Researchers use mathematical modeling to analyze dynamics of CAR T-cell therapy

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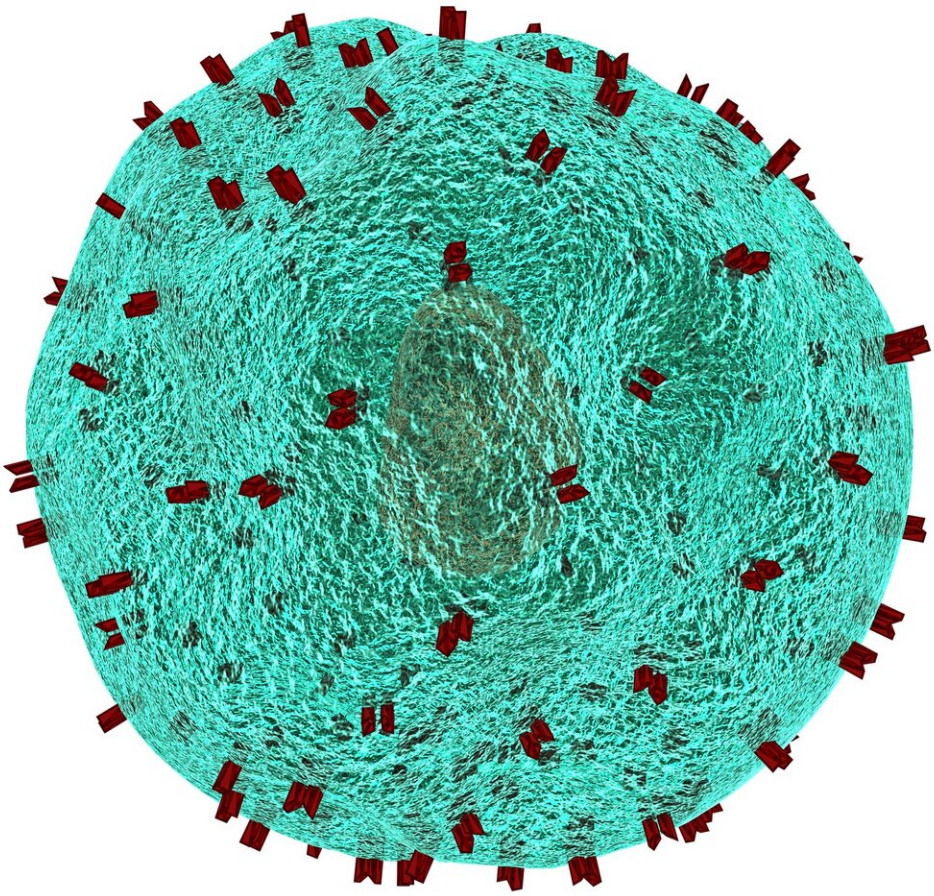

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Chimeric antigen receptor T-cell therapy, or CAR T, is a relatively new type of therapy approved to treat several types of aggressive B cell leukemias and lymphomas. Many patients have strong responses to CAR T; however, some have only a short response and develop disease progression quickly. Unfortunately, it is not completely understood why these patients have progression. In an article published in *Proceedings of the Royal Society B*, Moffitt Cancer Center researchers use mathematical modeling to help explain why CAR T cells work in some patients and not in others.

CAR T is a type of personalized immunotherapy that uses a patient's own T cells to target cancer cells. T cells are harvested from a patient and genetically modified in a laboratory to add a specific receptor that targets cancer cells. The patient then undergoes lymphodepletion with chemotherapy to lower some of their existing normal immune cells to help with expansion of the CAR T cells that are infused back into the patient, where they can get to work and attack the tumor.

Mathematical modeling has been used to help predict how CAR T cells will behave after being infused back into patients; however, no studies have yet considered how interactions between the normal T cells and CAR T cells impact the dynamics of the therapy, in particular how the nonlinear T cell kinetics factor into the chances of therapy success. Moffitt researchers integrated clinical data with mathematical and statistical modeling to address these unknown factors.

The researchers demonstrate that CAR T cells are effective because they rapidly expand after being infused back into the patient; however, the modified T cells are shown to compete with existing normal T cells,

which can limit their ability to expand.

"Treatment success critically depends on the ability of the CAR T cells to multiply in the patient, and this is directly dependent upon the effectiveness of lymphodepletion that reduces the normal T cells before CAR T infusion," said Frederick Locke, M.D., co-lead study author and vice chair of the Blood and Marrow Transplant and Cellular Immunotherapy Department at Moffitt.

In their model, the researchers discovered that tumor eradication is a random, yet potentially highly probable event. Despite this randomness of cure, the authors demonstrated that differences in the timing and probability of cures are determined largely by variability among patient and disease factors. The model confirmed that cures tend to happen early, within 20 to 80 days before CAR T cells decline in number, while disease progression tends to happen over a wider time range between 200 to 500 days after treatment.

The researchers' model could also be used to test new treatments or propose refined clinical trial designs. For example, the researchers used their model to demonstrate that another round of CAR T-cell therapy would require a second chemotherapy lymphodepletion to improve patient outcomes.

"Our model confirms the hypothesis that sufficient lymphodepletion is an important factor in determining durable response. Improving the adaptation of CAR T cells to expand more and survive longer in vivo could result in increased likelihood and duration of response," explained Philipp Altrock, Ph.D., lead study author and assistant member of the Integrated Mathematical Oncology Department at Moffitt.

More information: Gregory J. Kimmel et al, The roles of T cell competition and stochastic extinction events in chimeric antigen receptor

T cell therapy, *Proceedings of the Royal Society B: Biological Sciences* (2021). DOI: 10.1098/rspb.2021.0229