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(MIRNAS) — small molecules that silence genes — to engineer stem cells that could strengthen a mouse's immune defense against cancer. The results were published in January in the *Journal of Clinical Investigation*. [\[PubMed Abstract\]](#)



Michel Sadelain

Cell engineering offers a broad spectrum of clinical applications. A potential strategy for cancer immunotherapy is to program blood stem cells to develop into tumor-specific T cells by introducing an artificial T cell receptor (TCR) gene that enables T cells to recognize and mount an attack against tumor cells. However, when T cells develop in the thymus, a process known as negative selection eliminates certain cells to prevent the immune system from attacking the body's own tissues. If the introduced TCR gene can be shut off during T cell development, this will ensure that engineered cells survive negative selection. The challenge is to switch the gene back on when cells leave the thymus.

The investigators engineered blood stem cells with a TCR gene that is responsive to a miRNA called miR-181a, which switches genes off temporarily. After the cells were transplanted into mice, the gene's expression was silenced by miR-181a during negative selection — allowing T cells to develop normally — and then restored when the cells left the thymus. With the TCR gene switched on, mature T cells were able to recognize tumor cells.

"We tricked the thymus," Dr. Sadelain explained. He expects that the technique will be a powerful tool for research and prove useful for cancer immunotherapy and other applications. "MicroRNAs are recently discovered RNAs that are specific and dynamic regulators of gene function," he said. "We've used them to express genes in engineered cells at particular stages of development, with a subtlety that truly is remarkable."

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