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## Evidence that adult glioblastoma adapts to standard therapy through chromatin remodeling

Nora Rippaus<sup>1</sup>, James Manning<sup>1</sup>, Alastair Droop<sup>2</sup>, Muna Al-Jabri<sup>1</sup>, Matthew Care<sup>2</sup>, Alexander-F Bruns<sup>1,3</sup>, Michael D. Jenkinson<sup>4,5</sup>, Andrew Brodbelt<sup>4</sup>, Aruna Chakrabarty<sup>6</sup>, Azzam Ismail<sup>6</sup>, Susan Short<sup>1</sup> and Lucy F. Stead<sup>1</sup>

<sup>1</sup>Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, LS9 7TF, UK; <sup>2</sup>Leeds Institute of Data Analytics, University of Leeds, LS2 9JT, UK; <sup>3</sup>Now at Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, LS2 9JT, UK; <sup>4</sup>Walton Centre NHS Trust, Liverpool, L9 7LJ, UK; <sup>5</sup>Institute of Translational Medicine, University of Liverpool, L9 7LJ, UK; <sup>6</sup>Leeds Teaching Hospitals NHS Trust, St James's University Hospital, Leeds, LS9 7TF, UK

**Background:** Glioblastoma (GBM) tumours recur following standard treatment in almost all cases. We use 'omics technologies to simultaneously profile pairs of primary and matched recurrent GBM to specifically identify and characterise the cells that resisted treatment, with the aim of determining how to more effectively kill them.

**Material and Methods:** We have analysed high coverage RNAseq data from pairs of GBM tumours: primary de novo tumour and matched local recurrence from patients that underwent standard therapy. Our original cohort constituted 23 pairs and our validation cohort was an additional 22 pairs. We also cultured two plates of spheroids directly from a patient's GBM, treating one with radiation and temozolomide. We monitored growth and captured and sequenced RNA from single cells at two time-points: one week post-treatment when the deviation between untreated and treated spheroid growth curves was most pronounced; and three weeks post-treatment when the growth rate of treated spheroids had recovered. We investigated differential gene expression between primary and recurrent pairs, and single cells pre- and post-treatment, and performed a bespoke per patient gene set enrichment analysis.

**Results:** Differential gene expression analysis in 23 tumour pairs indicated a treatment-induced shift in cell states linked to normal neurogenesis and prompted us to develop a novel gene set enrichment analysis approach to identify gene regulatory factors that may orchestrate such a shift. This revealed the significant and universal dysregulation of genes, through therapy, that are targeted by a specific chromatin remodeling machinery. This finding was validated in an independent cohort of 22 further GBM pairs. To understand the therapeutic potential of this finding we must determine whether genes are dysregulated through therapy owing to a) their fixed expression in inherently treatment resistance cells in the primary tumour which get selected during therapy to increase the signal of that profile, or b) changes in expression during the process of cells acquiring treatment resistance. To inspect this, we analysed single cell gene expression data from GBM spheroids pre- and post-treatment. We found that there was significant dysregulation of the genes associated with the chromatin remodeling complex but only at the three-week post-treatment time-point.

**Conclusion:** Our results indicate that GBM cells are being transcriptionally reprogrammed in response to treatment; the mechanism of which may represent a therapeutic opportunity.