

TIL therapy for glioblastoma



Summary and findings:

Pristo EL, Hotchkiss KM, Corcoran AM, Noldner P, Okada H, Hickey JW, Conejo-Garcia J, Shaz B, Khasraw M.

The promise of TIL therapy for glioblastoma.

Trends Cancer. 2025 Nov 13:S2405-8033(25)00254-7. doi: 10.1016/j.trecan.2025.10.003. PMID: 41238472.

Here is a structured summary (with key findings and critical assessment) of **Pristo EL et al. “The promise of TIL therapy for glioblastoma”** (2025).

Background & Rationale

- The paper reviews the potential of **tumor-infiltrating lymphocyte (TIL) therapy** for Glioblastoma (GBM). [PubMed+1](#)
- TIL therapy — already showing efficacy in refractory melanoma and durable responses in lung cancer — relies on expanding a patient’s own T cells naturally infiltrating the tumor. In contrast with engineered monoclonal-cell therapies (e.g. CAR-T), TILs retain **polyclonality**, which may allow them to recognize a broad and evolving set of tumor-associated antigens, including neoantigens and unknown epitopes. [PubMed+2](#)
- The unique challenges of GBM — including profound intratumoral heterogeneity, immunosuppressive microenvironment, and low baseline T-cell infiltration (“cold” tumors) — paradoxically constitute a strong rationale for TIL therapy, because polyclonal TILs might adapt to the heterogeneous antigenic landscape and target diverse subclones. [PubMed+1](#)

Key Findings & Recent Advances

From the review (and supporting literature), the authors highlight several encouraging observations:

- **Feasibility:** Functional, tumor-reactive TILs can indeed be **isolated and expanded** from human glioblastoma specimens, including from “cold” GBM tumors where T-cell infiltration is minimal. [ScienceDirect+1](#)
- **Preserved Polyclonality & Broad Antigen Recognition:** Because TILs are not engineered to a single antigen, they can target multiple tumor-associated antigens — including neoepitopes — which may evolve over time, potentially reducing the risk of immune escape. [PubMed+1](#)
- **Potential to Overcome Heterogeneity and Immune Evasion:** Given GBM’s heterogeneity, a polyclonal T-cell pool may better address subclonal diversity than mono-specific therapies. The authors argue this makes TILs a particularly attractive immunotherapy modality for GBM. [ResearchGate+1](#)
- **Clinical Translation Is Within Reach:** Given the demonstrated feasibility and prior success of TIL therapy in other solid tumors, the paper positions TIL therapy as a promising and adaptable next-

Challenges & Limitations

The review also carefully outlines major hurdles that need to be addressed before TIL therapy can be widely implemented in GBM:

- **Immunosuppressive Tumor Microenvironment (TME)** – GBM TME is strongly immunosuppressive, which may impair TIL survival, expansion, infiltration, or effector function within the tumor. [PubMed+1](#)
- **Low Baseline T-cell Infiltration** – Many GBMs are “cold”: paucity of T-cells in situ may limit how many TILs can be harvested, especially in small resection specimens or biopsies. [QxMD Read+1](#)
- **Antigen Escape / Evolution** – Although polyclonality helps, GBM’s capacity for rapid evolution and antigen loss may still lead to immune escape under selection pressure. The degree to which TILs can adapt in vivo over time remains uncertain.
- **Manufacturing / Expansion Issues** – Expanding TILs to clinically relevant numbers while preserving functionality, specificity and avoiding exhaustion is technically challenging; prior experience in other tumors shows variable success. The review notes need for optimized protocols. [ResearchGate+1](#)
- **Need for Preclinical/Clinical Data** – While isolation and expansion are feasible, robust preclinical (in vivo) efficacy data in GBM models and early phase clinical trials are still limited. The review calls for more translational studies. [ScienceDirect+1](#)

Authors’ Perspective & Future Directions

According to the authors:

- TIL therapy represents a “compelling and adaptable platform” for GBM immunotherapy — possibly more suited to GBM’s biology (heterogeneity, antigen diversity) than single-target engineered approaches. [PubMed+1](#)
- Future work should focus on **optimizing TIL isolation and expansion protocols**, improving infiltration and persistence in the brain tumor microenvironment, perhaps combining with strategies to modulate the immunosuppressive microenvironment (e.g., checkpoint blockade, TME-modulating agents). [ResearchGate+1](#)
- Also, identifying which patients (or which tumor molecular subtypes) are most likely to benefit, possibly those with detectable endogenous infiltration or particular antigenic signatures.

Implications for Neuro-Oncology & Clinical/Research Relevance

Given your interest in neuro-oncology and pediatric BBB/drug delivery, these points are especially relevant:

- TIL therapy could **circumvent some limitations** of conventional therapies (surgery, chemo/radiation) and might target residual infiltrative tumor cells — a major challenge in GBM

management.

- The polyclonal antigen recognition of TILs may mitigate tumor heterogeneity — a key barrier in both adult and pediatric gliomas.
- However, success will likely depend on **effective delivery, trafficking and survival** of TILs in the brain — which may intersect with BBB/brain microenvironment challenges. This underscores the importance of combining TIL approaches with strategies to modulate the brain's immune milieu or enhance T-cell trafficking across the CNS.
- For pediatric neuro-oncology, although most data are from adult GBM, the conceptual framework might inform immunotherapy strategies for pediatric high-grade gliomas — provided careful evaluation of safety, toxicity, and tumor-specific biology.

Summary – Concluding Thoughts

Pristo EL et al. provide a timely, well-argued review that frames TIL therapy as a promising, biologically rational — yet still experimental — immunotherapeutic modality for GBM. They document that **tumor-reactive polyclonal TILs can be derived from GBM specimens**, argue that such polyclonality is especially suited to overcome GBM's heterogeneity and immune evasion, and call for accelerated preclinical and early clinical translation. However, significant technical and biological challenges remain, particularly the immunosuppressive microenvironment, TIL expansion/maintenance, and need for robust efficacy data.

If you like, I can **pull up a table** summarizing *all known clinical/preclinical attempts at TIL therapy in GBM — with status (in vitro, in vivo, clinical)*, to help you see gaps and opportunities for future research. Do you want me to build that for you now?



Yes

Great — I pulled the recent literature and trial records and assembled a concise table summarizing the known **preclinical and clinical attempts at TIL therapy for glioblastoma (GBM)**, with status and key results where available.

If you want, I can next convert this into a CSV or an interactive spreadsheet you can download.

Summary table — TIL therapy in GBM (preclinical → clinical)

#	Study / Group (first author or source)	Year	Model / Stage	Intervention / Notes	Status / Key result
1	Pristo EL et al., Trends Cancer	2025	Review (context +	Review of feasibility, rationale, and roadblocks for TIL	Argues feasibility of isolating/expanding

#	Study / Group (first author or source)	Year	Model / Stage	Intervention / Notes	Status / Key result
	(review)		synthesis)	therapy in GBM.	functional GBM-TILs and calls for translational studies. ScienceDirect+1
2	Maffezzini et al., Nature Communications	2025	Preclinical / translational	Describes methods for polyclonal expansion of tumor-reactive CD137+ TILs from GBM and proposes intratumoral/intraventricular delivery.	Demonstrates expansion of functional tumor-reactive TILs and supports clinical translation. Nature
3	ClinicalTrials.gov — NCT04943913 ("Study on TIL for the Treatment of Brain Glioma")	registered 2021–2022 (record updated)	Clinical — early phase (autologous TILs in malignant glioma)	Autologous TILs expanded from surgical specimens; protocol describes infusion back to patient (details per registry).	Trial registered / recruiting or planned per registry entry (early-phase safety/feasibility). Clinical Trials
4	Phase 1 single-center report / poster (conference abstract)	2025	Clinical — Phase 1 (single-center experience)	Single-center phase-1 experience using TILs derived from primary surgical specimens in recurrent GBM (poster/abstract).	Early clinical experience presented; supports feasibility and early safety signals (conference abstract). ResearchGate+1
5	Arruda LCM et al. — case / small-series report	2025	Clinical — case report / small series	Report describes TIL expansion using IL-2/IL-15 protocol and successful treatment of a rapidly progressing GBM patient (CD8+ clonotype data).	Single-patient success / immunogenomic evidence of response reported (proof-of-concept). Taylor & Francis Online
6	Liu Z. et al., (historical feasibility study)	2016	Preclinical / ex vivo human tissue	Demonstrated that TILs can be isolated from glioma specimens and expanded ex vivo; Karolinska noted preparation of a phase I trial.	Early feasibility established; provided rationale for later clinical attempts. PMC
7	Multiple preclinical studies / reviews (2020–2025)	2020–2025	Preclinical mouse/rat intracranial models	Several groups tested TIL-like or adoptive T-cell approaches (including combination strategies; intraventricular/intratumoral delivery explored).	Preclinical efficacy signals reported; many emphasize combination with TME-modulation. Representative reviews summarize landscape. PMC+1

Short interpretation / what the table shows

- **Feasibility is now well documented.** Multiple groups have shown TILs can be isolated and expanded from GBM tissue (ex vivo and preclinical studies). [PMC+1](#)
- **Translation to humans is nascent but active.** Clinicaltrials.gov lists at least one dedicated TIL trial for malignant glioma (NCT04943913), and 2025 conference reports / case reports describe early single-center/individual patient success. These are early safety/feasibility efforts rather than randomized efficacy data. [Clinical Trials+2](#)
- **Delivery & TME remain critical issues.** Preclinical work explores intratumoral/intraventricular delivery and combinations to overcome GBM's immunosuppressive microenvironment. [Nature+1](#)

Suggested next actions (if you want to use this for planning / a review / grant)

1. I can expand this table into a **downloadable spreadsheet (CSV/XLSX)** including trial identifiers, start/end dates, N of patients, primary endpoints, and contact PIs (where available).
2. I can **extract and summarize methods** used across preclinical studies (e.g., cytokine cocktails: IL-2 vs IL-15, CD137+ enrichment, expansion times, delivery routes).
3. I can pull **full trial registry pages and conference abstracts** (PDFs) and create an annotated bibliography in your preferred Vancouver style.

Which of those would you like next? (I can create the spreadsheet now and include direct trial links and short annotation lines.)