Publication Summary

CTCs & Glioblastoma

Background

Glioblastoma (GBM) is the most aggressive and lethal type of primary brain tumour, characterised by rapid growth and high invasiveness, with a median survival of only 15 months.[1] Tumour monitoring in GBM has been hindered by the limitations of invasive surgical tissue biopsies,[2] as well as the scarcity of circulating tumour DNA (ctDNA) in peripheral blood due to GBM being a low-shedding tumour, further compounded by the blood–brain barrier (BBB).[3]

Despite these obstacles, circulating tumour cells (CTCs) have been successfully detected in various glioma subtypes, including GBM, with one study reporting a CTC detection rate of 77% within patients across seven different glioma subtypes.[4] These findings reinforce the potential of CTC-based liquid biopsy approaches, despite previous concerns regarding the BBB.[4] Additionally, GBM cells frequently undergo epithelial-to-mesenchymal transition (EMT), leading to increased cell motility, invasiveness, and resistance to therapy.[5,6] Notably, Sullivan et al. found that GBM CTCs exhibit a more mesenchymal phenotype associated with high invasion capacity, potentially explaining rare cases of extracranial metastases in GBM.[7,8] However, some argue that the CTCs in GBM may be re-seeding the brain rather than causing metastases elsewhere in the body.[9]

Recent studies have demonstrated that the Parsortix® system can successfully isolate GBM CTCs and CTC clusters, potentially offering a novel avenue for capturing these rare cells from GBM patient blood.[2, 10, 12] By enabling the visualisation and molecular analysis of CTCs, the Parsortix system provides a powerful tool to improve our understanding of GBM biology, analyse clinically actionable biomarkers, and facilitate longitudinal assessments of tumour heterogeneity.[13] Furthermore, the ability of the Parsortix system to enrich CTCs of different phenotypes, including those undergoing EMT, presents a key advantage over other liquid biopsy analytes like ctDNA, due to GBM being one of the tumour types with the lowest levels of detectable ctDNA in blood.[8,14]

Peer reviewed publications using the Parsortix system

There are a growing number of peer reviewed publications in which the Parsortix system has been used to enrich and harvest CTCs from GBM patient samples. These are summarised below:

Krol et al., (2018) "Detection of Circulating Tumour Cell Clusters in Human Glioblastoma"[11]

CTC and CTC cluster presence at multiple timepoints in 13 GBM patients were investigated in an open-label phase 1/2a study with microtubule inhibitor BAL101553. **The research provides the first evidence of CTC clusters in GBM patient samples isolated by the Parsortix system and states that these clusters can pass through the blood brain barrier and enter the peripheral circulation**. The study identified **CTC clusters ranging from 2 to 23 cells** (Figure 1). Exome sequencing of CTC clusters identified mutations in 58 cancer-associated genes, including ATM, PMS2, POLE, APC, JAK2, BRCA2, ERBB4, and ALK. Deep sequencing of a matched primary tumour biopsy revealed that **16 out of 116 GBM CTC cluster mutations were found in the primary tumour.**[11] These findings highlight the use of CTCs as a blood-based analyte for minimally-invasive GBM assessment.

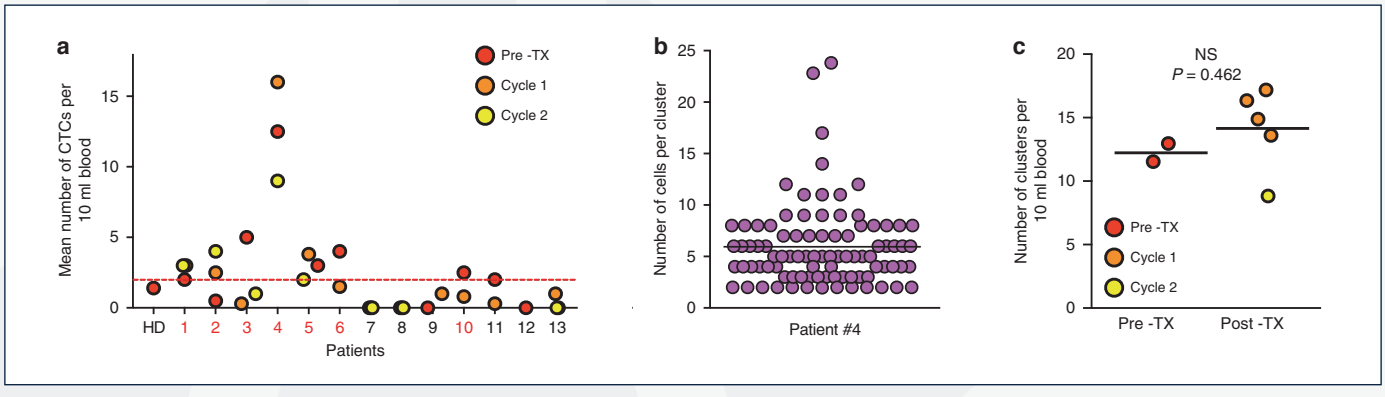

Figure 1: Circulating tumour cell (CTC) counts and clusters in glioblastoma patients.[11]

A Mean number of CTCs per 10 ml of blood across 13 GBM patients and 3 healthy donors (HD), with a red dashed line indicating the false-positive threshold (2 CTCs per 10 ml).

B Distribution of cells per CTC cluster for Patient #4, showing clusters ranging from 2 to >20 cells.

C Number of CTC clusters per 10 ml of blood in Patient #4, measured pre-treatment (Pre-TX) and post-treatment (Cycle 1 and Cycle 2). No significant change in cluster count was observed post-treatment (P = 0.462).[11]

Lessi et al., (2023) "Innovative Approach to Isolate and Characterise Glioblastoma Circulating Tumour Cells and Correlation With Tumour Mutational Status"[2]

This study optimised an approach for detecting and characterising CTCs in GBM demonstrating their **genetic link to the parental tumour**. Primary and recurrent GBM tumours identified 210 shared mutations, including variants in PKRCB, TBX1 and COG5 which were also detected in CTCs. In some cases, TERT promoter mutations were **found in both the tumour and CTCs** confirming the origin of the CTCs as the GBM primary tumour. Chromosomal copy number alteration (CNA) profiles demonstrated tumour heterogeneity, with CTCs exhibiting a greater number of alterations than bulk tumour tissue. While some CNAs were shared—such as deletion of chromosome 19 across all CTCs—others were unique to individual CTCs, with only one (CTC#2) harbouring an alteration also found in both primary and recurrent tumours (gain of chromosome 7). This discordance could be explained by CTCs arising from distinct subclones or acquiring additional genomic changes during dissemination. These findings underscore the potential of CTCs in tracking disease evolution and heterogeneity in GBM.[2]

Lessi et al., (2024) "Beyond the Expected: Circulating Tumour Cells in Glioblastoma Reveal Hidden Heterogeneity and Become Potential Diagnostic Biomarkers"[12] **(Abstract)**

This study highlights the potential utility of CTCs as non-invasive biomarkers for GBM diagnosis and monitoring. Using the Parsortix system, significantly higher CTC counts were observed in GBM patients **(average of 15.4 CTCs)** compared to healthy controls. **Primary GBM cases exhibited higher CTC levels (18.2) compared to recurrent cases (12.4).** CNA analysis revealed a novel finding: **approximately 51% of CTCs exhibited CNAs, while 49% displayed a wildtype** profile (no CNAs). This same distribution was observed in scRNAseq analysis of a GBM primary cancer cell line. These findings further emphasise the potential use of CTCs to provide real-time insights into GBM biology and disease progression.[12]

Conclusion

CTCs could help address critical unmet needs in GBM, which accounts for **80% of all malignant brain tumours**.[14]

With 16–40% of cases deemed inoperable,[15] liquid biopsy offers a minimally-invasive alternative for obtaining molecular insights in these patients. Genetic and transcriptomic profiling of CTCs via next-generation sequencing (NGS) could potentially aid in classifying GBM subtypes, guiding personalised treatments, and improving clinical trial enrolment. The studies discussed here demonstrate that liquid biopsy technologies such as the Parsortix system, hold potential to harness CTCs as a minimally-invasive blood-based analyte.

Additionally, CTC-based DNA methylation analysis may enable minimally-invasive testing for **MGMT promoter methylation**, which is observed in **40–50%** of GBM patients and is associated with significant clinical benefits regarding temozolomide treatment, almost doubling overall survival.[16] This could be particularly valuable for non-operable or recurrent cases, where tissue biopsies are not feasible. While further research is needed, advancements in CTC enrichment and molecular profiling are moving the field toward a viable, blood-based alternative to invasive biopsies. Tracking tumour evolution in GBM through liquid biopsies could transform patient management by improving diagnostic accuracy, treatment selection, and disease monitoring.

To learn more about how CTCs could help address critical unmet needs in GBM, contact:

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