SPERA - Recruitment of immune Effector cells against astrocytoma by MHC-Chlrotoxin chimeric proteins.

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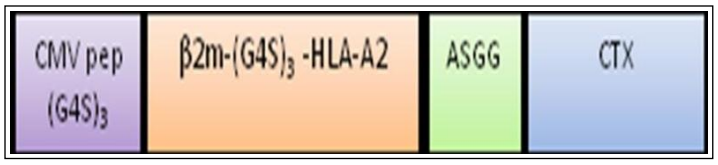
Introduction

Glioblastoma Multiforme (GBM) is the most common malignant primary brain neoplasm, having a mean survival time of 12 months. The lack of an efficient immune response to the tumor and its microinvasive nature have been explained by its immunosupressive capabilities and the immunosupressed local environment.

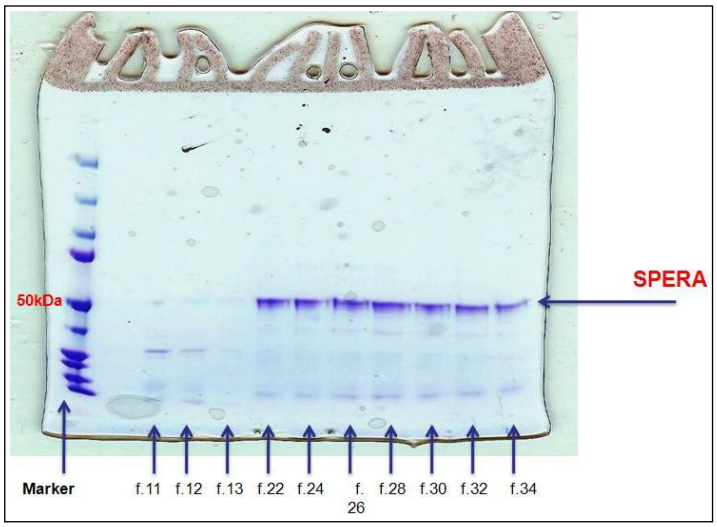


Methods

We designed a molecule that specifically binds Matrix metalloproteinase 2 (MMP-2) expressed most abundantly on GBM cells, and through its effector domain mobilize and recruit elements of the immune system to mount an effective antitumor reaction. The targeting pole of the molecule is the small 36-amino acid chlorotoxin, derived from the venum of the Israeli Yellow scorpion. The effector end of the chimera is a single chain HLA-A2 (Human leukocyte antigen subtype A2) covalently bound to a protein derived from the cytomegalovirus, to which most of the human population has developed a specific immune response.

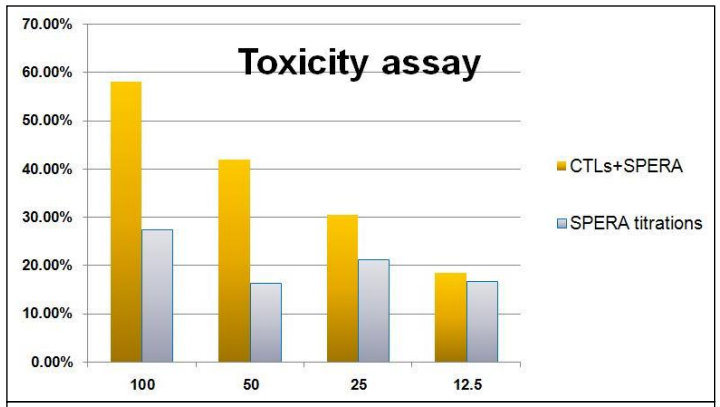
Results

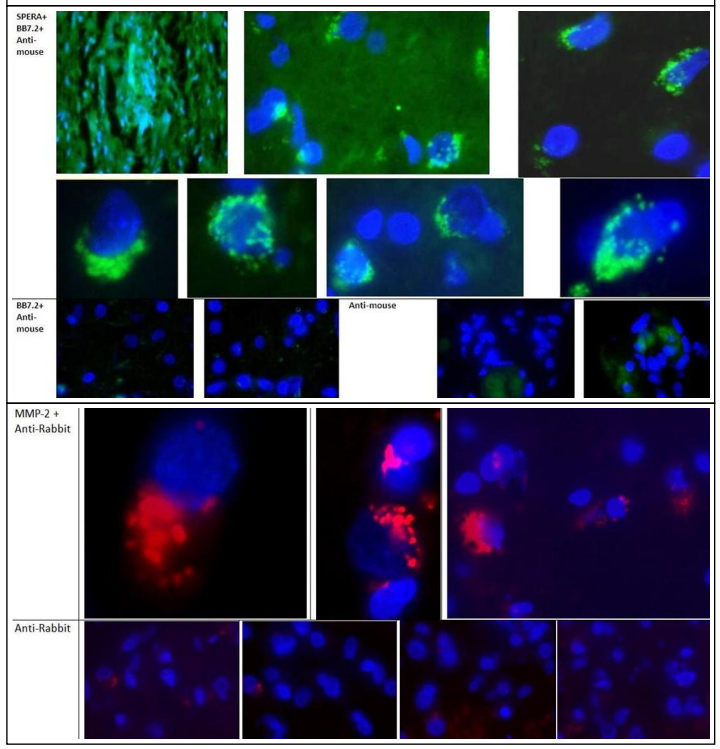
The SPERA construct was cloned and produced in e.coli, than purified. activity assays including immunohistochemistry, flow-cytometry and toxicity assays are very



Conclusions

This exemplifies a new family of molecules which contain a non-antibody compact and highly specific targeting domain, combined with the ability to recruit different lymphocyte populations using HLA-molecules bearing a single, preselected, highly antigenic peptide derived from immunogenic tumor, viral, or bacterial T cell epitopes. Moreover, the recruitment of potent memory CTL's to the tumor's milieu may be resistant to the previously described local immunosuppressive environment created in part by TH2 secretion profile, and may enables the shift to TH1 cytokine profile resulting in specific massive tumor destruction.





Learning Objectives

A new immuno-therapeutical approach to battle GBM