Andersen Lab

Alzheimer's disease is a multifactorial disease with numerous known pathological hallmarks. For decades, research has been shaped by heated debates over whether amyloid-β, tau, neuroinflammation, synaptic dysfunction, or other pathological processes should be treated. In the Andersen lab, we asked: why not treat all of them at the same time rather than argue over which one to treat? After all, we do already have effective drugs against individual aspects of Alzheimer's pathology. They do not work when used alone as monotherapy. However, it is possible that using the drugs together in combination therapy could allow us to cure Alzheimer's right now, this very day. Modern medicine has not pursued this strategy broadly, not because it is not aware of this, but because it cannot.

Medicine cannot do combination therapy for most multifactorial diseases. The problem is not the drugs; it is the delivery. Systemic drug delivery is inherently non-targeted, exposing cells and organs throughout the body to potentially toxic side effects. These risks compound as more drugs are combined, making complex therapeutic cocktails difficult or impossible to administer safely and very expensive to develop. To overcome this limitation, in the Andersen laboratory we are engineering immune cells to act as targeted delivery vehicles in research funded by the NIH Director's High-Risk, High-Reward Transformative Research Award program.

Our approach is analogous to an aircraft, in which each immune cell (airplane) has a pilot, a bomber, and munitions. The pilot directs the cell to a specific site of Alzheimer's pathology, such as senile plaques. The bomber independently controls the release of munitions. The munitions are drugs against different Alzheimer's pathologies. The airplanes are regulatory T cells (Tregs), a non-cytotoxic, immunosuppressive subset of T cells. The pilots are a type of targeting receptor known as chimeric antigen receptors, or CARs. The bombers are SNIPR receptors, which link the binding of extracellular ligands (e.g., amyloid-β) to the activation of synthetic transcriptional programs controlling genetically encoded munitions. Depending on the clone, the munitions regulated by these receptors include amyloid-β-clearing antibodies, immune modulators, and agents designed to support synaptic function. Each set of identical CAR (pilot), SNIPR (bomber), and munition (drug) expressed in a Treg (airplane) is a clone. Thousands of identical clones together form a squadron, the cellular equivalent of targeted monotherapy. When combined, different squadrons carrying different drugs form an air force, the cellular equivalent of targeted combination therapies.

So far, we have validated multiple pilots, bombers, and munitions in vitro in three publications and plan on at least one additional publication in the coming year. In vivo, we are now conducting preliminary adoptive cell-transfer studies using engineered human Tregs in a specially developed immunodeficient mouse model of Alzheimer's disease. Ultimately, our goal is to establish a generalizable platform in which complex multidrug therapies can change how modern medicine approaches multifactorial disease.