First-in-human trial with CAR macrophages shows promise targeting solid tumors

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Preliminary findings from Penn Medicine in an ongoing first-in-human clinical trial examining the safety, tolerability and feasibility of chimeric antigen receptor macrophage (CAR-M) has helped to establish the

viability of this innovative immunotherapy, which advances the trailblazing scientific discovery of CAR T cell therapy—also pioneered at Penn—for solid cancer tumors and offers a promising new strategy in the fight against cancer. Preliminary data from the Phase 1 multi-center clinical trial, which uses a novel, gene-based cancer therapy with CAR-engineered macrophages to target recurrent or metastatic HER2-positive solid tumors, was presented during the recent Society for Immunotherapy of Cancer (SITC) annual meeting.

"Existing immuno-oncology treatments have offered improved outcomes for some cancer patients, yet CAR-T cells, which are engineered to recognize tumor-specific antigens and are successful in some blood cancers, have not been effective in solid tumors to date," said Saar Gill, MD, Ph.D., scientific co-director of the Cell Therapy and Transplant Program at the Abramson Cancer Center at the University of Pennsylvania and an associate professor of Hematology-Oncology in the Perelman School of Medicine. "Seeing macrophages show high CAR expression, viability, and purity, successfully manufactured from cancer patients and are well tolerated, has us excited to be conducting this trial to help us understand the impact CAR-M cells have on targeting solid tumors."

CAR-M is an individualized therapy that begins with isolation of primary monocytes from blood drawn from a patient, which are then modified with the desired antigen-specific chimeric receptor—for example, anti-HER2. The resulting CAR-M modified cells are cryopreserved and will be infused back into the patient. CAR-M may be able to reach immunologically 'cold' tumors, or those that are typically undetectable or unresponsive to the immune system, to help activate them to be more receptive to treatment.

"We are motivated by the potential of CAR-M cell therapy for HER2-positive solid tumors," said Kim A. Reiss, MD, an assistant

professor of Hematology-Oncology at Penn and principal investigator of the trial. "Tumor cells alone are unable to stimulate the process of T-cell activation, but with macrophages, they engage the tumors differently by penetrating them to induce a reaction, making CAR macrophage therapy quite different than CAR T cells, and something we are enthusiastic about studying further."

CAR T cell therapy, a form of immunotherapy that uses specially altered T cells—a part of the immune system that fights diseases, including cancer—was pioneered by a team led by Carl H. June, MD, the Richard W. Vague Professor in Immunotherapy in the department of Pathology and Laboratory Medicine at Penn and director of the Center for Cellular Immunotherapies. CAR T cell technology involves the collection of a patient's T cells and genetically reprogramming them in the lab to recognize markers on specific cell types in the body. These specially targeted T cells can then be multiplied using cell culture techniques and re-infused into the patient to attack a specific cell type. The first CAR T cell therapy was developed by researchers from Penn and Children's Hospital of Philadelphia and approved by the U.S. Food and Drug Administration in 2017 for use against certain leukemias—and later approved for lymphoma—that arise from immune cells called B cells.

The CAR-M platform was pioneered in Gill's laboratory to capitalize on the ability of macrophages and monocytes to enter and survive within tumors—a major differentiator of this type of cell compared with T cells. In addition, Gill and colleagues engineered macrophages to express a chimeric antigen receptor akin to that present on CAR T cells, thus giving the macrophages the ability to specifically recognize tumor cells. Another difference between macrophages and T cells is their effector function: While T cells typically kill tumor cells by poking them full of holes, macrophages (a term for "big eaters") tend to kill by engulfing and devouring tumor cells. Macrophages can also break down and digest the engulfed cells and use their byproducts to stimulate a broader immune

response.

The preliminary data presented at SITC demonstrated that the CAR-M known as CT-0508 has the ability to alter the solid tumor microenvironment and change the composition of myeloid cells and T-cells. These findings also represent the first clinical data with genetically engineered macrophages in humans. The U.S. Food and Drug Administration recently granted Fast Track designation to CT-0508 for clinical trials evaluating the efficacy and safety of the therapy in patients with solid tumors.

Led by Dr. Gill, scientists at Penn engineered the human macrophages to express CAR constructs. The engineered CAR-M cells have the ability to target proteins on cancer cells and penetrate solid tumors, ingest malignant tissue, and stimulate adaptive immunity in mouse models. Dr. Gill, Dr. Michael Klichinsky, and Penn co-founded Carisma Therapeutics to further study and develop this technology through clinical research efforts.

Provided by University of Pennsylvania

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