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ORAL PRESENTATION Open Access

A bispecific chimeric antigen receptor molecule enhances T cell activation through dual immunological synapse formation and offsets antigen escape in glioblastoma

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Background

Antigen escape tumor cell variants prevail in tumors recurring after treatment with chimeric antigen receptor (CAR) T cells with a single specificity. Recurrent tumors preserve alternative non-targeted tumor associated antigens.

Hypothesis

A bispecific CAR will mitigate antigen escape enhancing the antitumor activity of T cells.

Methods and results

HER2 and IL13Rα2 are currently targeted in Phase I glioblastoma (GBM) trials using CAR T cells. We created a bispecific CAR molecule with a HER2-specific scFv joined in tandem to an IL13Rα2-binding moiety in the CAR exodomain (Tandem CAR) and a CD28.ζ signaling endodomain. We used computational modeling to interrogate this design. GBM patients' Tandem CAR T cells showed distinct binding to soluble HER2 and IL13Rα2 and killed primary autologous GBM cells. Three-dimensional reconstitution and quantification of confocal images of the Tandem CAR T cell/tumor interface revealed enhanced bifunctional immunological synapses compared to conventional CARs. Further, Tandem CAR T cells exhibited significantly enhanced inexhaustible activation dynamics when compared to conventional HER2 or IL13Rα2 CAR T cells and better controlled established GBM in an orthotopic murine model by offsetting both HER2 and IL13Rα2 escape.

Conclusion

Tandem chimeric antigen receptors enhance T cell activation and mitigate antigen escape through bifunctional immunological synapse formation in GBM.

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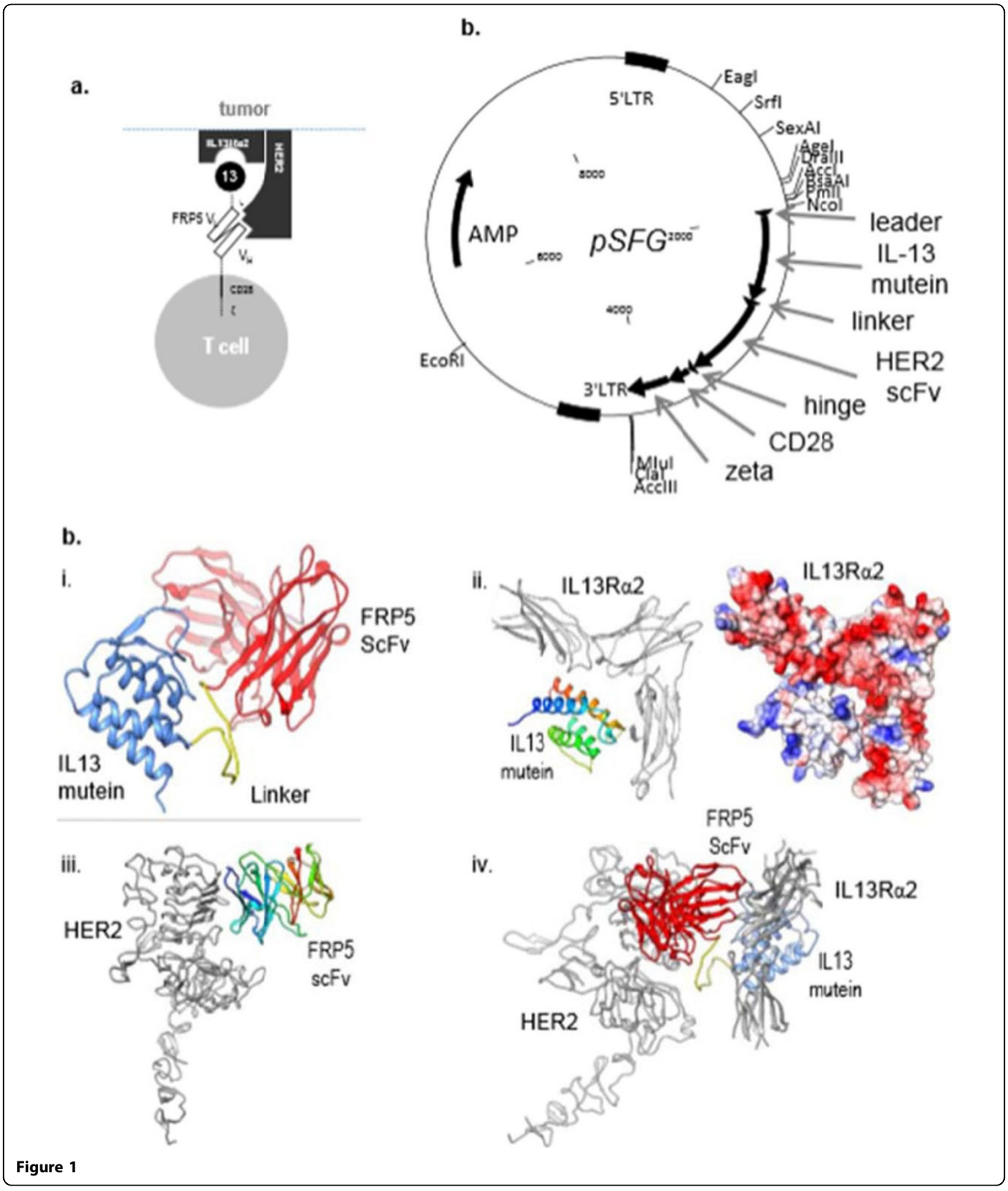
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13
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b.
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AMP
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mutein
HER2

Figure 1

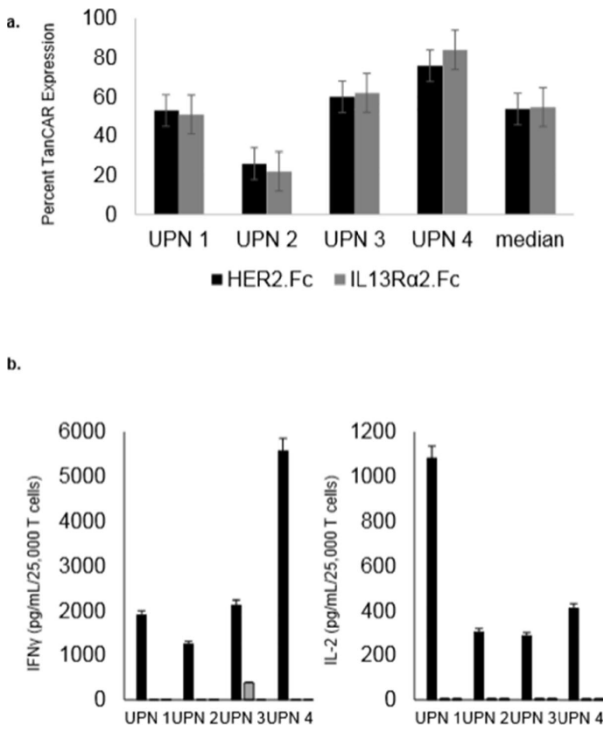


Figure 2

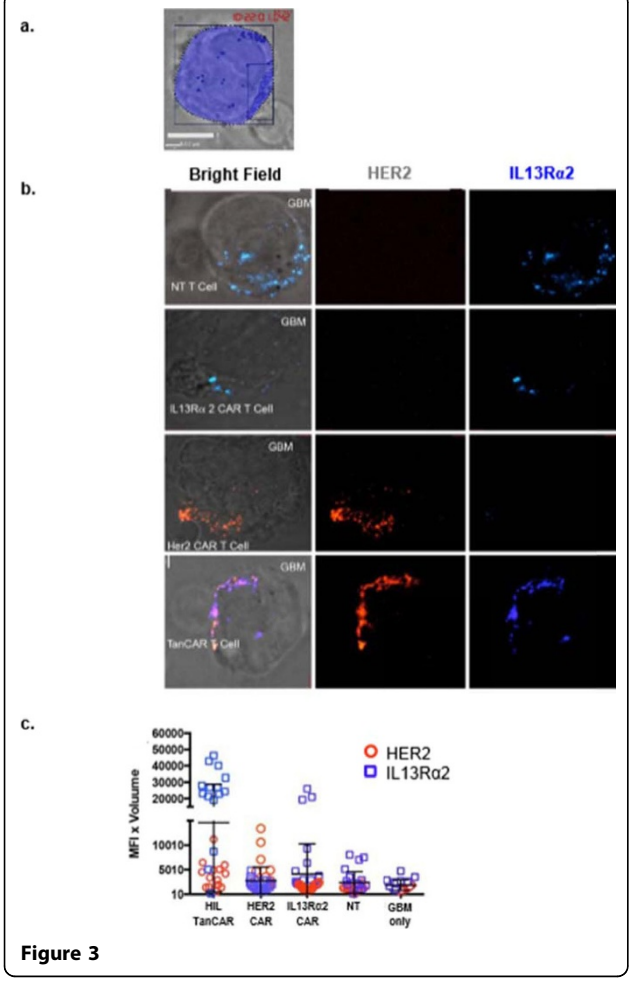
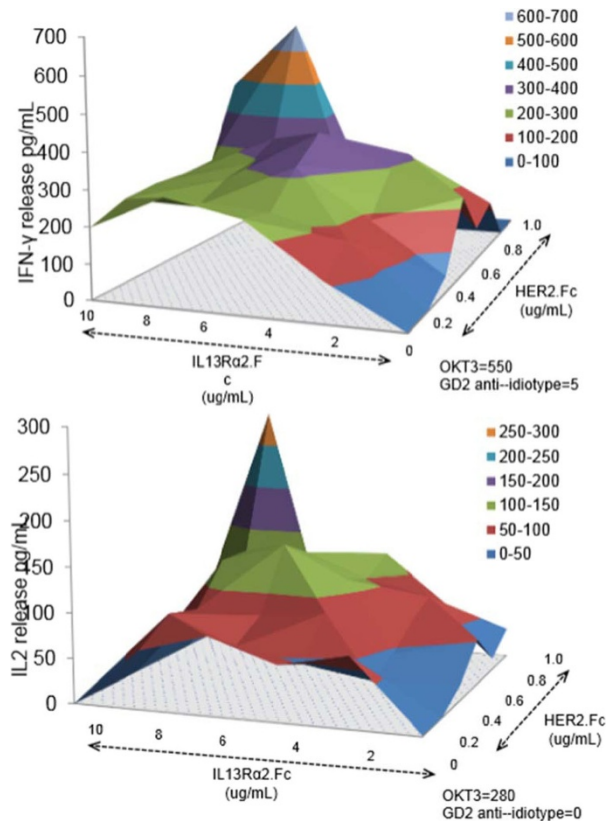


Figure 3



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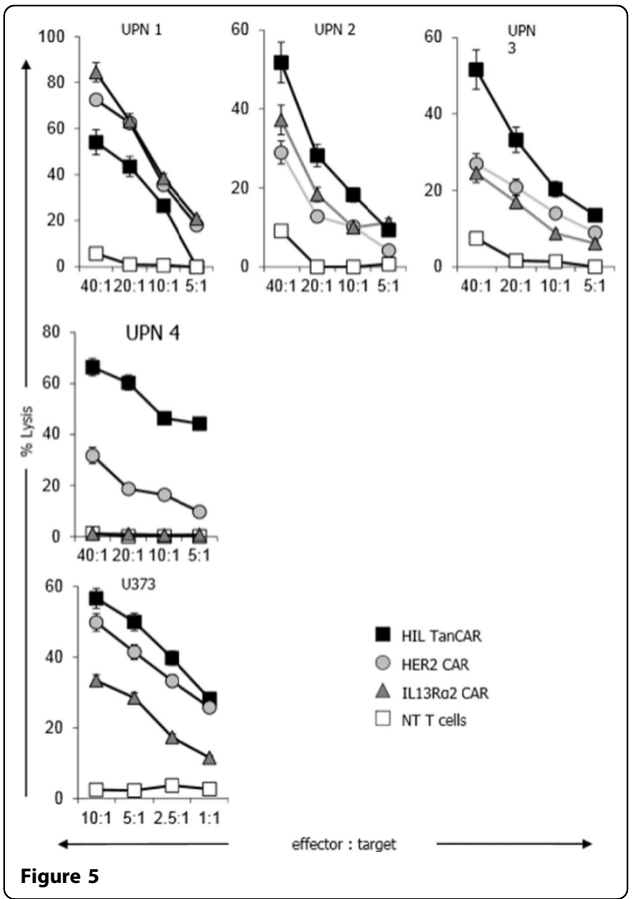

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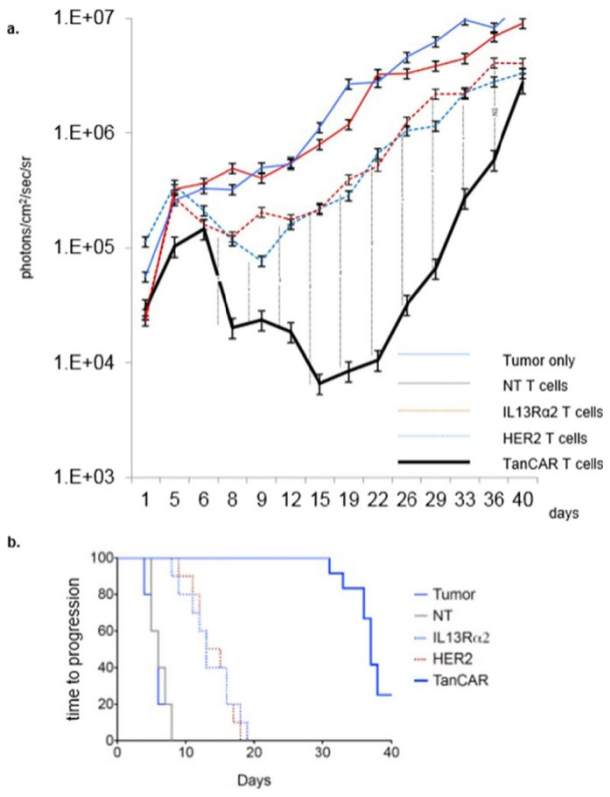

Figure 6

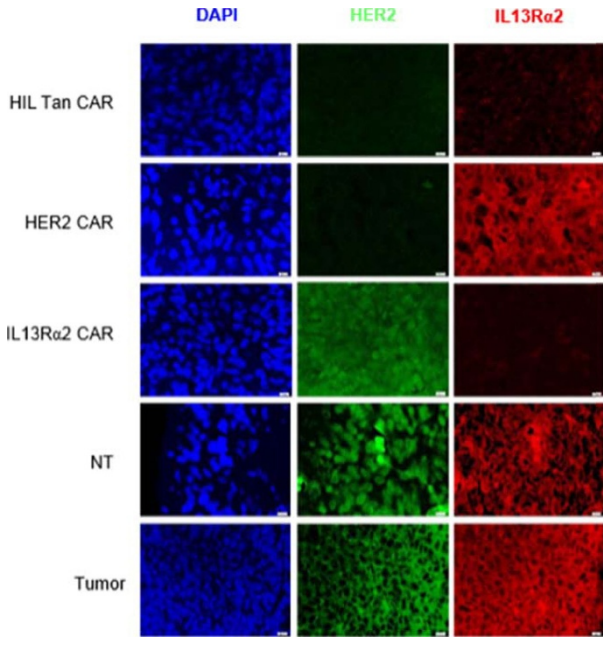

Figure 7