GCORE: Glioblastoma-Related Chimeric Antigen Receptor T Cell Therapy Outcome Re-Engineering

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Brain cancer, or glioblastoma, is one of the most aggressive cancers, given the nutrient-dense environment of the brain. This cancer is very deadly, given the significance of the brain for the body's functionality. Most glioblastoma treatments use chemotherapy, which has a life expectancy of 10 months. Newer treatments like CAR-T cell therapy using antigen-seeking T cells are more promising, with 15-month survival rates (trial NCT0317014), but still show tumor relapse. To understand why relapse occurs, the literature points to hypoxia-related phenotypic persistence. Hypoxia was modeled in Python based on Gauss's law for electricity, but applied to oxygen diffusion; the interior of a tumor reaches low oxygen levels (~0 mmHg). Modeling produced similar results, as the tumor grows, its expansion outpaces oxygen intake within the interior, leading to cell stress and death. To survive, interior cells activate HIF1-a, suppressing the tumor's signature antigen GD2, making cells unrecognizable to most CAR T therapies, and instead express CAIX (preventing denaturation). Treatment and tumor interactions were modeled in Physicell, according to prior glioblastoma research. A baseline GD2-targeted CAR T simulation resulted in only a 1.3% reduction in the hypoxic niche. Additional treatments were then engineered, including CAIX-targeted CAR T cells, HIF1-a inhibition, and hyperbaric oxygen manipulation. Dual T-cell modification targeting both GD2 and CAIX antigens, combined with HIF1-a inhibition, showed the most promising results, achieving 99.3% tumor reduction over the 14-day trial period. While this model is not perfect, it provides a realistic framework for testing cancer treatments in silico, offering a powerful alternative to expensive and time-consuming clinical testing.

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