Supplementary Information

Transcriptomic Rewiring of Glioblastoma Organoids Reveals an NPC2-associated Neuronal Mimicry Program

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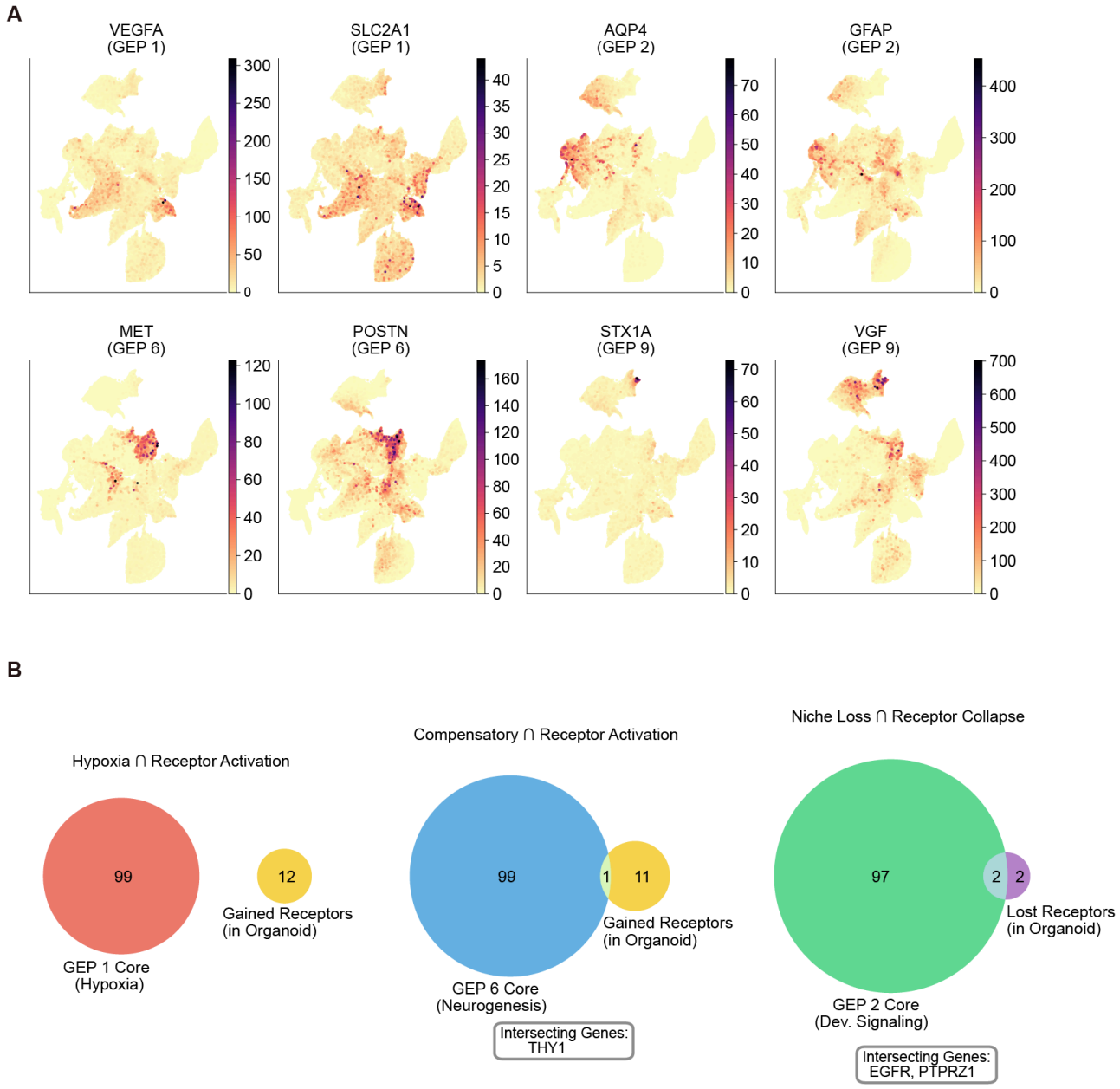
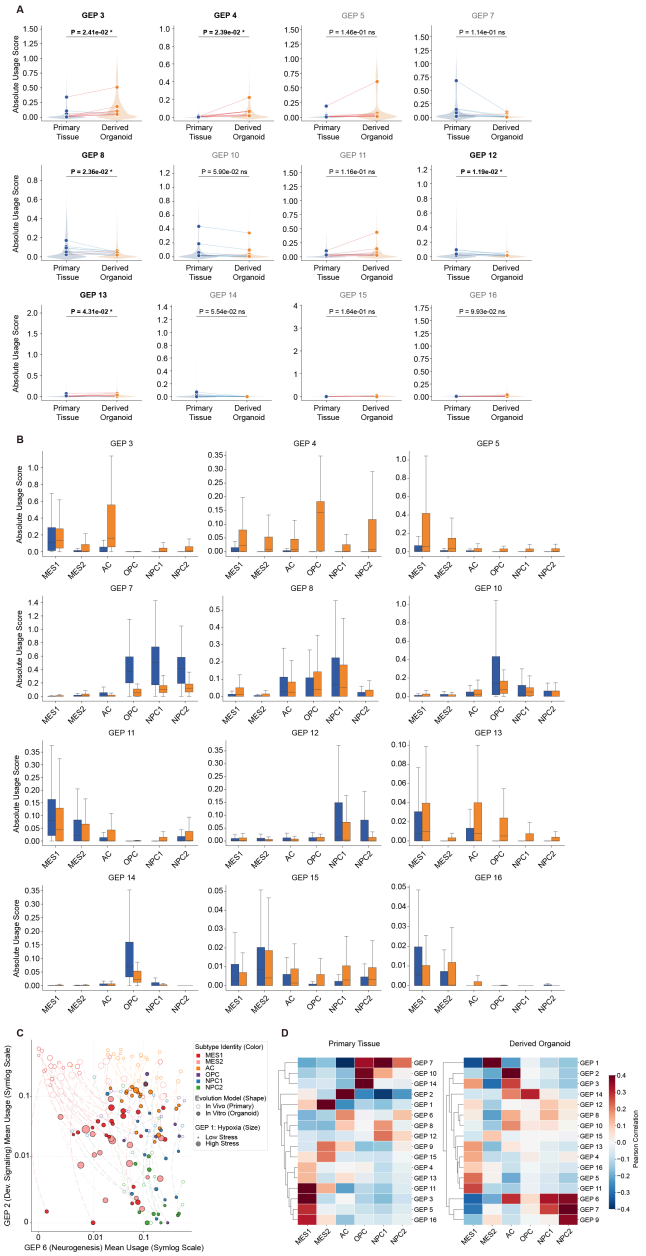


Supplementary Figure S1. Single-gene feature of key GEPs and receptors intersection analysis.

(A) UMAP feature plots illustrating the log-normalized expression levels of representative core genes for critical GEPs. The UMAP embedding is identical to Figure 4B, derived from the cNMF usage weights.

(B) Venn diagrams illustrating the intersection between the top 100 core defining genes of key cNMF programs (GEP1, GEP6, and GEP2) and the significantly altered targeted receptors (FDR < 0.05, |log2FC| > 0.5) in malignant cells following *in vitro* organoid culturing.



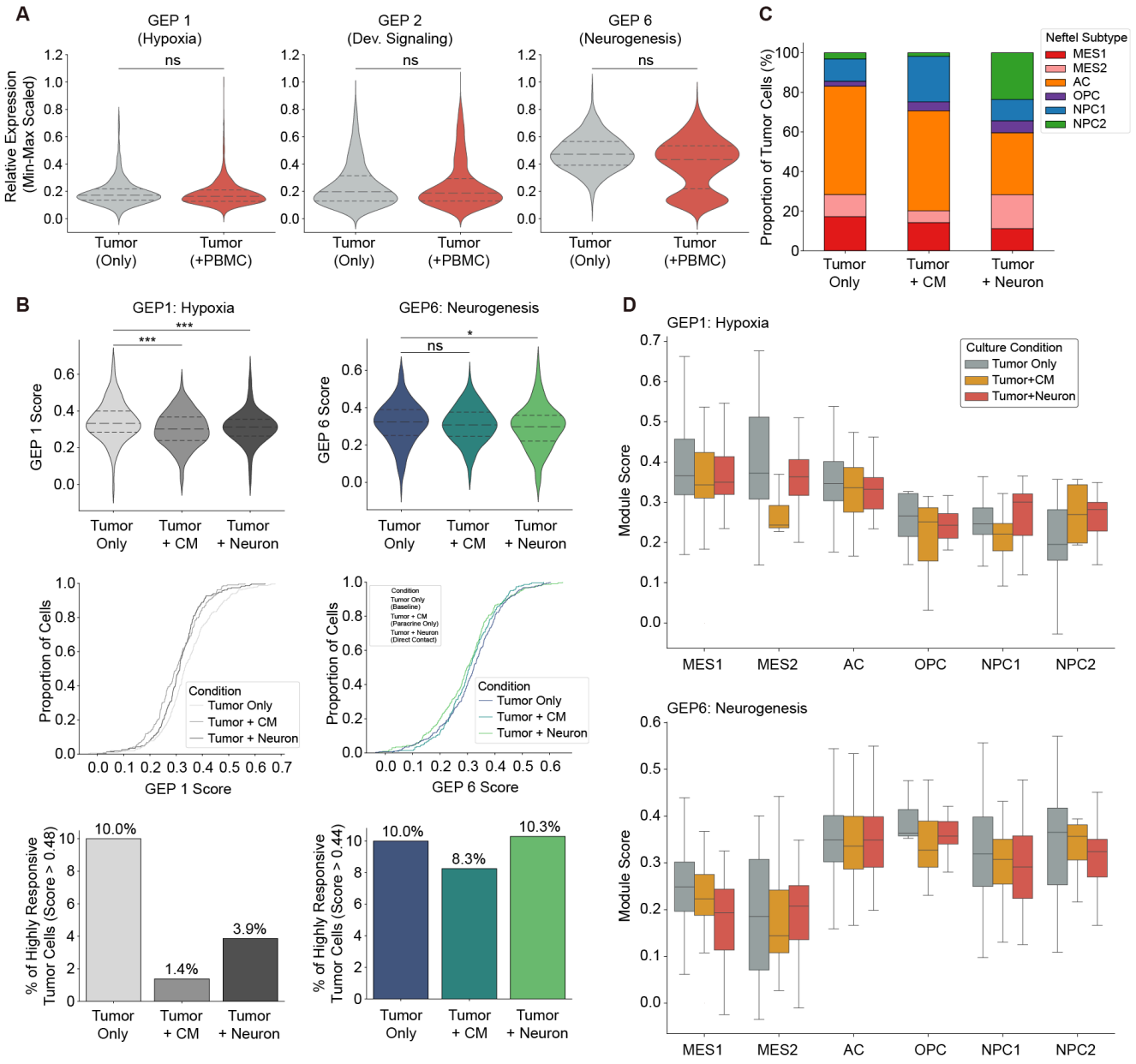
Supplementary Figure S2. Full cNMF program profiles and evolutionary manifolds.

(A) Split violin plots for the rest of 16 GEPs comparing overall usage scores between primary tissues and organoids.

(B) Full subtype-resolved boxplot grid for the rest of 16 GEPs across the six Neftel subtypes in both model systems.

(C) Three-dimensional scatter plot (rendered as a 2.5D projection) visualizing the simultaneous co-evolution of GEP1, GEP2, and GEP6 usage across the *in vivo*-to-organoid model trajectory, with each axis representing one core program and data points colored by Neftel subtype.

(D) Side-by-side Pearson correlation heatmaps between GEP usage scores (rows) and Neftel subtype assignments (columns) computed separately for primary tissue cells (left) and organoid cells (right).



Supplementary Figure S3. Extended co-culture analysis.

(A) Extended violin plots (analogous to Fig. 6A) displaying Min-Max scaled enrichment scores for other GEPs (GEP1, GEP2 and GEP6) in purified malignant cells, comparing standard organoid (grey) with immune-reconstituted co-culture (red).

(B) Violin and bar plots (analogous to Fig. 6D) depicting enrichment scores of GEP1 (Hypoxia) and GEP6 (Neurogenesis) across the three *in vitro* configurations (Tumor Only, Tumor+Neuron, Tumor+CM).

(C) Stacked bar plot illustrating the relative proportions of the six Neftel GBM transcriptional cell states among purified malignant cells, derived from scRNA-seq data across three *in vitro* configurations.

(D) Boxplots (analogous to Fig. 6E) detailing module scores of GEP1 and GEP6 across the six Neftel malignant subtypes, compared among the three *in vitro* configurations.