Fodor says. For higher cell numbers and for whole-genome coverage, sequencing capacity would become a limiting factor. ■

T-cell Therapy Targets Glioblastoma

A team of researchers successfully engineered T cells to express a chimeric antigen receptor (CAR) that targets a mutation associated with a particularly aggressive form of glioblastoma, laying the foundation for a phase I clinical trial.

In a preclinical study, researchers redirected humanized CAR T cells to bind to the EGFR variant III mutation (EGFRvIII), a common variant of EGFR in human tumors that occurs in about 30% of patients with glioblastoma and is associated with poorer prognosis. Investigators designed CAR T cells using humanized single-chain variable fragments (scFv) that showed specificity for EGFRvIII over wild-type EGFR. In mice, the EGFRvIII CAR T cells successfully controlled tumor growth, and deeper regression was observed when they were combined with temozolomide chemotherapy, a standard treatment for glioblastoma (Sci Transl Med 2015;7:275ra22).

"Studying genetically engineered T cells is a hot area because of the tremendous success there has been with leukemia," says the study's senior author Marcela Maus, MD, PhD, assistant professor of hematology/oncology at the University of Pennsylvania Abramson Cancer Center in Philadelphia. "This phase I trial will be the first time that we are trying this particular method of engineering T cells to target glioblastoma in humans."

Although CAR T-cell therapy has shown promise for treating blood cancers, solid tumors have been more challenging because many targetable surface antigens on solid tumors are also expressed in normal cells. However, the authors noted that EGFRvIII might be an ideal CAR target because it is specific to malignant cells and plays a critical role in maintaining oncogenesis.

The researchers, including scientists from Novartis Institutes for BioMedical Research, tested a panel of scFvs *in silico* and *in vitro* in order to determine the degree of specificity to EGFRvIII and cross specificity with wild-type EGFR. They then further tested the lead humanized CAR for safety in mouse models grafted with normal EGFR-expressing human skin.

The investigators also tested the lead humanized CAR for efficacy in three mouse models implanted with human glioblastoma cell lines, says Maus. The CAR T cells controlled or shrank most tumors whether the tumors were intracranial or under the skin. Administered intravenously, the engineered T cells controlled the tumor most effectively when given in combination with temozolomide.

The study is the basis for a new phase I trial, based at Penn and the University of California, San Francisco, that is currently enrolling up to 12 adults with EGFRvIII-positive glioblastoma who have either relapsed after standard therapy or have residual disease following surgery, says Maus. Investigators will remove patients' own T cells and reprogram them to target EGFRvIII-expressing tumor cells when they are returned to the patients via intravenous injection. ■

Improving PET Evaluation of Brain Tumors

To survive and proliferate, cancer cells undergo metabolic reprogramming and avidly consume various nutrients, including glucose. ^{18}F-fluorodeoxyglucose (^{18}F-FDG), a glucose analog, is usually the radiolabeled tracer of choice when PET is used to evaluate tumors.

However, not all cancers can be clearly imaged with ^{18}F-FDG–based PET, including glioma, an aggressive form of brain cancer. "It's difficult to distinguish these tumors, because normal brain cells also metabolize high amounts of glucose," says Sriram Venneti, MD, PhD, a neuropathologist at the University of Michigan in Ann Arbor and first author of a recent study showing that ^{18}F-fluoroglutamine (^{18}F-FGln), an analog of the amino acid glutamine, is a more specific PET tracer for glioma in mice and humans (Sci Transl Med 2015;7:274ra17).

Highly dependent on glutamine, many cancers synthesize it and import still more from extracellular sources. Hypothesizing that "this addiction could be leveraged to noninvasively assess brain tumors," Venneti collaborated with colleagues at Memorial Sloan Kettering Cancer Center in New York, NY, and the University of Pennsylvania in Philadelphia to develop ^{18}F-FGln.

In several mouse models of glioma, the researchers found that the uptake of ^{18}F-FGln was significantly higher in tumors than in normal brain tissue. In contrast, the uptake of ^{18}F-FDG was equivalent in tumors and normal tissue. With ^{18}F-FGln, tumor-to-background ratios ranged from 4:1 to 6:1, enabling clear tumor delineation; this ratio was approximately 1:1 with ^{18}F-FDG. The researchers verified that the marked ^{18}F-FGln uptake seen in glioma was not influenced by neuroinflammation or a leaky blood–brain barrier.

Venneti's team then compared ^{18}F-FGln with MRI in imaging glioma-bearing mice before and after treatment with chemotherapy and radiation. ^{18}F-FGln's uptake dropped significantly after treatment; however, MRI scans before and after were not appreciably different.

Ralph DeBerardinis, MD, PhD, an associate professor at the University of Texas Southwestern Medical Center in Dallas, is encouraged that ^{18}F-FGln–based PET "reports therapy-induced metabolic changes in these mice long before tumor size changes" on MRI. "This is exactly what glucose-based PET monitors in many other cancers, but has been difficult to capture in gliomas," he says.

Additionally, ^{18}F-FGln–based PET may help separate pseudoprogression—a treatment-related MRI pattern mimicking disease progression—from actual tumor recurrence, "a difficult distinction to make in the clinic," Venneti adds.

Testing the agent in patients who had undergone surgery, Venneti and his colleagues saw avid uptake and retention of ^{18}F-FGln in three patients whose gliomas recurred, but not in three others whose tumors had not. Where ^{18}F-FDG outlined only part of the tumor in one patient, ^{18}F-FGln