the behavior and ability of T cells to target solid tumors."

Improving targeting

Dr. Anne Rios says that they "initially looked at the behavior of so-called TEG cells, a highly promising therapy based on T-cells that are activated once they notice metabolism changes in tumor cells, developed in the lab of our collaborators; Zsolt Sebestyén and Jürgen Kuball. However, we were able to apply BEHAV3D to different kinds of T cell therapies, as well as cancer subtypes. Therefore, we believe that this platform can be very useful for further improving the targeted attack on solid tumors by the various T-cell therapies currently under development."

More information: Anne Rios, Uncovering the mode of action of engineered T cells in patient cancer organoids, *Nature Biotechnology*

(2022). DOI: 10.1038/s41587-022-01397-w.
www.nature.com/articles/s41587-022-01397-w