

T cell circuits that sense antigen density with an ultrasensitive threshold

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Science **371** (6534), 1166-1171.

DOI: 10.1126/science.abc1855 originally published online February 25, 2021

Designing smarter anticancer T cells

Biological signaling systems can exhibit a large, nonlinear—or "ultrasensitive"—response, which would be useful to engineer into therapeutic T cells to allow for better discrimination between cancer cells and normal tissues.

Hernandez-Lopez *et al.* modified human T cells using a two-step mechanism that allowed them to kill cells expressing large amounts of cancer marker protein but not cells expressing a small amount of the same protein. A first synthetic receptor recognized the antigen with low affinity. That receptor signaled to increase expression of a chimeric antigen receptor (CAR) with high affinity for the same antigen. The circuit proved effective in cell culture and mouse cancer models, offering hope of extending the CAR T cell strategy against solid tumors.

Science, this issue p. 1166

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