

Figure S1: dREG identifies highly enriched active enhancers and promoter marks in MCF-7 cells

- (A) Heatmap depicting PRO-seq, Dnase-I-seq, H3K27ac, and H3K4me3 near 39,753 transcriptional regulatory elements (TREs) identified using dREG-HD from PRO-seq data (left) in TamS and TamR MCF-7 cells.
- (B) Transcription and dREG scores in the locus near the *CCND1* gene in B7^{TamS} and G11^{TamR} MCF-7 cells.
- (C) Luciferase activity in B7^{TamS} and G11^{TamR} MCF-7 cells in the presence of an enhancer located approximately 300kb downstream of *CCND1*. All data normalized to renilla control. Data are represented as mean \pm SEM (n=3). ** p < 0.01, **** p < 0.0001.

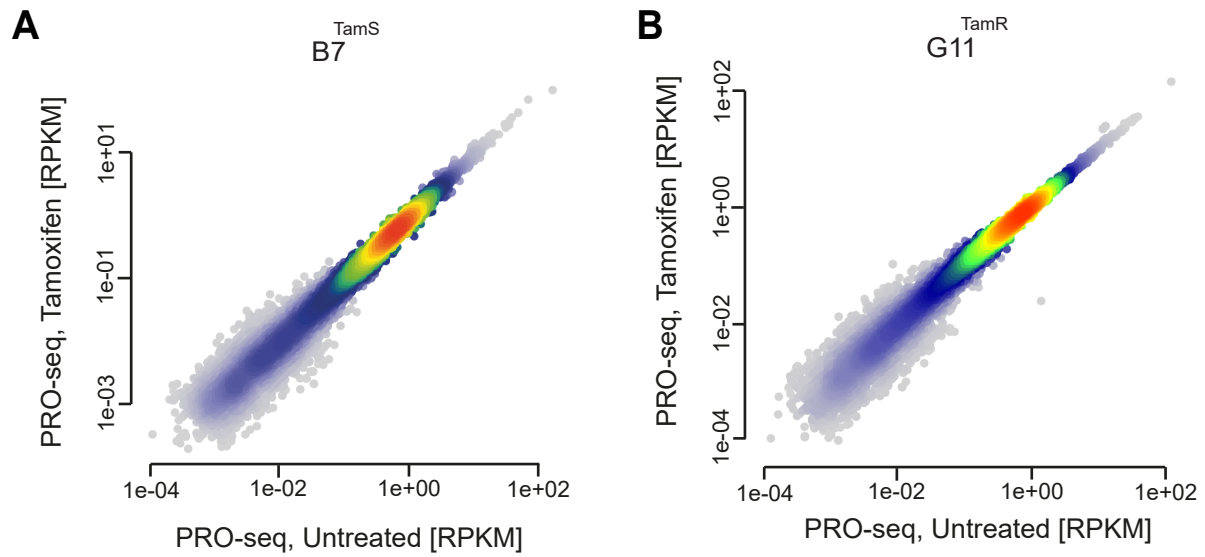


Figure S2: PRO-seq densities are unaffected after tamoxifen treatment

(A-B) Density scatterplot showing the correlation of PRO-seq densities between tamoxifen treated and untreated B7^{TamS} (A) and G11^{TamR} (B) MCF-7 cells.

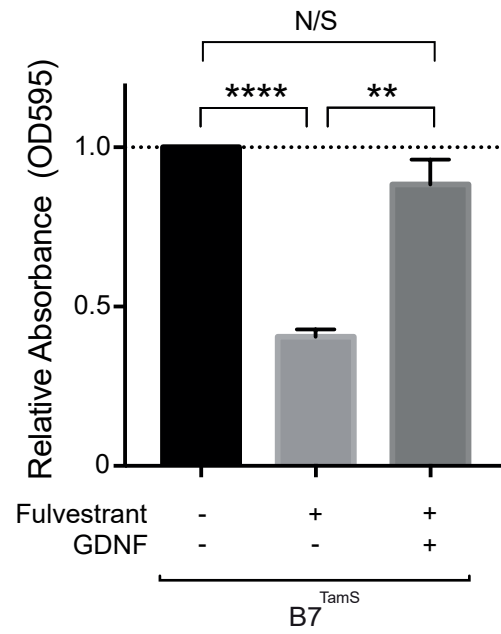


Figure S3: GDNF induces fulvestrant resistance in TamS cells

(A) Cell viability of B7^{TamS} cells in the presence or absence of 10 ng/ml GDNF and/or 100 mM fulvestrant for 4 days. Data are represented as mean \pm SEM (n=3). ** p < 0.005, **** p < 0.0001.

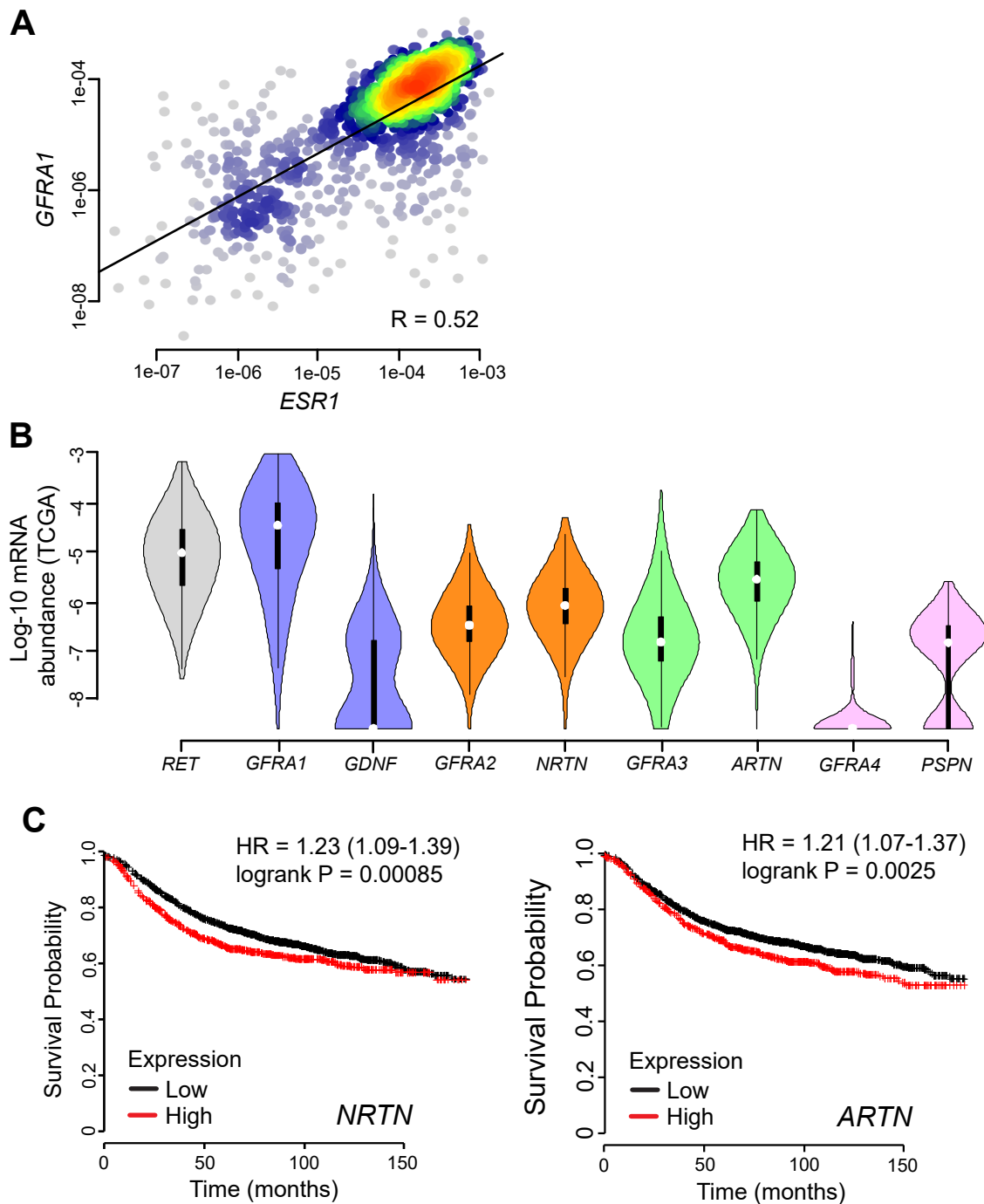


Figure S4: RET ligand expression is low compared to RET and GFR α 1 receptors

- (A) Density scatterplot showing the relationship between *GFRA1* and *ESR1* expression levels in 1,177 primary breast cancer samples in the cancer genome atlas (TCGA). Pearson's $R = 0.52$; $p < 2.2 \times 10^{-16}$.
- (B) Violin plots depicting the absolute normalized expression level of receptor-tyrosine kinase receptors and ligands in 1,177 primary breast cancer samples (TCGA). For each color, the pair of genes represents receptor (left) and ligand (right). Gray represents the *RET* gene which encodes the RET tyrosine kinase receptor required for signal transduction of all four RET ligands.
- (C) Kaplan Meier (KM) plots of survival probability in a cohort of breast cancer patients with low (black) or high (red) *NRTN* or *ARTN* expression. Patients are split based on the upper quartile of RET ligand expression.

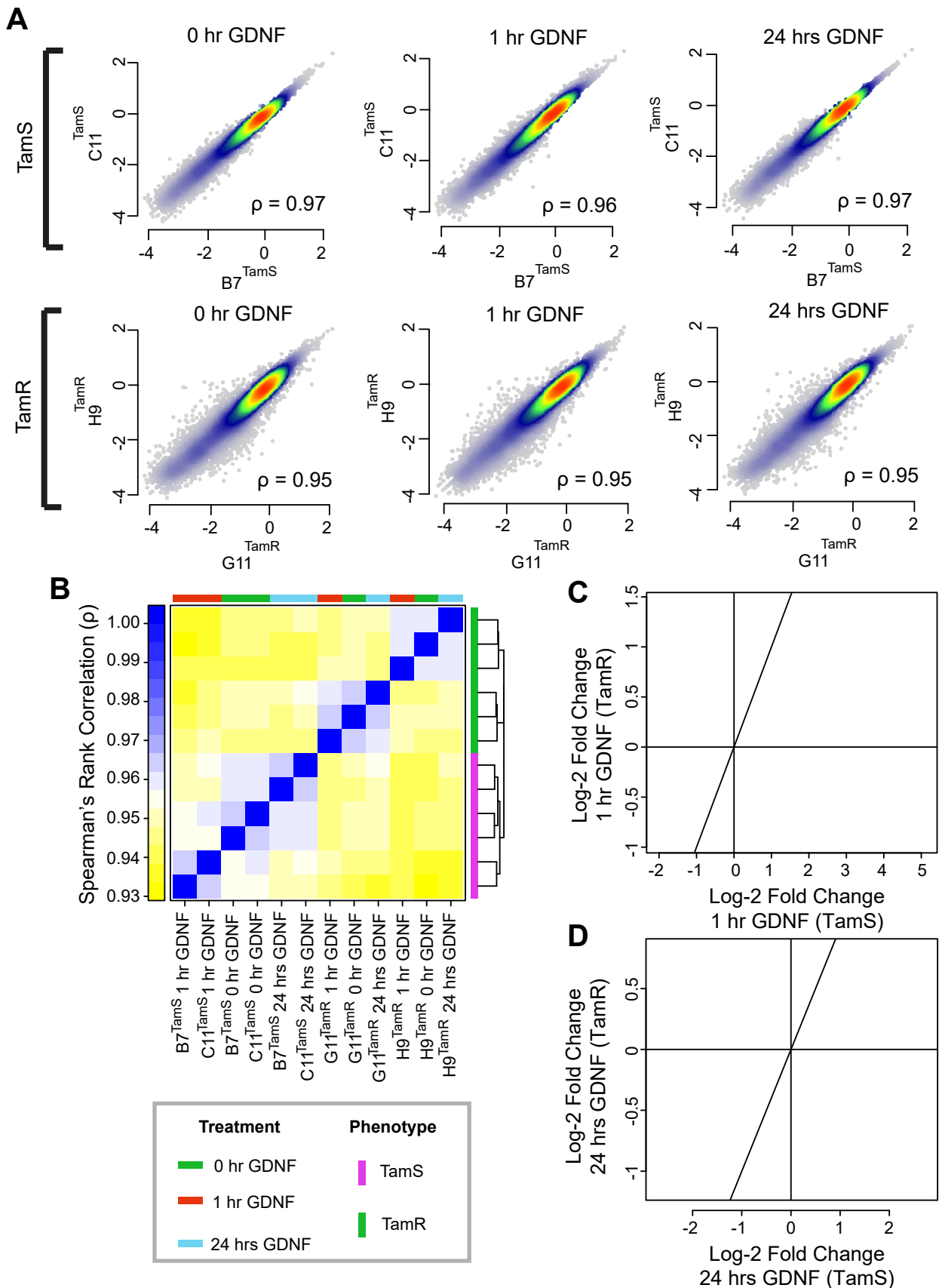


Figure S5: Highly correlated transcriptional patterns in biological replicates across the time course

- (A) Density scatterplot showing global transcription levels between TamS (B7 and C11; top) or TamR (G11 and H9; bottom) MCF-7 cell lines at 0, 1, or 24 hours GDNF treatment. The Spearman's rank correlation (ρ) values are shown for each plot.
- (B) Heatmap shows Spearman's rank correlation of RNA polymerase abundance of TamS and TamR lines between the indicated samples. Sample order is determined by hierarchical clustering. Colorscales show 0, 1, or 24 hours of GDNF treatment (above) or TamS or TamR (right) as shown below the heatmap.
- (C-D) Scatter plots depict transcriptional changes between TamS and TamR MCF-7 cells following 1 hour (C) or 24 hours (D) of GDNF treatment.

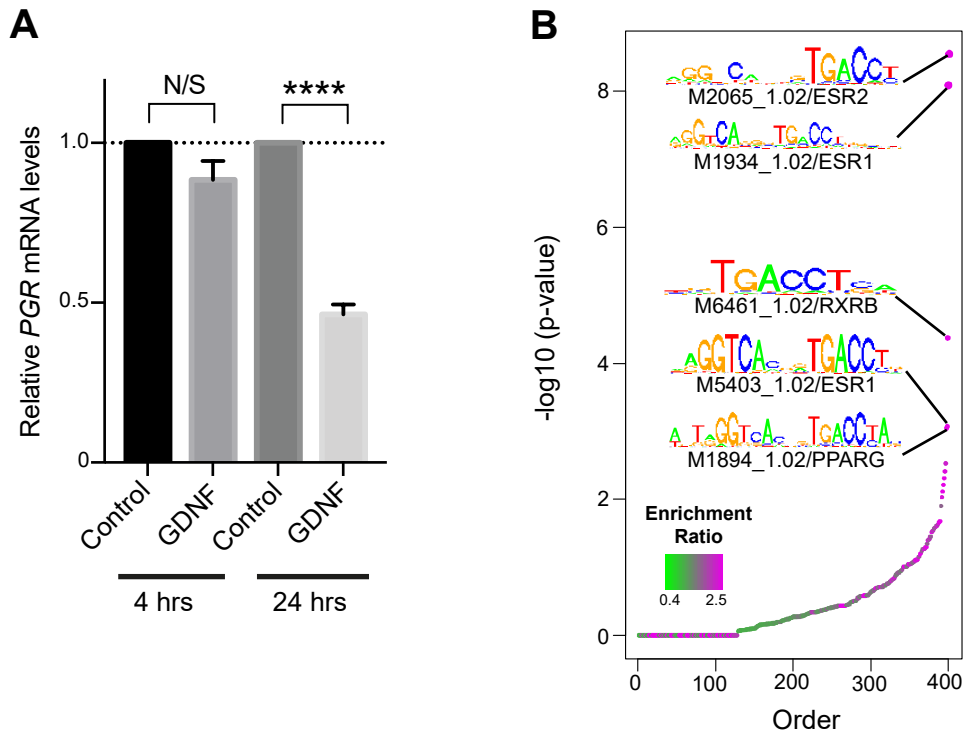


Figure S6: GDNF causes decrease in *PGR* mRNA expression and ER α binding sites

(A) *PGR* mRNA expression level in G11^{TamR} cells after treatment without (water) or with 10 ng/mL GDNF for 4 or 24 hrs. Data are represented as mean \pm SEM (n=3). **** p < 0.0001.

(B) Motifs enriched in TREs that have different amounts of RNA polymerase before and after 24 hours of GDNF treatment.