American Association for Cancer Research (AACR) Special Conference in Cancer Research: Brain Cancer, March 23-25, 2026. Poster number A002

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CCR5 inhibition with the human monoclonal antibody leronlimab enhances temozolomide- and radiation-induced killing of glioblastoma multiforme cells

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INTRODUCTION

Glioblastoma multiforme (GBM) is associated with short survival and is characterized by invasion and colonization of the whole brain(1). Resistance to DNA-damaging agents (radiation [RT], temozolomide [TMZ]) and immune checkpoint inhibitors (ICI) correlates with diffuse brain colonization, tumor heterogeneity, and death. Spatially resolved GBM sequencing identified microenvironment-driven gene expression programs in the tumor "core" vs. invasive "edge". The "core" exhibits a mesenchymal-like (MES) gene signature, and hypoxia driven immunosuppression. Glioma stem cells (GSCs) in the core are more resistant to chemotherapy and radiation. As heterotypic signals via CCR5 signaling are implicated in GBM progression(2-5) and recent studies have shown a humanized CCR5 inhibitor, monoclonal antibody leronlimab, crosses the blood brain barrier, and is associated with a well characterized safety profile. Here, we assessed the impact of leronlimab in GBM stemness and diffuse brain colonization.

MATERIAL AND METHODS

These studies sought to determine the potential role of leronlimab in GBM therapeutic responses. Analysis of patient GBM gene expression and analysis of GBM cell lines were conducted to define the potential role of CCR5 inhibition as a therapeutic adjunct to current treatments.

1. CCR5 expression is upregulated in GBM and correlates with poor prognosis in patients

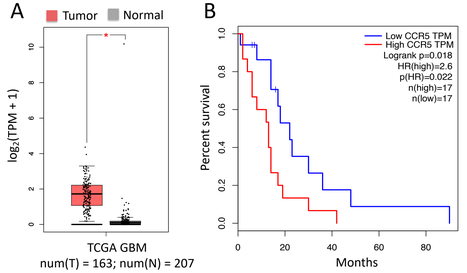

Figure 1. A) CCR5 expression is significantly upregulated in GBM patient tumors compared to normal tumor tissue (from TCGA)**. B)** Kaplan-Meier curves showing correlation of higher CCR5 expression level with lower overall survival (OS) in GBM patient cohort (quartile stratification) from TCGA.

2. CCR5 expression is associated with inflammatory signaling in TCGA GBM

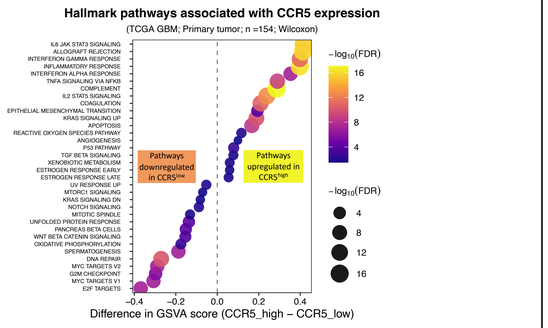

Figure 2. CCR5^{high} tumors (median split) are significantly enriched for inflammatory and mesenchymal programs. Dot plot showing MSigDB hallmark pathway enrichment associated with CCR5 expression in primary GBM (from TCGA).

3. CCR5 expression correlates with mesenchymal subtype, immune-rich, T cell dysfunction and tumor "core"

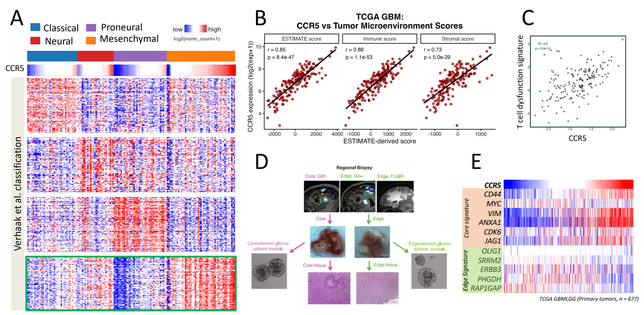

Figure 3. CCR5 expression correlates with mesenchymal subtype and T cell dysfunction scores. **A)** CCR5 expression across Verhaak GBM subtypes in the TCGA cohort (n = 152), showing enrichment in the mesenchymal subtype. **B)** CCR5 expression positively correlates with ESTIMATE-derived immune and stromal scores in GBM cohort from TCGA, suggesting an immune-rich tumor microenvironment. **C)** CCR5 expression correlates significantly with the T cell dysfunction score in the GBM cohort from TCGA. **D)** Schematic representation of isolation of core and edge GBM tissues, adapted from *Bastola S. et al. (2020), Nature communications*. **E)** Heatmap showing correlation of core and edge gene signatures with CCR5 in TCGA.

4. CCR5 is enriched in glioma neurospheres

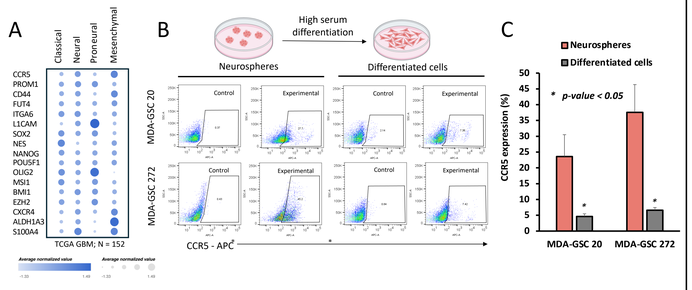

Figure 4. A) Dot plot showing normalized expression pattern of CCR5 and glioma stemness markers within transcriptional subtypes of GBM. **B-C)** Flow cytometry analysis shows significant lowering of CCR5 expression upon differentiation of neurospheres in high serum conditions. Data is shown as Mean ± SEM (n=3).

5. Leronlimab synergistically enhances Temozolomide and radiation induced cell killing

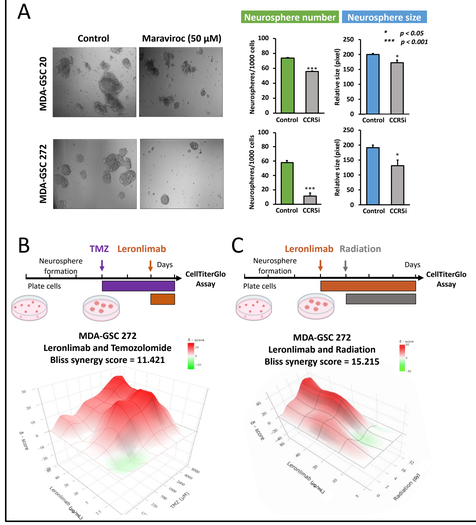

Figure 5. A) CCR5 inhibition leads to significant reduction in neurosphere number and size. Data is shown as Mean ± SEM (n=3). Schematic representation of drug treatment period and bliss synergy plots for the combination of leronlimab with **B)** temozolomide and **C)** radiation in MDA-GSC 272 cell line. The 3D surface shows the Bliss synergy score across increasing concentrations of TMZ and leronlimab. Positive scores (red) indicate synergistic interactions, whereas negative scores (green) indicate antagonistic interactions.

6. Leronlimab reduces diffuse brain colonization of MDA-GSC 272 in mice studies

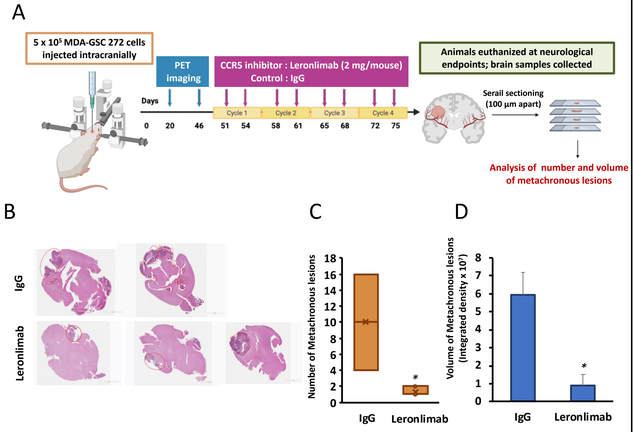

Figure 6. A) Schematic representation of preclinical study in which GSC 272 cells were injected into the brains of immune deficient mice. **B)** H and E staining of representative sections from either IgG or leronlimab treated mice. **C)** Number and **D)** volume of metachronous GBM lesions which colonize the brains of mice in IgG control vs. leronlimab treated mice.

CONCLUSIONS

1. CCR5 expression correlates with the mesenchymal GBM subtype, immune cell infiltration, T cell exhaustion and poor prognosis.
2. CCR5 promotes cancer stemness and neurosphere formation.
3. Inhibition of CCR5 synergistically enhances GBM cell killing by TMZ.
4. A humanized antibody to CCR5, leronlimab, reduces diffuse brain colonization in mice.

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