Conquer Cancer - The Sontag Foundation Young Investigator Award in honor of the 10th Anniversary of The Brain Tumor Network

Hila Shaim, MD
The University of Texas MD Anderson Cancer Center

Combining IL-12-Expressing Oncolytic HSV1 with TGF-β and Corticosteroid-Resistant Natural Killer Cells to Target Glioblastoma

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MENTORED BY
Katy Rezvani, MD, PhD and Frederick Lang, MD

EMAIL
hshaim@mdanderson.org

Lay Abstract

Glioblastoma (GBM) is the most aggressive form of brain cancer. Current treatments such as surgery, radiation, and chemotherapy provide only limited survival benefit. Despite significant advancements in immunotherapy across many cancer types, it has failed to achieve significant success in GBM. To address these challenges, this project explores a cutting-edge combination of genetically engineered natural killer (NK) cells and an oncolytic herpes simplex virus (oHSV) engineered to deliver IL-12, a potent immune-boosting cytokine. NK cells are a vital part of the immune system's defense against cancer. They can effectively target and kill tumor cells without requiring specific antigens. However, in GBM, the tumor environment secretes molecules like TGF-β that weakens the immune system's ability to fight tumors, suppressing NK cell activity, leading to immune evasion. To overcome this, we have developed genetically modified cord blood NK cells (CB-NK-TGFBR2-/NR3C1-) that resist suppression by TGF-β and remain functional even in the presence of corticosteroids, which are commonly used to manage the swelling surrounding the tumor. We have shown that these engineered NK cells are able to kill GBM cells in both laboratory and animal models while avoiding suppression by the tumor. Moreover, those genetically modified NK cells are currently tested in humans in a groundbreaking phase I clinical trial and appear to be well tolerated. This

study has two goals. First, determining the anti-tumor activity of combining the IL-12-loaded oHSV virus with CB-NK-TGFBR2-/NR3C1- cells in both laboratory models and in a mouse model. By combining these two therapies, we aim to achieve a more potent and targeted attack on GBM. Second, exploring the underlying mechanisms driving the enhanced anti-tumor activity of this combination therapy. Specifically, I plan to focus on how this oHSV helps CB-NK-TGFBR2-/NR3C1- cells overcome the suppression imposed by the tumor and its environment. Understanding how the combination therapy potentiates NK cell function and protecting them from the tumor and its environment could lead to significant insights into overcoming immune suppression in GBM. This project has the potential to advance new and innovative approaches to treating GBM, offering hope to patients for whom current treatments are ineffective. By combining cutting-edge virotherapy with engineered NK cells, the study could lead for a more effective and less toxic treatment for GBM.

Short Professional Biography

Dr. Shaim is board certified in clinical pathology and internal medicine. She is currently doing her hematology-oncology fellowship at MD Anderson Cancer Center and is a T32 scholar. Her career goal is to become a physician scientist, focusing on the development of novel cell-based therapies that involve chimeric antigen receptor, gene editing and tissue regeneration. The good manufacturing practice (GMP) translational settings is of particular interest to her. Ultimately, she desires to use her clinical experience to facilitate her research and thereby be able to bring medical advances back into the clinic. She has been heavily involved in research to generate promising cell therapies. The NK cell-based cell therapy product for glioblastoma (GBM) that she designed is currently undergoing a phase I clinical trial.
