Drug-response analysis and single nucleus RNA sequencing on patient-derived neurospheres to reveal drug response and resistance mechanisms in glioblastoma

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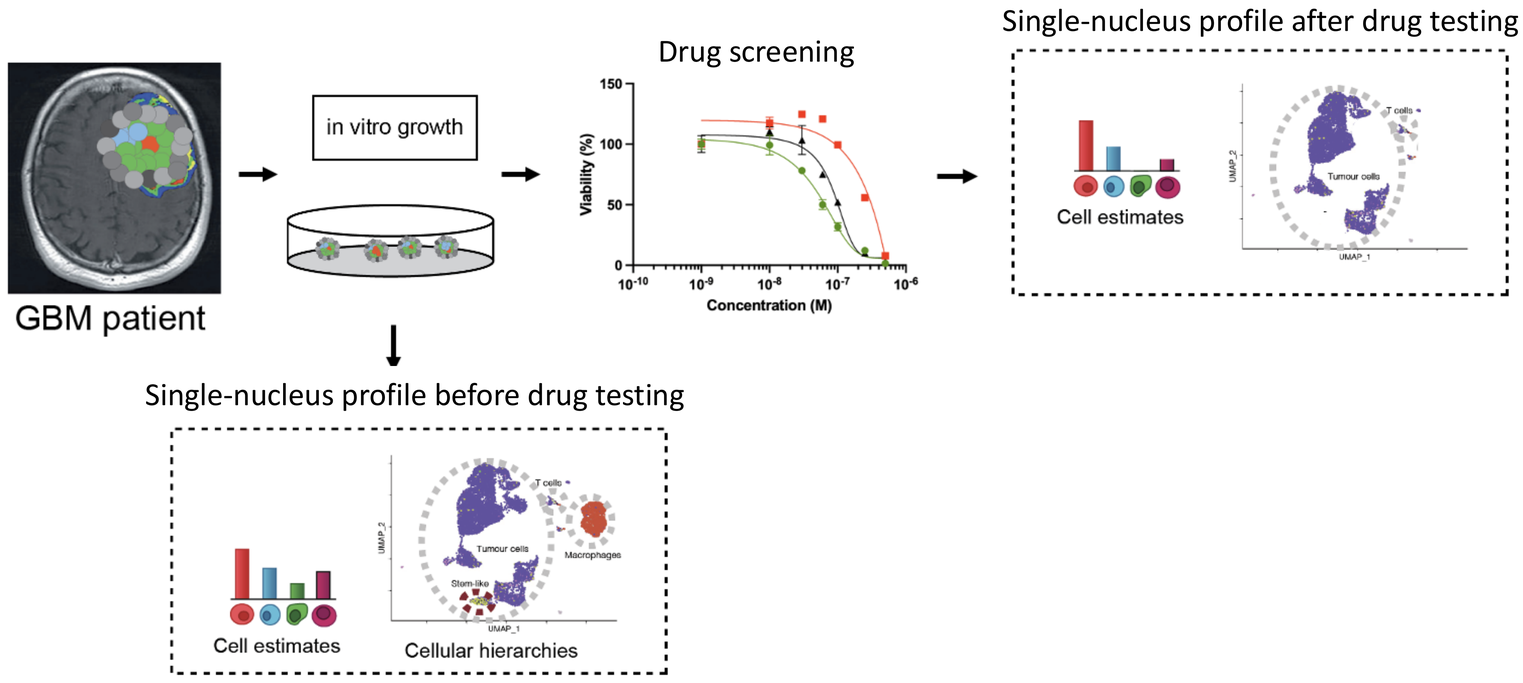
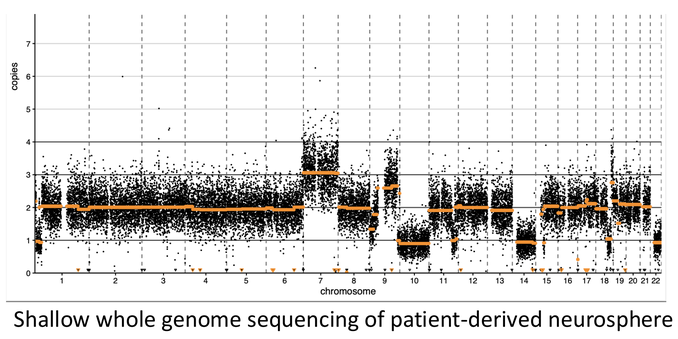
Background: Glioblastoma is an aggressive primary malignant brain tumour with poor survival. Unsuccessful improvement of treatment could be due to transcriptional plasticity of the cancer cells including stem-like cancer cells. Short-term cultured patient-derived neurospheres consisting of cancer cells and stem-like cancer cells are used in this project to find individual drug sensitivities via drug screening. Drug resistance mechanisms on transcriptome level is further explored at high resolution using single nucleus RNA sequencing (snRNA-seq) on drug- and mock-treated neurospheres to find drug vulnerabilities.

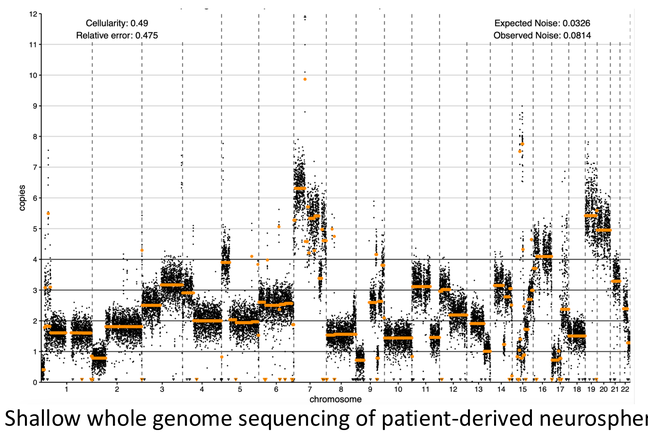
Methods:



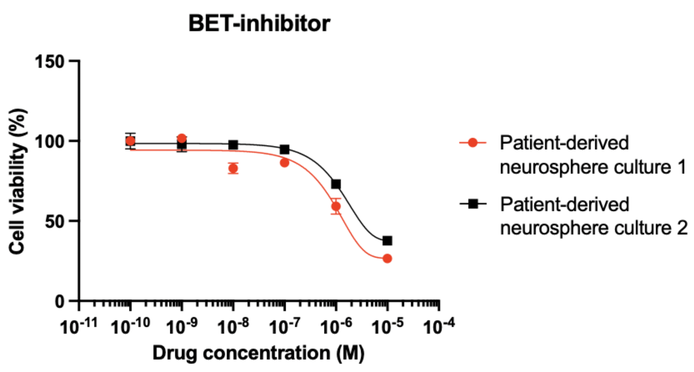
Results:

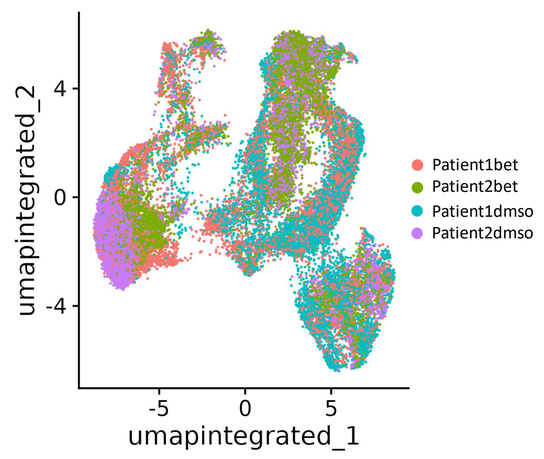


Shallow whole genome sequencing of patient-derived neurosphere culture 1

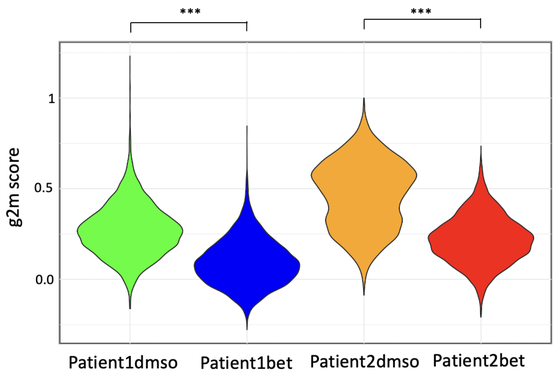


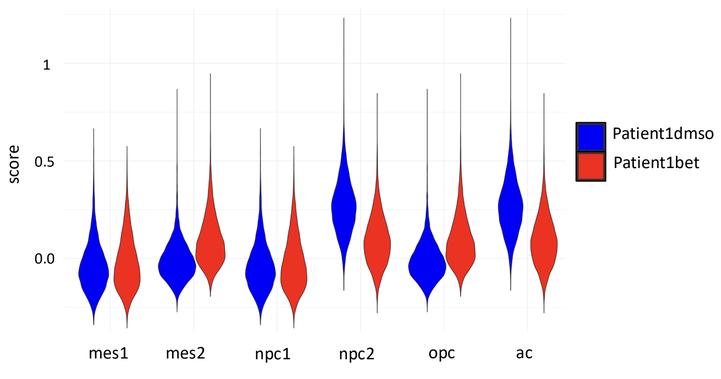
Shallow whole genome sequencing of patient-derived neurosphere culture 2





Cell cycling decreases globally in treated neurospheres





Conclusion: We find overall high concordance between the initial tumour surgical sample, assessed by whole-genome sequencing, and patient-derived neurospheres at the level of large-scale copy number changes. Transcriptional subtypes change during treatment including response to a BET-inhibitor on sensitive patient-derived neurospheres. We conclude that combining high-throughput drug screening with snRNA-seq on DMSO-treated and drug-treated neurospheres is a feasible way to access response and resistance mechanisms in glioblastoma, and targeting transcriptional states could be a promising way to treat glioblastoma patients.