Relevance of Chemokines in Mobilising γδ T Cells in the Biliary Tract Cancer Microenvironment

Potential for γδ T Cell–Based Adoptive Cell Therapy

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BACKGROUND & RATIONALE

Biliary tract cancer (BTC) is lethal — ~3,000 UK cases/year, only **13% 3-year survival**. 65–70% present unresectable; current therapies reach complete response in just **2–5% of advanced cases.**

Why γδ T cells?

Cytotoxicity is **MHC-independent** — decisive in BTC, where MHC-I is frequently downregulated. Vγ9Vδ2 recognise phosphoantigens via BTN3A1; Vδ1 engage NKG2D.

Infiltration bottleneck

Therapeutic efficacy is limited by **insufficient tumour infiltration**, yet the BTC chemokine landscape is uncharacterised.

AIM

Map the BTC-TME chemokine landscape at single-cell resolution; define γδ T-cell recruitment and escape.

METHODS

3	19	119,840
GEO COHORTS	BTC PATIENTS	QC-PASSED CELLS

Datasets GEO GSE210066 · GSE201425 · GSE213452 — cholangiocarcinoma & gallbladder cancer.

Pipeline Seurat v5: QC, log-norm, HVG selection, PCA → **Harmony batch correction** → UMAP.

Annotation SNN + Louvain clustering; Wilcoxon markers vs CellMarker 2.0.

Quantification Mean $\log_2$ expression and % cells expressing for **17 chemokines** & **5 receptors**.

CONCLUSIONS

BTC has a **selective multi-axis chemokine profile** supporting CCR5⁺ / CCR2⁺ / CCR1⁺ / CXCR6⁺ γδ T cells.

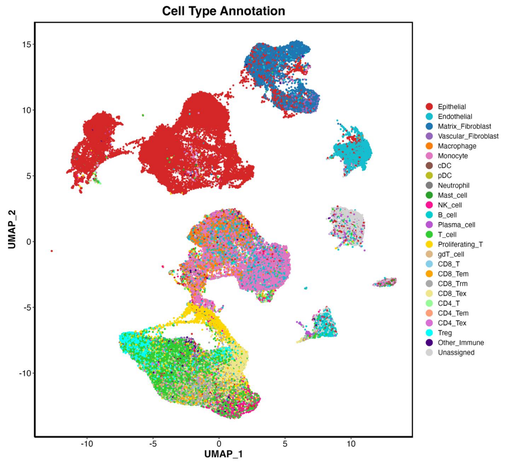
Three CCR5 ligands (CCL3/4/5) give **redundant chemotaxis resistant to immune evasion**.

A **recruitment paradox** co-recruits MDSCs, Tregs and TAMs.

Patient **heterogeneity** → **pre-treatment chemokine profiling**.

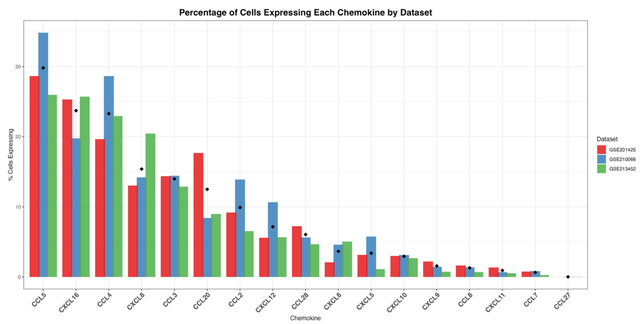
RESULTS | Cellular Atlas & Chemokine Hierarchy

Figure 1 | Single-cell atlas — 26 annotated populations



UMAP of **119,840 cells** (19 patients) post-Harmony — epithelial, stromal, lymphoid and myeloid compartments; γδ T-cell cluster resolved.

Figure 2 | Dominant chemokines across the BTC TME



A dominant multi-axis signature emerged:

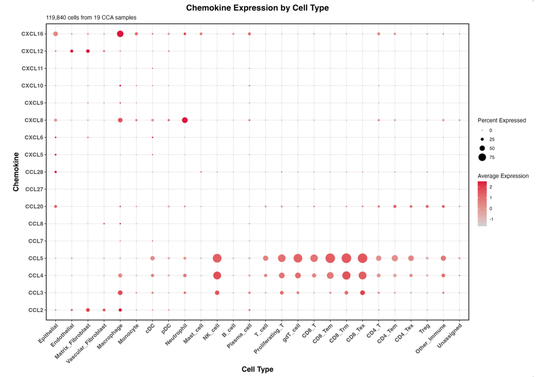
CCL5 ≈ 30% · **CXCL16 ≈ 24%** · **CCL4 ≈ 23%**

CXCL8 · CCL3 · CCL20 13–15% | **CCL2 · CXCL12 · CCL28** 6–10%

CXCL9/10/11 < 5% — IFN-γ recruitment axis suppressed

RESULTS | Sources & Framework

Figure 3 | Who produces what?



Lineage-stratified producers

CCL5 · CCL4 NK cells, γδ T, CD8⁺ Tem/Trm/Tex

CCL2 fibroblasts, macrophages, endothelium

CXCL16 macrophages & biliary epithelium

CXCL8 neutrophils & macrophages

MULTI-AXIS RECRUITMENT FRAMEWORK

Primary **CCL5/CCL4–CCR5, CCL2–CCR2**
→ Vγ9Vδ2 & Vδ1 T cell infiltration

Secondary **CCL3–CCR5/CCR1**
→ redundant, resists evasion

Epithelial **CXCL16–CXCR6**
→ intraepithelial γδ T cell homing

Suppressed **CXCL9/10–CXCR3**
→ IFN-γ producing γδ T cell deficit

THERAPEUTIC IMPLICATIONS

1 **Enrich CCR5⁺ · CCR2⁺ · CXCR6⁺ γδ T cell subsets**

2 **Supplement CXCL10 & CCL3**

3 **Block CCR2 & CXCR1/2 (anti-MDSC/TAM)**

4 **Co-transfer multi-compartment γδ T cells**

PATIENT-FRIENDLY LAY SUMMARY

In plain language

Background

Bile-duct and gallbladder cancers are aggressive and hard to treat. **Only 1 in 8 people survive 3 years,** and current drugs help only a few. We need new options.

A rare immune cell, the **γδ T cell**, can kill tumours without the "identity tags" (MHC) that most immune cells need — and those tags are often missing in bile-duct tumours. **The problem: γδ T cells struggle to get inside the tumour.**

Methods

Tumours release chemical **"signposts" called chemokines** that guide immune cells. We examined **119,000 individual cells** from **19 patients**, mapping 17 chemokine signals and 5 matching receptors.

Results

Three strong signals — **CCL5, CXCL16, CCL4** — are a good match for γδ T cells. But two problems appeared:

- Two key γδ T cell signals (CXCL9/10) are almost **missing**.
- Some of the same signals **also attract immune-blocking cells** (MDSCs, Tregs, TAMs).

Conclusion

BTC tumours have the basic "map" to draw γδ T cells in, but also recruit cells that block the attack. A rational next step is to **profile each patient's tumour and tailor γδ T-cell therapy to match.**

KEY REFERENCES **1** Banales JM et al. Cholangiocarcinoma 2020: mechanisms and management. Nat Rev Gastroenterol Hepatol. 2020;17:557–88. **2** Glatzel A et al. CCR5 is a selective feature of Vγ9Vδ2 γδ T cells. J Immunol. 2002;168:4920–9. **3** Korsunsky I et al. Fast, sensitive and accurate integration of single-cell data with Harmony. Nat Methods. 2019;16:1289–96.

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