

Targeting Tumor Cells of Malignant Glioma with Cellular Scalpels Derived from Engineered Cytolytic T-cells: Opportunities For Molecular Imaging

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Recent advancements in the fields of molecular immunology, gene transfer, and cell processing have facilitated the translational application of T-lymphocyte genetic modification technologies for immune-based cancer therapeutics. City of Hope's Cancer Immunotherapeutics Program has focused on developing technologies for re-directing the antigen specificity of T-cells by their genetic engineering to express chimeric antigen receptors. At the forefront of this program is the use of chimeric antigen receptor re-directed cytolytic T-cells for targeting malignant glioma. Based on the glioma-specific expression of an Interleukin-13 receptor (IL13R α 2), investigators at the City of Hope have constructed the IL13-zetakine, consisting of a membrane tethered human IL-13 cytokine extracellular domain and a cytoplasmic CD3- ζ tail. This chimera, when expressed by T-cells, re-directs their antigen-specific effector functions to IL13R α 2+ targets, including tumor cells of high-grade gliomas.

Investigators at City of Hope have delineated the immunobiology of IL13-zetakine re-directed CTL for glioma immunotherapy in in vitro model systems. These data have formed the basis of an FDA-authorized IND (BB-IND#10109) for evaluating the feasibility and safety of adoptively transferred autologous IL13-zetakine+/HyTL+ CTL clones for recurrent/progressive glioblastoma multiforme. This trial is currently open and accruing patients at the City of Hope. However major insights regarding the interactions of T-cells with tumor cells and the tumor microenvironment can be made if orthotopic model systems can benefit from animal imaging systems that permit the selective imaging of the location and quantity of tumor cells and T-cells.

To this end, glioma cell lines expressing Renilla luciferase and human IL13-zetakine re-directed T-cells expressing firefly luciferase have been generated. Using selective substrates for these luciferases and the Xenogen biophotonic in vivo imaging system, preliminary experiments have provided proof-of-concept data that two cell populations (T-cells and tumor cells) can be imaged in individual animals. Thus the Xenogen system, in concert with mouse MRI and micro-PET, afford the opportunity to gain critical insights into the dynamics and interplay of therapeutic T-cells and tumor cells in the orthotopic brain model system.

Animal modeling of imaging genetically engineered T-cells has direct applicability to developing strategies to image these cells administered to human study participants. Already in the glioma clinical trial at City of Hope, patients will be imaged at the UCLA Crump Institute of Molecular Imaging with the ^{18}F HGBG molecular probe for imaging HSV-TK expressing cells. Animal imaging systems developed in the context of this proposal have an exceptional potential to be translated to human clinical imaging studies of genetically-modified T-cells.