A “MAJESTIC” New Way to Engineer CAR-T Cells to Attack Cancers

Researchers unveil a less toxic, more efficient method to genetically engineer immune cells that target tumor cells.

August 29, 2023 By Damon Runyon Cancer Research Foundation

Chimeric antigen receptor (CAR) T therapy, in which a patient’s own immune T cells are genetically engineered to target and kill their tumor cells, have been the subject of intensive research efforts since the first patients were treated in 2011. Fueled by the promise of immune cells that can serve as a “living drug” against cancer, scientists are committed to making CAR T cells safe and effective for more patients. Their investment is warranted: after a decade in remission, those first patients to receive CAR T cells were declared “cured” of leukemia.

Genetically modified CAR T cellCourtesy of Damon Runyon Cancer Research Foundation

But currently, nearly two-thirds of patients receiving CAR T therapy for blood cancer experience relapse, and up to 80% of patients experience serious side effects.

Motivated by the possibility of a cure on the other side of these hurdles, former Damon Runyon-Dale F. Frey Breakthrough Scientist Sidi Chen, PhD, and his colleagues at Yale University have just unveiled a new system for engineering less toxic, more efficient, and longer-lasting CAR T cells. To accomplish this, the team zeroed in on a major challenge of developing CAR T cells: inserting new genes into a patient's immune cells such that they are permanently integrated into the genome, and not just temporarily expressed. Put in human terms, consider how much harder it is to form a new habit than to try something once or twice!

The system developed by Dr. Chen and his colleagues combines several existing gene delivery tools: mRNA, enzymes called transposases, and viruses. First, the immune cell receives mRNA instructions for building an enzyme (called a “Sleeping Beauty” transposase) that can move segments of DNA (transposons) from one location in the genome to another. Then, a virus called AAV—which does not cause disease and is essentially a protein shell surrounding DNA—delivers the desired gene attached to a transposon into the cell. The newly built transposase inserts the transposon and the new gene into the immune cell’s genome, and voilà! A stably engineered T cell. The sleek new system has been dubbed MAJESTIC (mRNA AAV-Sleeping-Beauty Joint Engineering of Stable Therapeutic Immune Cells).

“This technology has strong merits over existing CRISPR technologies to generate cell therapy products,” Dr. Chen says. He envisions MAJESTIC being employed to genetically engineer a range of cell types, including other immune cells, allowing for the development of next-generation cell therapies in the years to come.

This research was published in Nature Biomedical Engineering.

This post was originally published August 23, 2023, by Damon Runyon Cancer Research Foundation. It is republished with permission.
