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Ex vivo-led drug discovery in glioblastoma

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Background: Glioblastoma is a devastating cancer, with an average life-expectancy of 12−15 months after diagnosis, despite current multimodal therapies. Glioblastoma is characterised by extensive inter-patient and intratumoural heterogeneity, including inherently resistant glioblastoma stem cell subpopulations, which commonly result in therapy resistance. Therefore, there is an urgent need to develop more effective treatment regimens for these currently incurable tumours.
Methods: The Ex VIvo DEtermiNed cancer Therapy (EVIDENT) trial in glioblastoma utilizes heterogeneous cell populations from freshly dissociated patient tumour tissue. These are distributed onto an in-house drug panel of 50−100 selected therapies, including approved and pre-FDA approved drugs. Following staining for cell type niches, automated ultra-high content immunofluorescence microscopy is then used to quantify drug efficacy, particularly those that specifically target the tumour cell population.
Results: To date, using pre-established primary glioblastoma cultures, we have optimised immunofluorescence regimes to discern differentiated and stem cell populations, and have carried out extended dose-response curves for a number of drugs. Additionally, the project has recruited 7 patients to date (September 2021), with future work planned to validate the approach for more patient-derived primary cultures and integrate genetic data alongside phenotypic results. Using tumour samples from a number of patients (inter-tumour heterogeneity) and within the same tumour mass (intra-tumour heterogeneity), we have already found several interesting differential drug responses amongst glioma stem cell populations that we are currently following up with additional studies.
Conclusion: The EVIDENT project aims to provide rapid, high-throughput, personalised medicine and will be of immense value for both understanding the complex biology of glioblastomas and driving future clinical trials. This protocol development shows the clinical and experimental feasibility of this ambitious project which we hope will accelerate the identification of novel and repurposed therapies, and help direct delivery of the right therapy to the right patient, at the right time.
Keywords: glioblastoma; ex vivo; high throughput screening; personalised medicine; pre-clinical

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Mapping the myeloid landscape of glioblastoma tumours

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Glioblastoma is the most aggressive form of brain tumour with a characteristically immunosuppressed microenvironment comprised of several different niches. Although these tumours contain a milieu of immune cells, the predominant populations comprise peripherally-derived tumour-associated macrophages (TAMs) and brain-resident microglia. Despite microglia and TAMs being two ontogenetically distinct populations, their distribution and potentially differing functions across the glioblastoma landscape are not well defined. Surgically resected glioblastoma tissue was immunofluorescently labelled to define tumour niches and infer myeloid-cell function. Single-cell image analysis was conducted to define microglia (P2RY12+ Iba1+) and TAMs (P2RY12- Iba1+) and to quantify protein expression across tumour niches delineated by Ki67, GFAP, and lectin immunoreactivity. We found that microglia predominantly reside in the tumour periphery, displaying a higher expression of activation markers CD163, CD14, and CD68 towards the tumour core. TAMs predominantly resided in the tumour core and perivascular niche, in close proximity to blood vessels and areas of vascular leakage. Unlike microglia, TAMs displayed high expression of CD163, CD14 and CD68 independent of location. These findings demonstrate that microglia and TAMs reside in distinct tumour niches and express different proteins that may differentially drive tumour growth and malignancy. Understanding this myeloid landscape will be critical in informing potential niche-targeted immune therapies.
Keywords: microglia; tumour associated macrophages; heterogeneity; microenvironment