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A Novel Immunotherapy for Treating Glioblastoma Multiforme

-The last few years have seen an explosion of impressive clinical results in the field of immunotherapy, representing some of the most promising advancements in disease treatment. One immuno-oncology platform that has demonstrated incredible therapeutic potential is the bispecific T cell engager (BiTE) technology. This technology harnesses a patient's own immune system to target tumor-specific receptors and initiate cell death. However, there are some cancers for which a universal receptor has not been reported, such as glioblastoma multiforme (GBM), which is a common and highly aggressive brain tumor.

Chlorotoxin is a small 36-amino acid scorpion-derived peptide which is able to specifically bind cancer cells, including glioma cells, without off-target toxicity to other tissues. This peptide has been extensively studied for its cancer targeting abilities in vitro, particularly for GBM, and versions have already been tested in the clinic in Phase 2 trials for targeted imaging and radiotherapy. Despite the promising clinical applications, chlorotoxin production often resulted in insoluble aggregations, likely due to the formation of disulfide bonds.

Researchers at Arizona State University have developed a novel bispecific antibody fusion protein, based on the BiTE design, which tethers a truncated chlorotoxin to the variable region of a monoclonal antibody targeted to CD3 on both CD8+ and CD4+ T cells. Use of a truncated chlorotoxin reduces the number of disulfide bonds that are formed during production, but doesn't impact the ability of the peptide to target glioma cells. This fusion protein brings T cells into contact with GBM in order to initiate perforin/granzyme-mediated apoptosis of tumor cells with high specificity for GBM cells and the selectivity to prevent off-target toxicity against healthy cells.

Potential Applications

- Cancer immunotherapeutics
  - Gliomas, specifically GBM, and tumors of neuroectodermal origin

Benefits and Advantages

- The truncated chlorotoxin reduces the possibility of disulfide bond formation to allow for more efficient production without reducing target binding
- May be able to penetrate the blood-brain-barrier
- Chlorotoxin is capable of binding 100% of GBM cells, making it more effective at targeting the entirety of the tumor
- Does not require recognition by the major histocompatibility complex (MHC), allowing for T cell-mediated elimination of target cells regardless of TCR specificity
  - Overcomes the problem of MHC-downregulation by cells such as GBM which use this immune evasion tactic
- Selectively binds GBM cells without off-target toxicity

For more information about this opportunity, please see

Schaefer – Thesis - 2021

For more information about the inventor(s) and their research, please see

Dr. Mor's departmental webpage

Dr. Blattman's departmental webpage