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Cancer killing clue could lead to safer and more powerful immunotherapies

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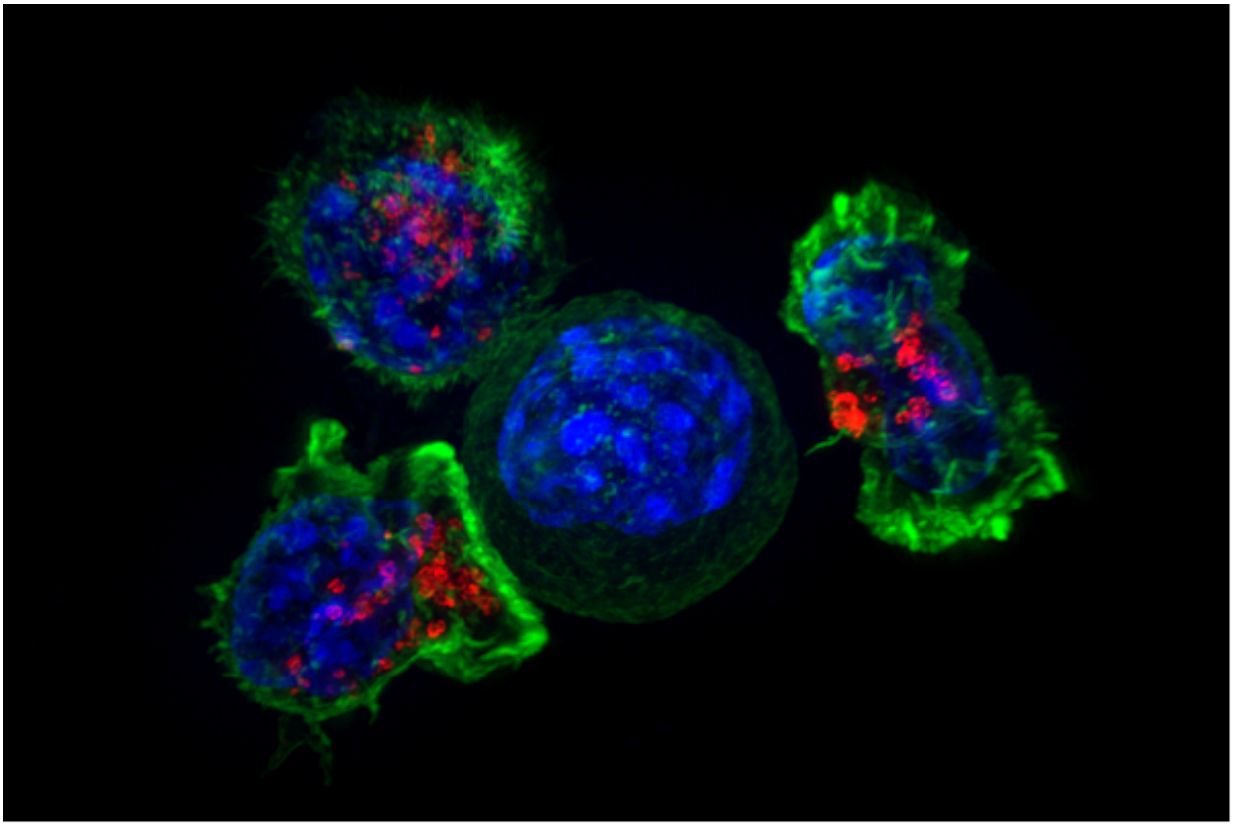

Killer T cells surround a cancer cell. Credit: NIH

New research could help to safely adapt a new immunotherapy—currently only effective in blood cancers—for the treatment of solid cancers, such as notoriously hard-to-treat brain

tumours.

The study, led by Dr. Misty Jenkins from the Walter and Eliza Hall Institute of Medical Research, explains the crucial mechanisms by which CAR-T cell therapy is able to rapidly target and kill cancer cells, and why it may cause serious side effects.

CAR-T cell therapy is an innovative form of immunotherapy that uses synthetically engineered T cells to redirect the patient's own immune system to fight their cancer. Approved by the US Food and Drug Administration (FDA) in 2017, it has been successfully used to treat blood cancers such as childhood leukaemia and some lymphomas.

Unfortunately, CAR-T cell therapy has had mixed results in solid cancers, often causing significant side effects such as 'cytokine storms' - a potentially fatal inflammatory response that can lead to organ failure in some patients.

Dr. Jenkins led the study, working with collaborators Mr Alex Davenport, Associate Professor Phillip Darcy and Associate Professor Paul Neeson from the Peter Mac. It was published today in the journal *Proceedings of the National Academy of Sciences*.

Dr. Jenkins said the new research revealed for the first time how CAR-T cells interacted with cancer cells.

"We found that CAR-T cell receptors have the ability to rapidly identify and bind to tumour cells that would otherwise remain undetected in the immune system, and promptly kill them.

"We have previously shown a correlation between cytokine production and the length of time the immune cells were latched onto the cancer cells. The longer the cells were in contact, the more cytokines were

produced, causing ever increasing degrees of damage from inflammation," she said.

Dr. Jenkins said a deep understanding of the biological factors contributing to the success and side effects of CAR-T cells would help to inform a better design and safer delivery methods for the personalised therapy.

"Our research is teaching us how to make CAR-T cells even more efficient, and without the toxic side effects, so that we can safely extend the therapy to cover a broader range of cancers," she said.

Dr. Jenkins said her research focused on how CAR-T cell therapy could successfully be used to treat brain cancer. Brain cancer has some of the poorest survival rates of any cancer in the world and desperately requires new treatment approaches.

"The brain is an incredibly delicate and challenging environment to work within," Dr. Jenkins said.

"Brain tumours are often resistant to traditional treatments, such as chemotherapy; and surgically removing tumours can come with a lot of collateral damage.

"Finding an optimum design for CAR-T cell therapy where we can kill tumour cells with limited invasion, inflammation and side effects could significantly improve the treatment of brain cancer.

"Answering fundamental biological questions about how immune cells and cancer cells function and interact, as we have done in this study, is invaluable in the quest to find formidable treatments for fatal cancers," she said.

In 2017 Dr. Jenkins received a Carrie's Beanies 4 Brain Cancer Foundation grant and a Financial Market's Foundation for Children Grant to continue her work to develop CAR-T cell therapies and other forms of immunotherapy for treating children with brain cancer.

More information: Maria Letizia Giardino Torchia el al., "Intensity and duration of TCR signaling is limited by p38 phosphorylation of ZAP-70T293 and destabilization of the signalosome," *PNAS* (2018). www.pnas.org/cgi/doi/10.1073/pnas.1713301115

Provided by Walter and Eliza Hall Institute