Antibody therapy training phagocytes to destroy tumors now tested on patients

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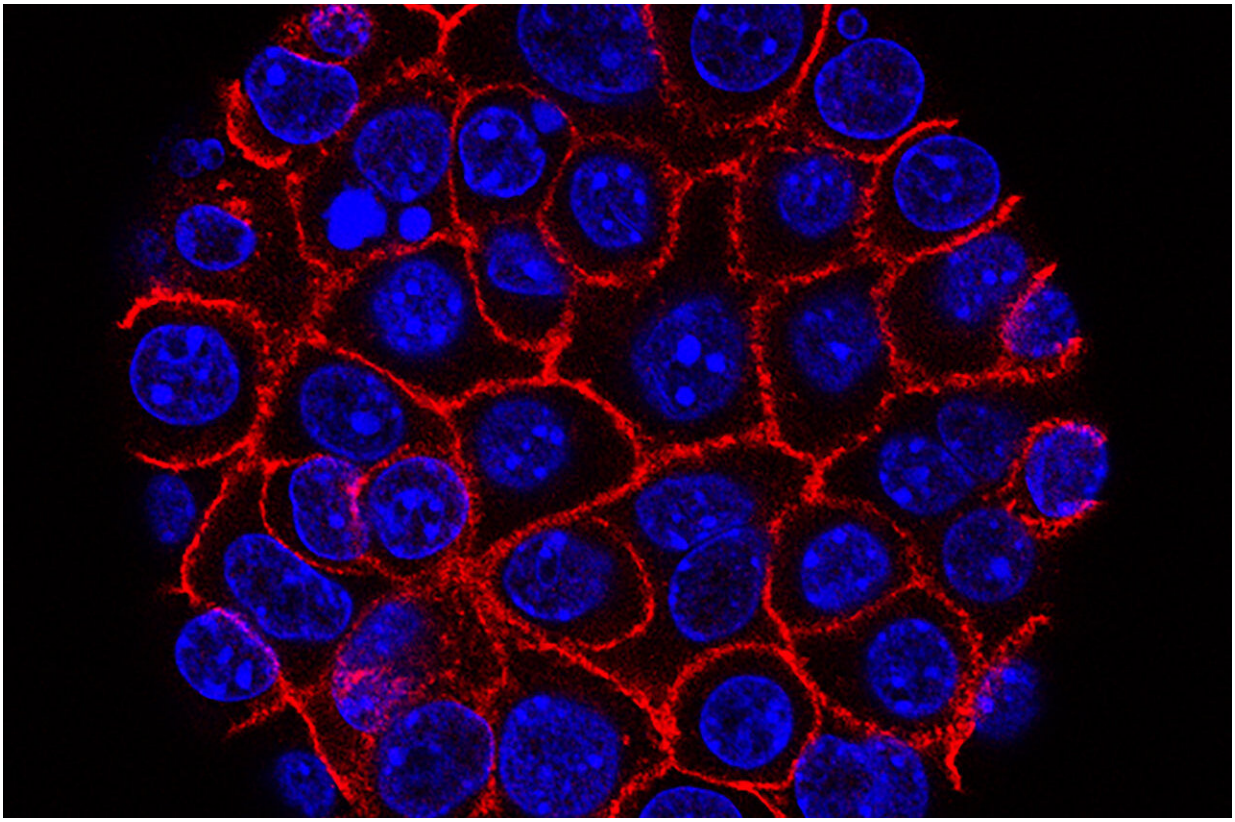

Credit: Min Yu (Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC),USC Norris Comprehensive Cancer Center

Developed by researchers at the University of Turku in Finland, an immunotherapeutic antibody therapy re-educates macrophages to

activate passivated cytotoxic T cells to kill cancer. The antibody therapy prevented the growth of tumours in several mouse models, and the development of the therapy has now progressed to patient testing in a phase I/II clinical trial.

One reason behind many unsuccessful cancer treatments is the cancers' ability to hijack the immune system to support its own growth. This is assisted by the so-called tumour-associated macrophages that can be educated by cancer cells to dampen anti-tumour immune responses. Macrophages are phagocytes that form the first line of defence towards invading pathogens and they have a crucial role in maintaining tissue homeostasis. Macrophages have a large repertoire of functions in immune activation and resolving inflammation.

In collaboration with Academician of Science and Professor of Immunology Sirpa Jalkanen, Academy Research Fellow Maija Hollmén's research group investigated the possibility to utilise tumour-associated macrophages to increase the immunological detection and killing of cancer cells. Professor Jalkanen has studied the function of Clever-1 for a long time. Previously, her group has observed that Clever-1 controls leukocyte trafficking between tissues.

Published in the journal *Clinical Cancer Research*, the study found that blocking Clever-1 function on macrophages activated the immune system and was highly effective in inhibiting cancer progression.

By inhibiting Clever-1 functions, tumour-associated macrophages that normally impair adaptive immune cell activation, such as cancer cell killing by cytotoxic T cells, were managed to be re-educated so that they had increased ability to present antigen and secrete pro-inflammatory cytokines leading to increased activation of killer T cells.

"These results are highly promising and present a completely new way to

activate anti-cancer immunity," says Doctoral Candidate Miro Viitala, who is the main author of the article.

"Macrophages are an ideal drug development target as they express several molecules that can be activated or impaired to transfer the macrophages into cells that destroy cancer. In itself, this would increase beneficial inflammation in the tumour microenvironment, which would improve the efficiency of immune checkpoint inhibitors in those patients whose response is weak due to lack of tumour-specific T cell activation," continues Viitala.

The antibody therapy targeting Clever-1 worked in the studied tumour mouse models as efficiently as the PD-1 antibody therapy that is in clinical use. The PD-1 antibody maintains the functionality of the killer T cells. It is notable that the Clever-1 antibody therapy targeting macrophages also increased the activity of the killer T cells efficiently.

In certain mouse models of cancer, a combination of anti-Clever-1 and anti-PD-1 therapies prevented tumour growth and formation of metastases more effectively than either treatment alone.

"Every cancer is different. Therefore, it is important to explore the types of cancer where Clever-1 antibody therapy most effectively works on and to find biomarkers that can be used to identify beforehand the patients that will benefit the most from this kind of therapy," concludes Viitala.

More information: Miro K Viitala et al, Immunotherapeutic Blockade of Macrophage Clever-1 Reactivates the CD8+ T Cell Response Against Immunosuppressive Tumors, *Clinical Cancer Research* (2019). DOI: 10.1158/1078-0432.CCR-18-3016