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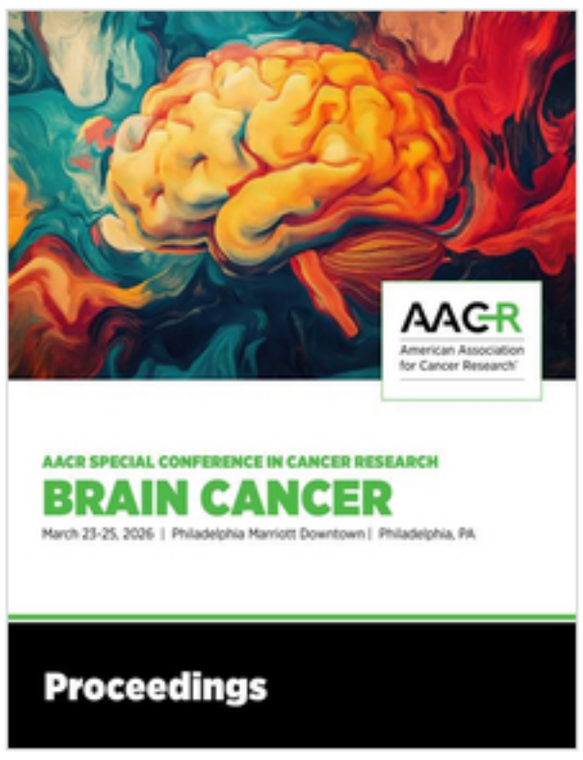

CELLULAR THERAPIES FOR NERVOUS SYSTEM TUMORS | MARCH 23 2026

Abstract A033: Ex vivo Cbl-b silenced, autologous TIL therapy in glioblastoma demonstrates proof-of-concept efficacy and translational potential FREE

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Abstract

Purpose:

Glioblastoma (GBM) remains largely refractory to immunotherapy due to extensive intratumoral immunosuppression and functional exhaustion of tumor-infiltrating lymphocytes (TILs). This study evaluated whether ex vivo silencing of the intracellular immune checkpoint Cbl-b could enhance the antitumor efficacy of autologous TIL therapy in GBM.

Experimental Design:

Tumor-reactive lymphocytes were isolated from human glioblastoma specimens and expanded using a closed, feeder-free xpsTIL manufacturing process. Transient Cbl-b silencing was achieved by electroporation with the clinically validated EPiC platform. T-cell phenotype, cytokine secretion, cytotoxic activity, and T-cell receptor (TCR) repertoire diversity were assessed in vitro . Therapeutic efficacy was evaluated in immunocompetent subcutaneous and orthotopic glioma mouse models, including studies in combination with temozolomide.

Results:

$CD8^+$ TILs isolated from glioblastoma exhibited high Cbl-b expression, implicating intrinsic suppression of effector function. xpsTIL expansion reproducibly achieved >10^4-fold proliferation while preserving a highly polyclonal, tumor-exclusive TCR repertoire. EPiC-mediated electroporation resulted in >95% downmodulation of Cbl-b expression, leading to enhanced IL-2 and IFN-γ production and increased anti-tumor cytotoxicity. In orthotopic glioma models, adoptive transfer of Cbl-b–deficient TILs significantly improved tumor control, achieving cure rates of approximately 20% as monotherapy and up to 70% when combined with temozolomide (0% cure with temozolomide alone). Treated animals demonstrated modest protection upon intracranial tumor rechallenge.

Conclusions:

Ex vivo Cbl-b silencing reprograms glioblastoma-resident TILs to overcome tumor-intrinsic and therapy-induced immunosuppression, enabling durable antitumor immunity without systemic checkpoint blockade. Cbl-b–silenced xpsTILs represent a promising, clinically scalable cell therapy approach for glioblastoma.*A large language model (ChatGPT) was used to assist in structuring and refining the abstract text; all scientific content was generated, reviewed, and validated by the authors.*

Citation Format:

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