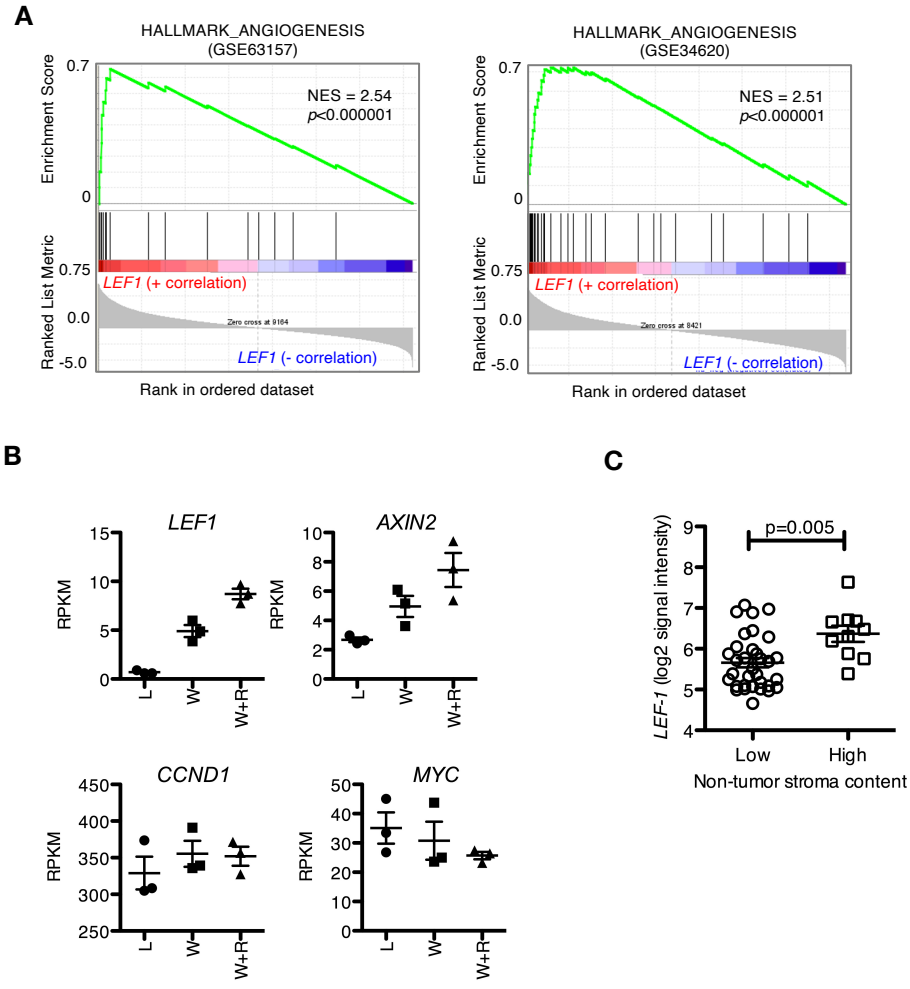
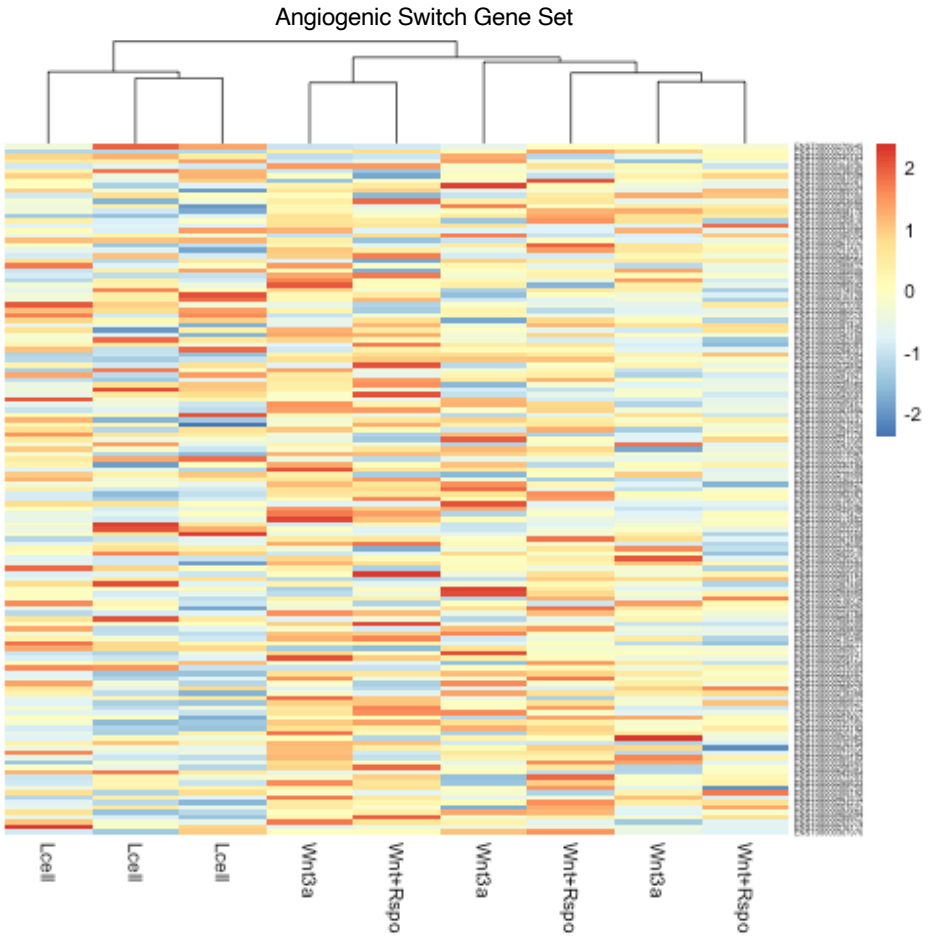
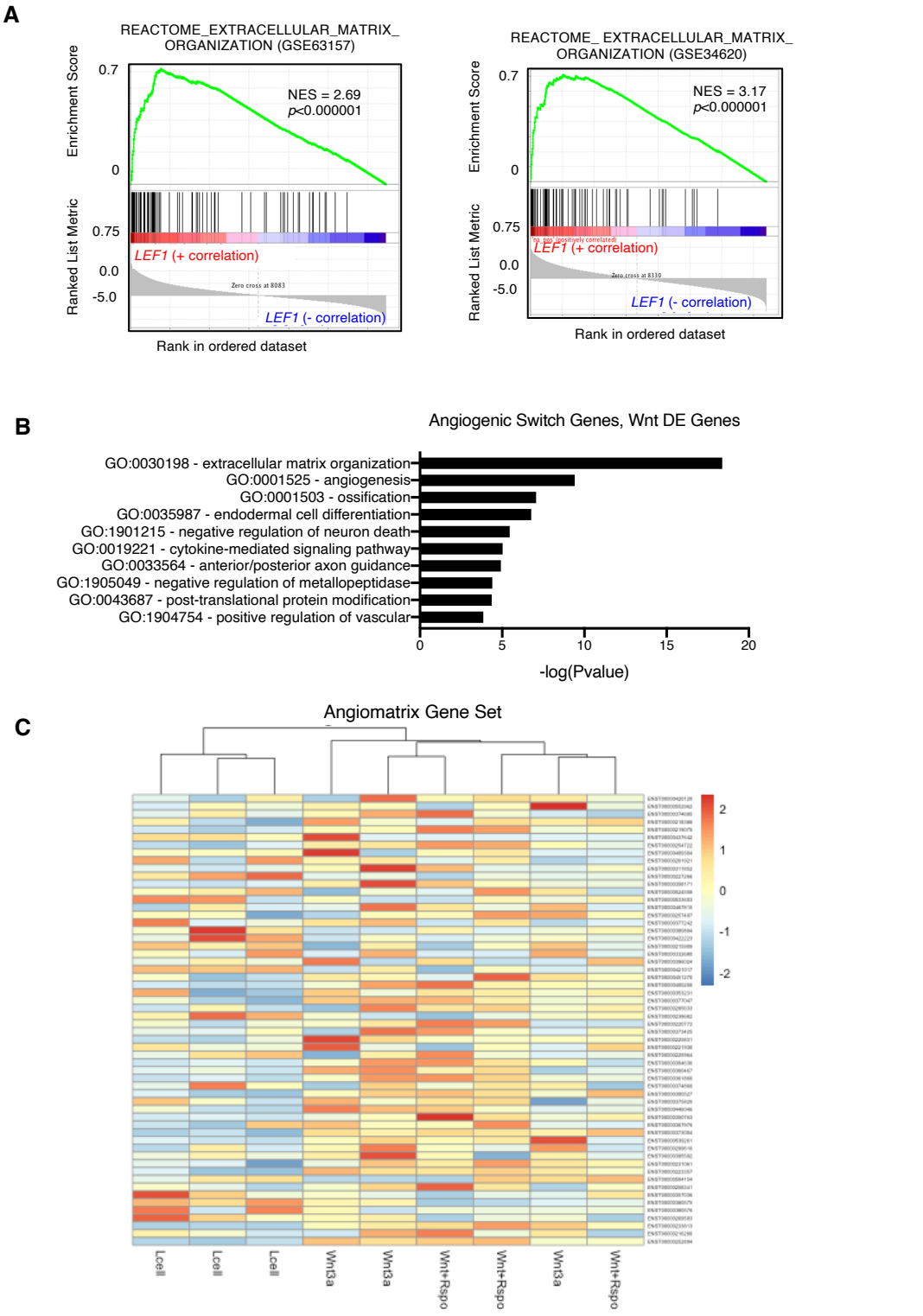


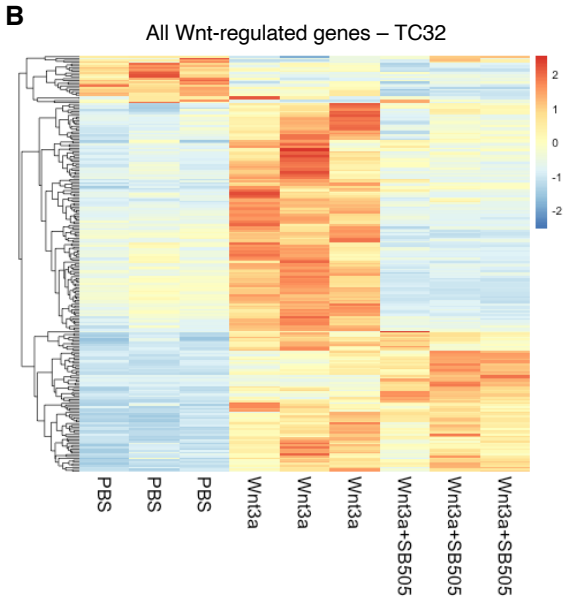
Supplemental Figure 1. (A) Unbiased GSEA of *LEF1*-correlated genes in two independent patient cohorts (GSE63157 (N=46 Ewing tumors) and GSE34620 (N=117 Ewing tumors)) ranked on the basis of *LEF-1* correlations, from positive to negative. Reproducible enrichment of the hallmark angiogenesis gene signature is shown. For GSEA, multiple test comparison was computed using false discovery rate. Only gene sets with FDR < 0.05 are displayed. (B) RPKM of *LEF1, AXIN2, CCND1,* and *MYC* of CHLA25 cells treated with control L-cell conditioned media (L), Wnt3a conditioned media (W), or Wnt3a conditioned media + RSPO2 (W+R) (RNAseq data from CHLA25 cells, GSE75859). (C) Expression of *LEF1* in tumor biopsies that were designated as stroma-rich (high; N=10) or stroma-poor (low; N=33). Data from GSE63157 and Ref. 15. Student's t-test used to compute – value.

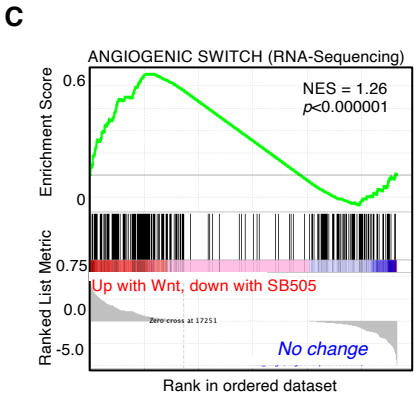


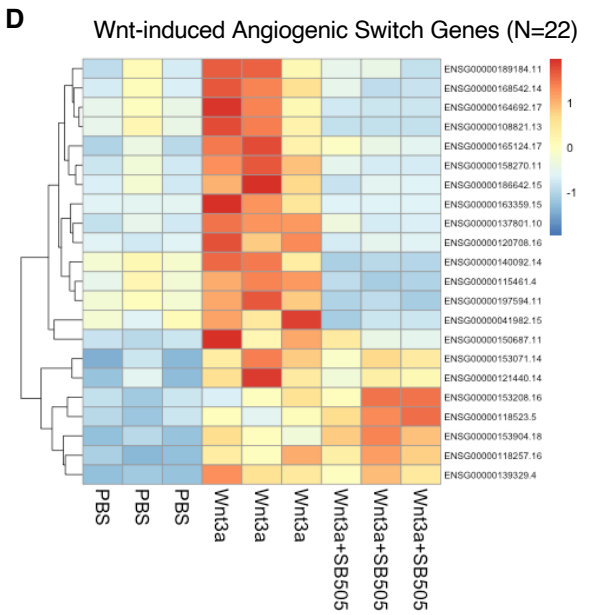
Supplemental Figure 2. Unsupervised hierarchical clustering of angiogenic switch gene expression in beta-catenin/TCF active (Wnt3a, Wnt+RSPO) and beta-catein/TCF-inactive (Lcell) Ewing sarcoma cells. Data from Ref. 11 (GSE75859) wherein CHLA25 Ewing sarcoma cells were treated with control or Wnt3a conditioned media +/- RSPO2 and beta-catenin/TCF active and non-active cells were isolated by FACS on the basis of TCF-GFP reporter activity. Data are expressed as fold change in expression relative to the mean.



Supplemental Figure 3. (A) Unbiased GSEA of ECM organization gene set among *LEF1*-correlated genes in two Ewing patient tumor cohorts. For GSEA, multiple test comparison was computed using false discovery rate. Only gene sets with FDR < 0.05 are displayed. (B) Gene ontology analysis of overlap between Wnt/beta-catenin-induced transcripts (RNAseq data from CHLA25 cells, GSE75859) and angiogenic switch genes. For gene ontology, p-values were computed using student's t-test and multiple test correction was performed using the Benjamini and Hoechberg method. Adjusted p-values are shown. (C) Unsupervised hierarchical clustering of angiomatrix gene expression in beta-catenin/TCF active (Wnt3a, Wnt+RSPO) and beta-catein/TCF-inactive (Lcell) Ewing sarcoma cells. Analysis performed as described in Supplemental Figure 2.







E

Wnt-induced Angioswitch Genes: Blocked by SB505124

Ensembl Transcript ID	HGNC symbol
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ENSG00000168542.14	COL3A1
ENSG00000164692.17	COL1A2
ENSG00000108821.13	COL1A1
ENSG00000165124.17	SVEP1
ENSG00000158270.11	COLEC12
ENSG00000186642.15	PDE2A
ENSG00000163359.15	COL6A3
ENSG00000137801.10	THBS1
ENSG00000120708.16	TGFBI
ENSG00000140092.14	FBLN5
ENSG00000115461.4	IGFBP5
ENSG00000197594.11	ENPP1
ENSG00000041982.15	TNC
ENSG00000150687.11	PRSS23
ENSG00000153071.14	DAB2
ENSG00000121440.14	PDZRN3
ENSG00000153208.16	MERTK
ENSG00000118523.5	CTGF
ENSG00000153904.18	DDAH1
ENSG00000118257.16	NRP2
ENSG00000139329.4	LUM

Supplemental Figure 4. (A) Experimental design of RNA-seq experiment to identify if induction of Wnt-responsive genes is dependent on downstream activation of TGF-beta signaling. (B) Heatmap showing relative expression levels of all Wnt-regulated genes following exposure to Wnt3a +/- SB505124. (C) GSEA of transcripts ranked based on upregulation with Wnt and downregulation with SB505124 shows significant correlation with the angiogenic switch (298 genes) gene signature. For GSEA, multiple test comparison was computed using false discovery rate. Only gene sets with FDR < 0.05 are displayed. (D) Heatmap showing relative expression levels of Wnt-induced angiogenic switch genes following exposure to Wnt3a +/- SB505124. (E) Corresponding official gene ID for ensembl transcripts represented in heatmap in (D). Genes shown in red are Wnt3a-induced genes whose induction was blocked by TGF-beta inhibition.