A novel oncolytic immunotherapy, VET3-TGI, overcomes TGFB1 mediated immunosuppression, augments type-1 immune response, and displays potent therapeutic activity in multiple mouse tumor models.

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KALIVIR IMMUNOTHERAPEUTICS

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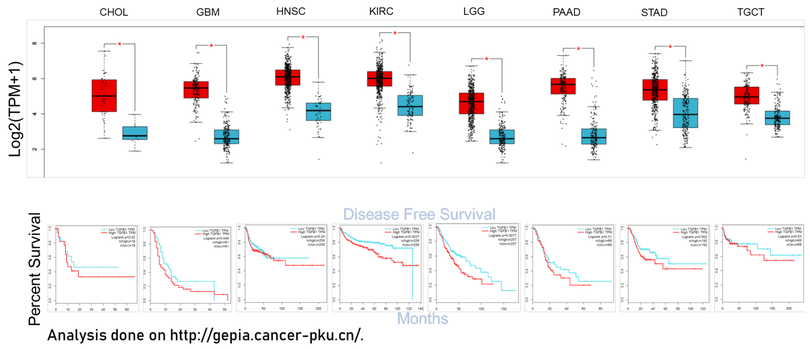
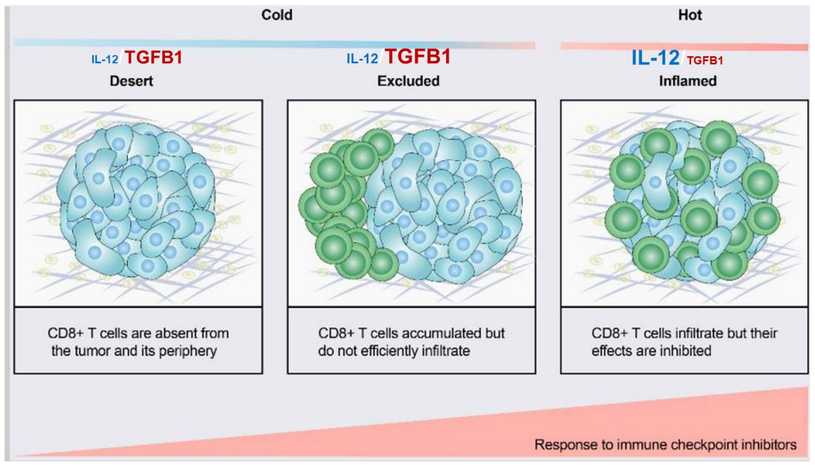
Introduction

TGFB1 mediated immune resistance is a major mechanisms of immune suppression seen in multiple tumor types. TGFB1 immune resistance is mediated through its pleiotropic effects on vasculature, fibrogenesis and regulatory/effector immune cells within the tumor microenvironment. Blockade of TGFB1 (TGFBi) will likely improve response to immunotherapy. Further, IL-12 is a cytokine that, through IFNg induction, promotes type 1 inflammatory response, M1 macrophage skewing and effector CD8 T cell response. Combining TGFB1 blockade with IL-12 may therefore maximize therapeutic benefits through simultaneously reducing immunosuppression and enhancing anti-tumor immune response. Current studies have selected a vaccinia-based oncolytic immunotherapy, combining locally expressed IL-12 and TGFBi within the tumor microenvironment, for efficient control of multiple tumor models. In addition, CXCR3 expression from the viral backbone resulted in enhanced systemic virus delivery to CXCR3 ligand rich tumors.

TGFβ1 is increased in tumors and high levels associated with poor survival.



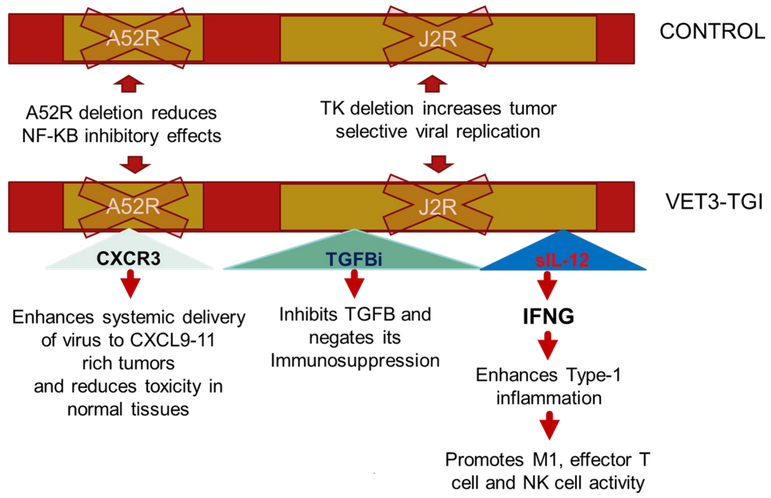
IL-12 Vs. TGF-β can skew differently the immune landscape of tumors



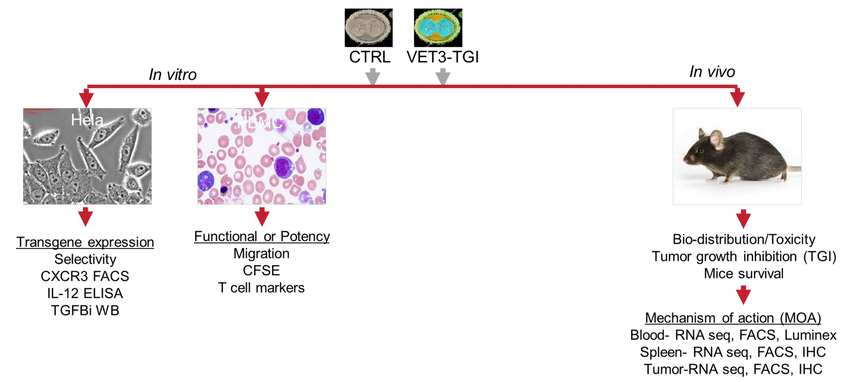
Liu YT and Sun ZJ, Theranostics 2021

Materials

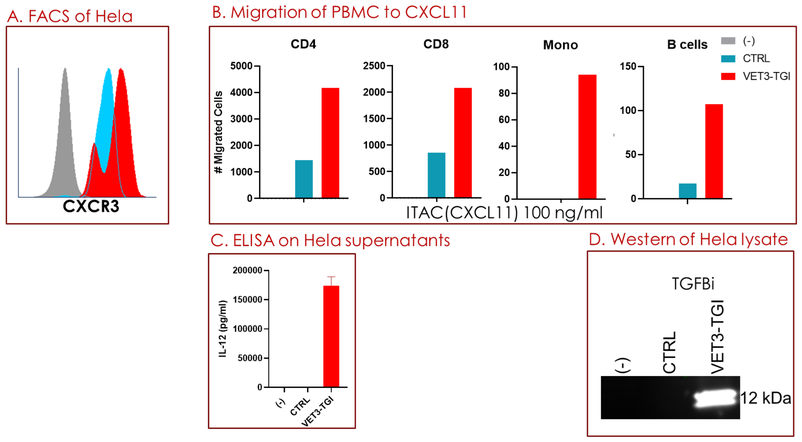
VAVC constructs



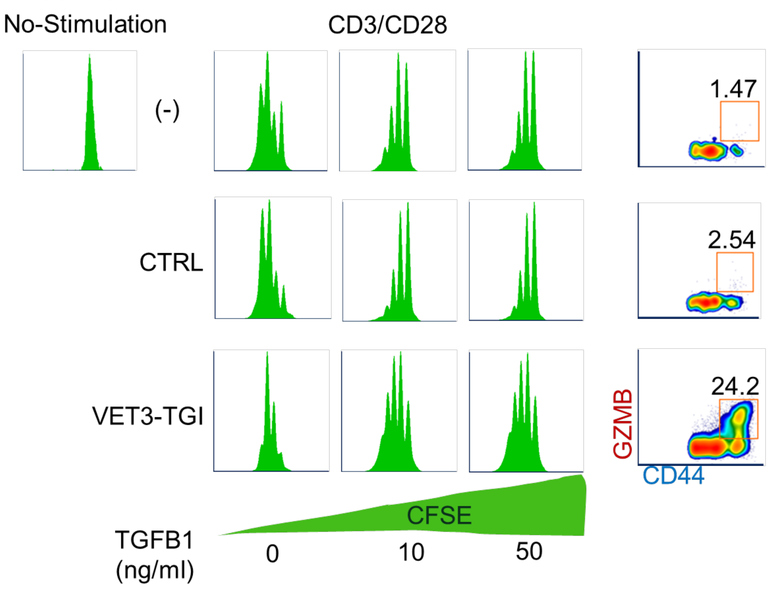
Methodology and Results



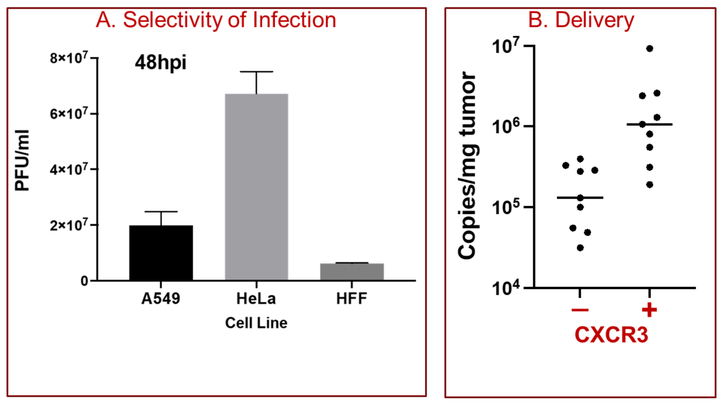
VET3-TGI shows expression of transgenes



VET3-TGI rescues CD8 T cells from suppression by TGF-b and induces more GZMB.

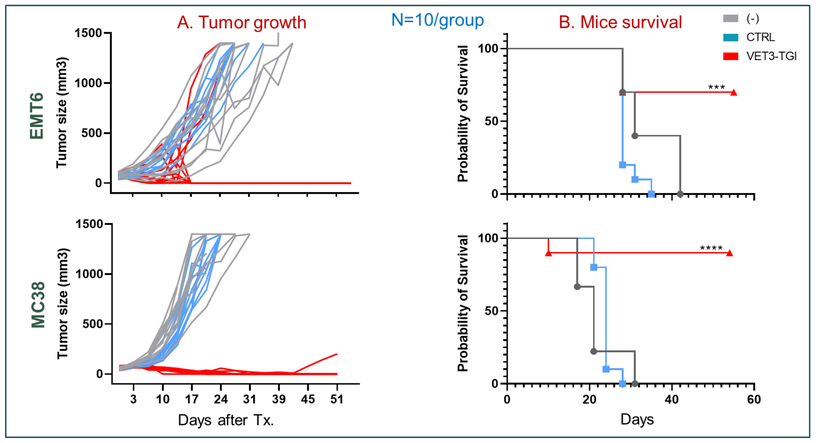


In vitro selectivity and enhanced *in vivo* tumor specific delivery of VET3-TGI

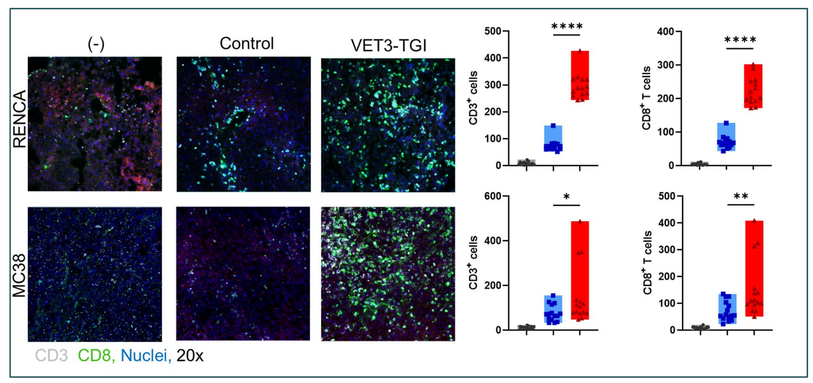


qPCR of viral genomes in the tumor recovered 24h after IV delivery of (1e7 PFU) of virus without (-) or with (+) CXCR3 to subcutaneously implanted Renca tumors in BALB/c mice

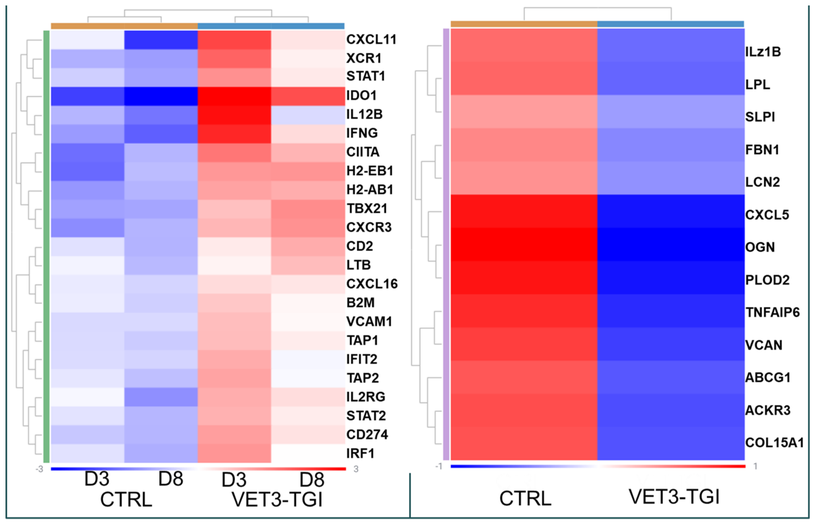
VET3-TGI decreases tumor burden and increases mice survival in multiple tumor models



VET3-TGI treatment increases CD3⁺CD8⁺ T cell infiltrate in tumors



VET3-TGI induces type II IFNG associated but negates TGFB1 associated gene signatures in tumors



CONCLUSIONS

- VET3-TGI demonstrated selectivity for cancer cell lines and expression of transgenes *in vitro*
- *In vitro* potency assays confirmed that VET3-TGI infected PBMC migrated towards CXCR3 ligands, and that VET3-TGI reduced immunosuppressive effects on CD8 T cells and upregulated GZMB expression.
- *In vivo* studies demonstrated that VET3-TGI showed CXCR3 dependent increased systemic delivery.
- VET3-TGI was highly efficacious, showing >80% complete responses in multiple tumor models.
- Mechanism of action analyses suggest that VET3-TGI profoundly modified the tumor microenvironment: increased IFNg associated genes and decreased TGF-b associated genes; IHC analysis suggested that it also increased CD8 T cell infiltration in tumors.
- **Encouraged by this data, VET3-TGI has been selected as our lead clinical candidate. A human version of this virus is currently undergoing clinical manufacture and toxicology testing.**