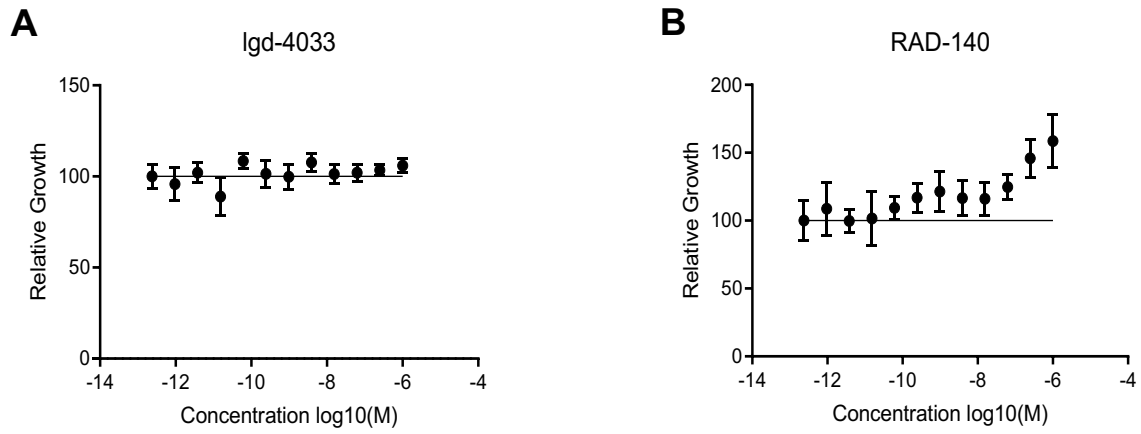
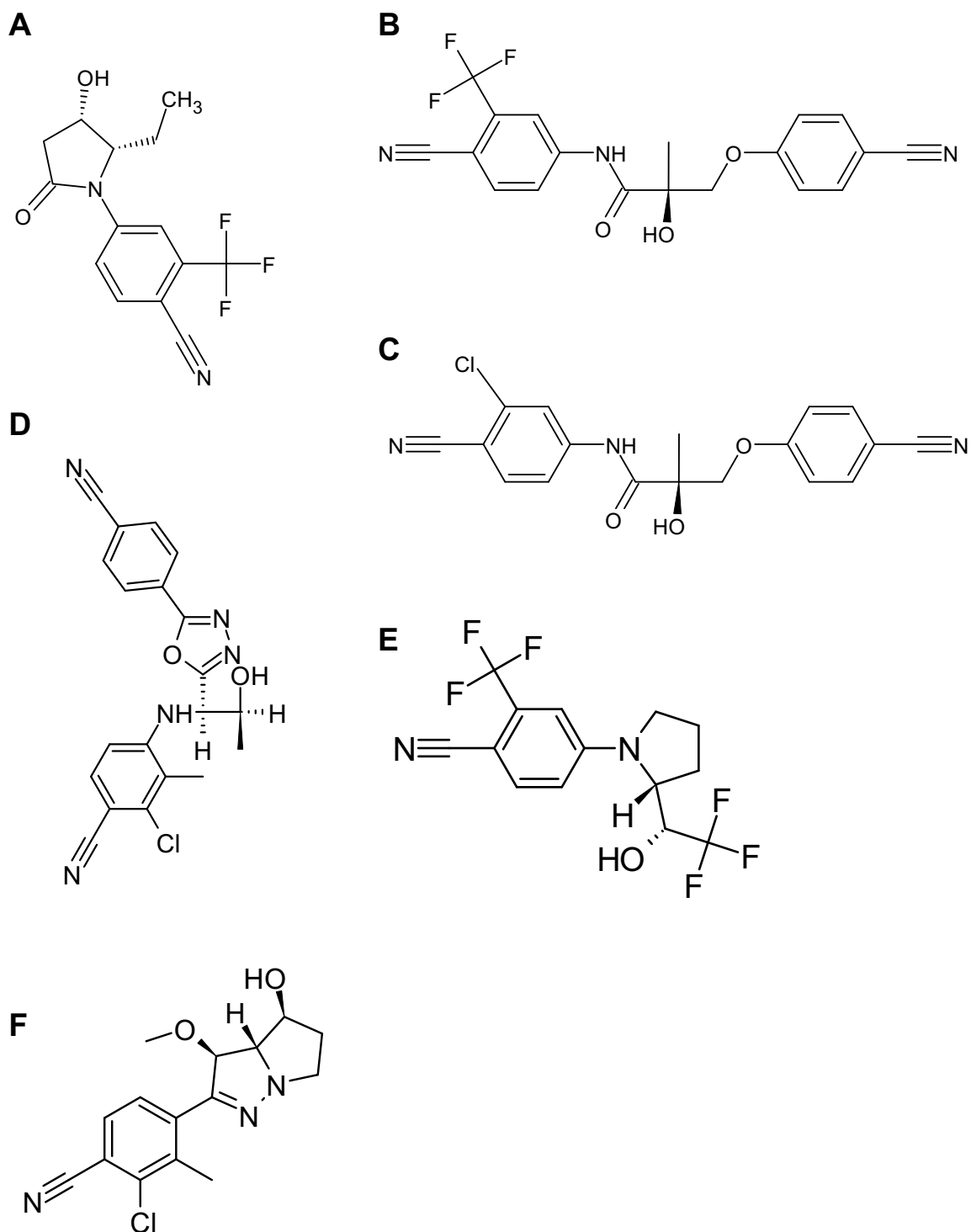


Supplemental Figure 1



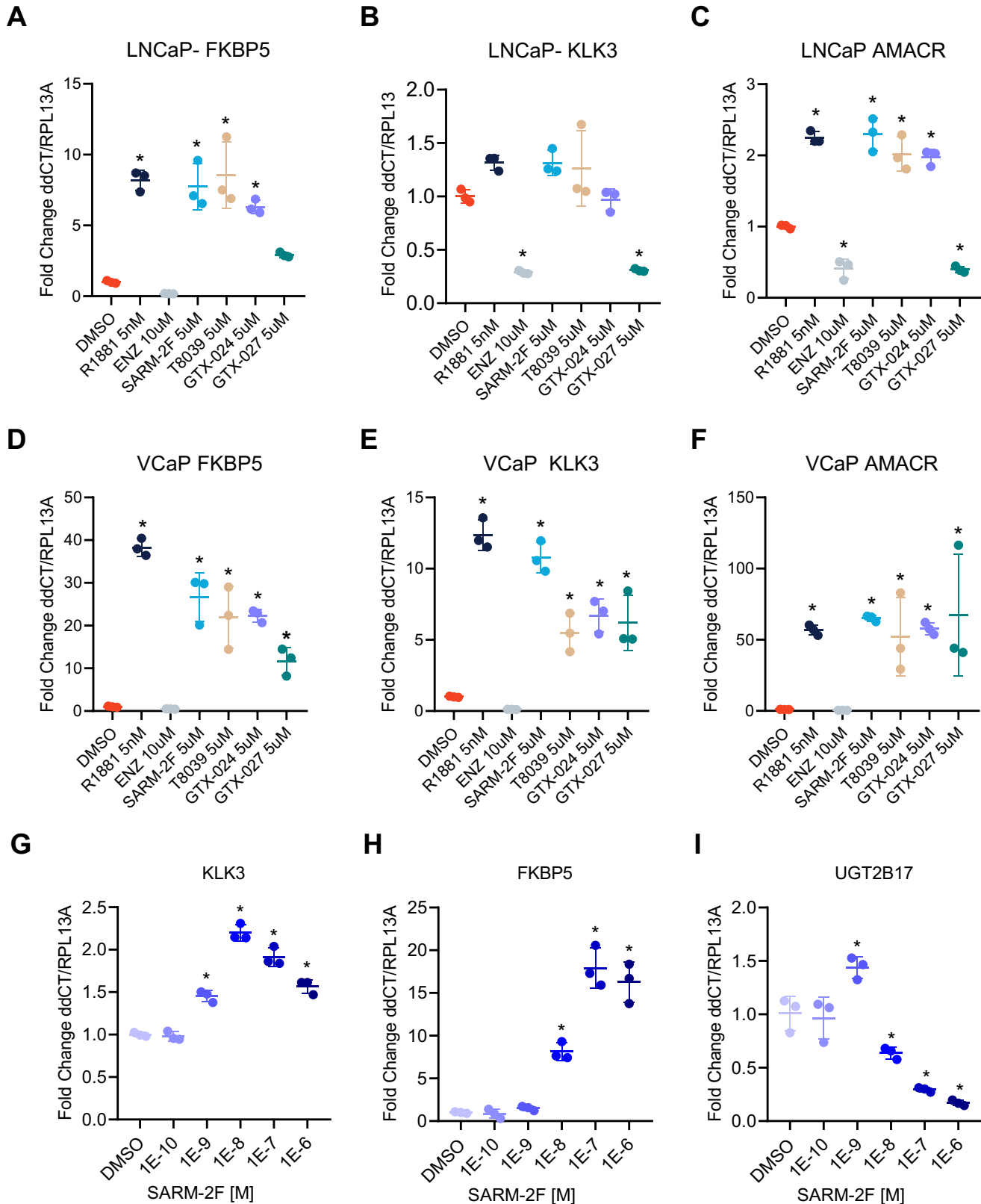
Supplemental Figure 1: SARM effects on cell growth. Dose response curves were performed on LNCaP cells of SARMs **A)** lgd-4033 and **B)** RAD-140. (n=4) (Data represent mean $\pm$ SD).

Supplemental Figure 2



Supplemental Figure 2: Non-steroidal Selective Androgen Receptor Modulators.
Structures of **A**) SARM-2F, **B**) GTX-024, **C**) GTX-027, **D**) RAD-140, **E**) LGD-4033, and **F**) Compound-26.

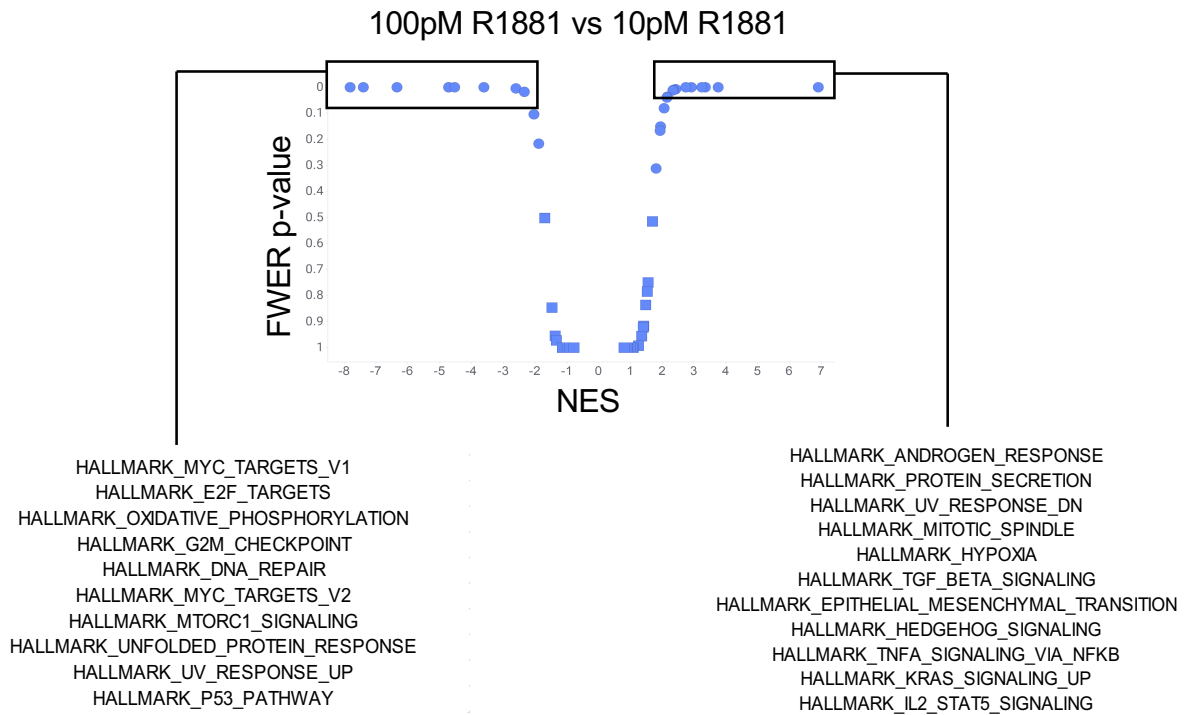
Supplemental Figure 3



Supplemental Figure 3 SARM effects on gene expression. qRT-PCRs of FKBP5, KLK3 and AMACR in **A-C**) LNCaP and **D-F**) VCaP cells. (n=3) (* = p<0.05) (Data represent mean $\pm$ SD). qRT-PCRs of AR-induced genes **G**) KLK, **H**) FKBP5, and AR-repressed gene **I**) UGT2B17 in LNCaP cells cultured 48hrs with a dose-range of SARM-2F. (n=3) (* = p<0.05 one-way ANOVA Dunnett's multiple comparisons test) (Data represent mean $\pm$ SD).

Supplemental Figure 4

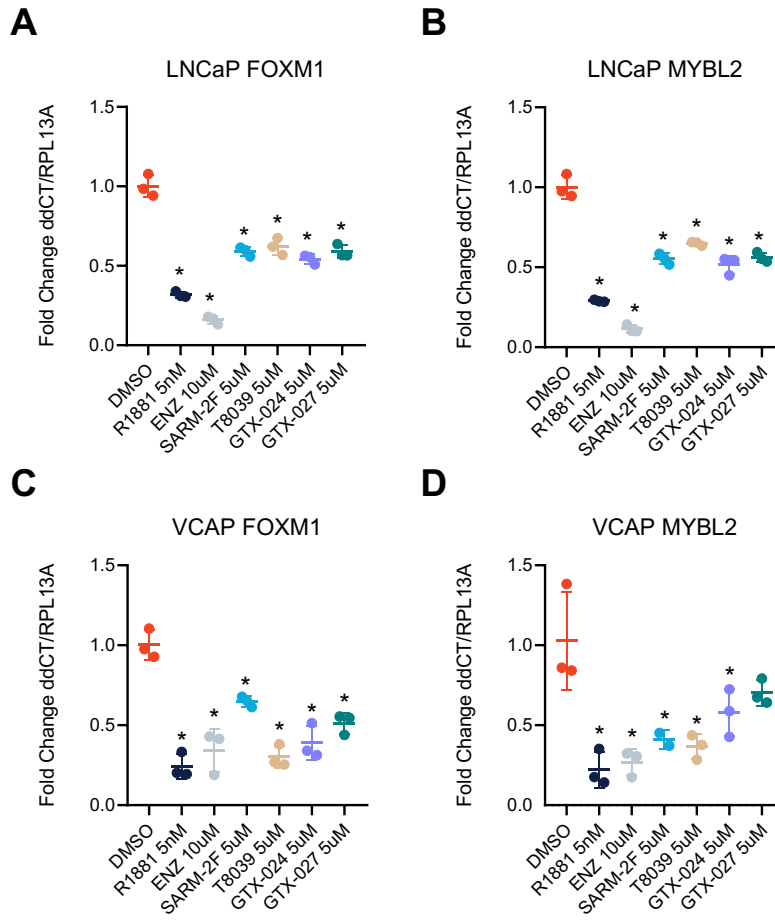
A



Supplemental Figure 4: GSEA comparison of SARMs and steroidal ligand concentrations.

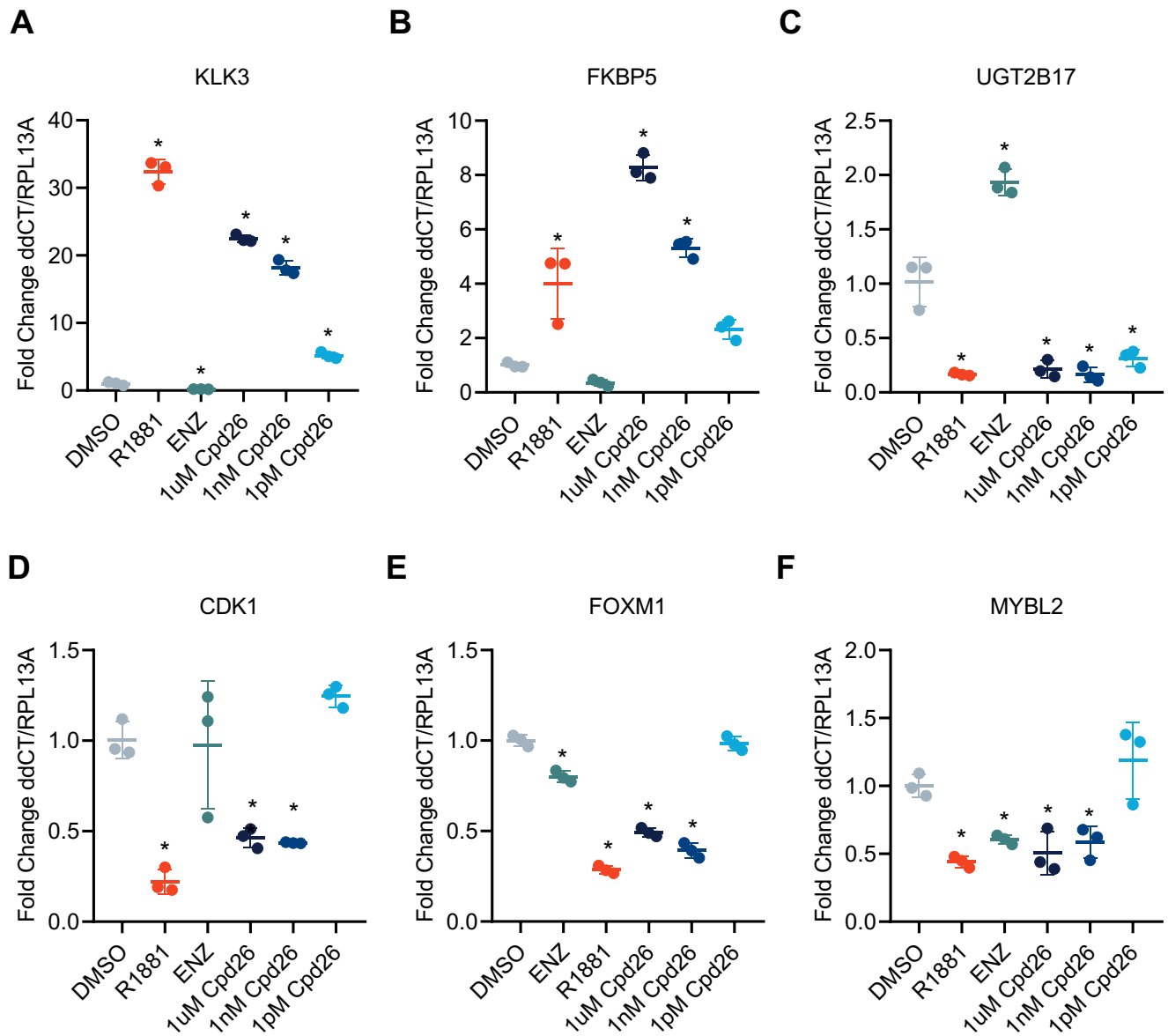
A) Plot of FWER p-values vs NES scores of HALLMARK genesets for 100pM R1881 vs 10pM R1881 GSEA analyses.

Supplemental Figure 5



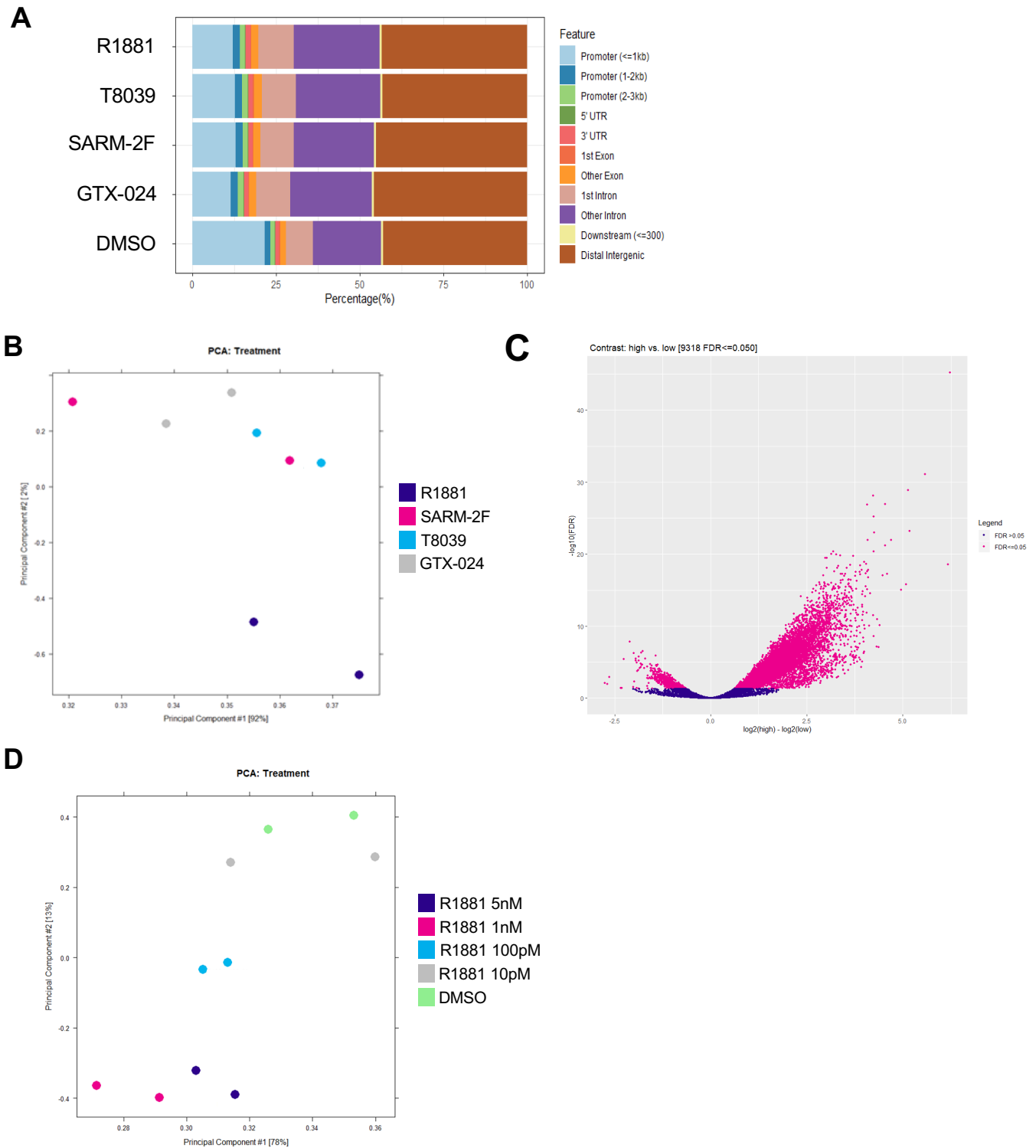
Supplemental Figure 5: SARMS suppress cell-cycle gene expression.

qRT-PCR quantitation of FOXM1 and MYBL2 in **(A,B)** LNCaP and **(C,D)** VCaP cells exposed to the synthetic androgen R1881, the AR antagonist ENZ and various SARMS. (n=3) (* = $p < 0.05$ one-way ANOVA Dunnett's multiple comparisons test) (Data represent mean $\pm$ SD).



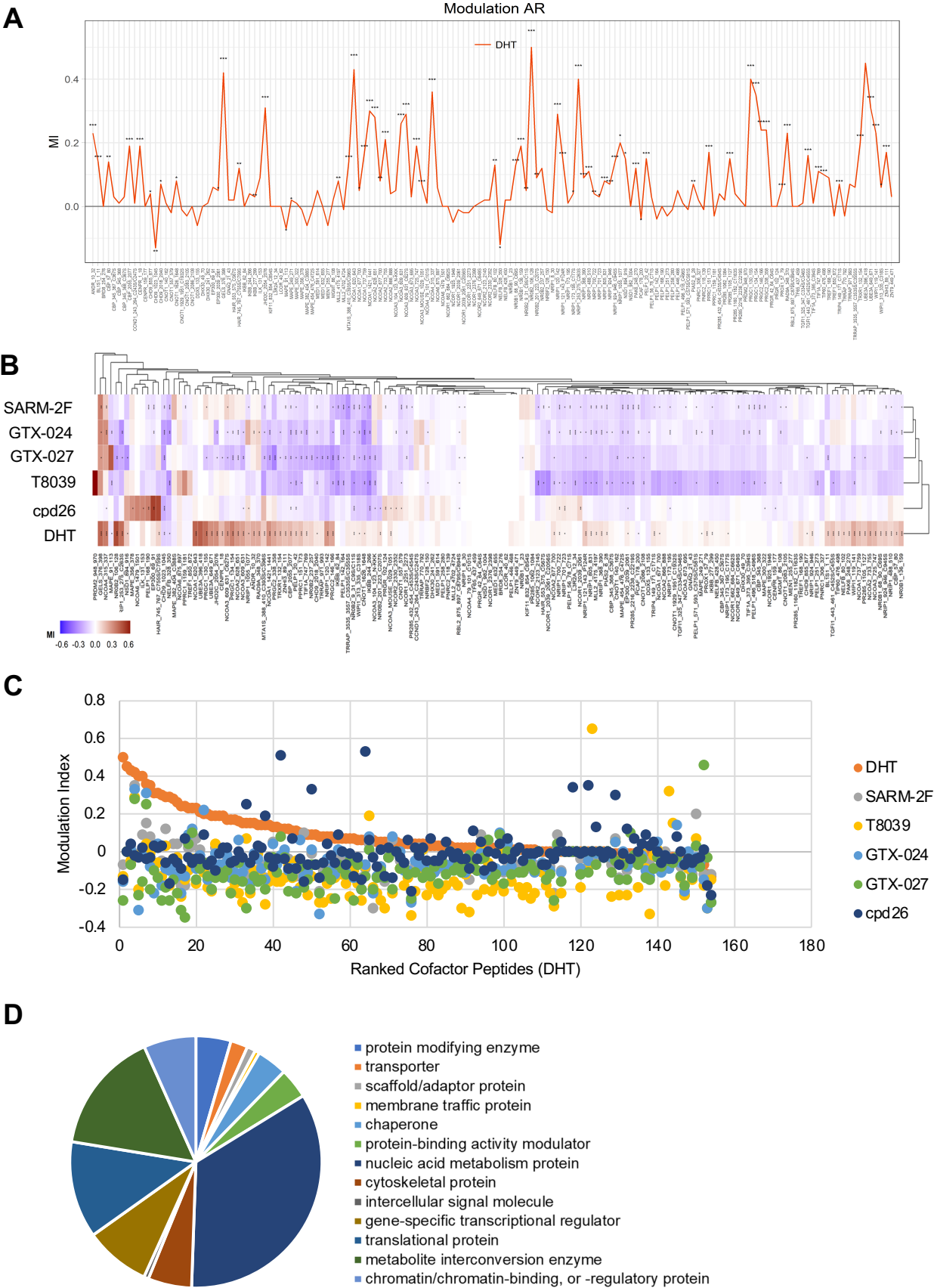
Supplemental Figure 6: SARM cpd26 induces AR-regulated gene expression changes in VCaP cells. qRT-PCR quantitation of AR-induced genes **A)** KLK3, and **B)** FKBP5, AR-repressed gene **C)** UGT2B17, and cell-cycle related genes **D)** CDK1, **E)** FOXM1 and **F)** MYBL2 in VCaP cells 48 hours after treatment. (n=3) (* = $p < 0.05$ one-way ANOVA Dunnett's multiple comparisons test). (Data represent mean $\pm$ SD).

Supplemental Figure 7



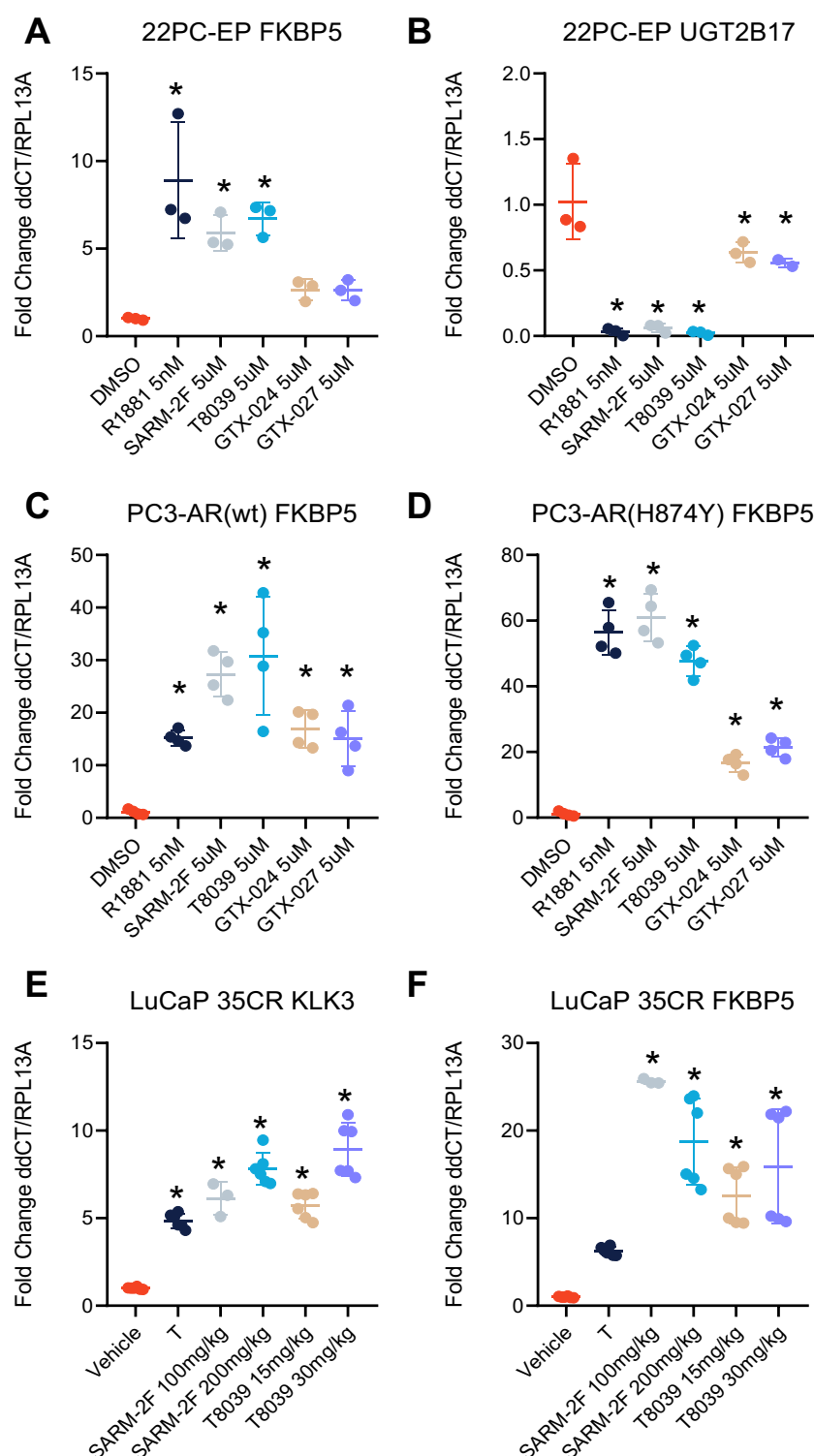
Supplemental Figure 7. Comparison of steroid and SARM induced AR cistromes using CUT&RUN. A) Annotation of genomic features bound by R1881 and SARM liganded AR. **B)** Principal component plot comparing the AR cistromes of SARM and high-dose R1881 treated cells. **C)** Volcano plot of differentially bound sites between low and high-dose AR sites. **D)** Principal component plot comparing AR cistromes of a dose-range of R1881 treated cells.

Supplemental Figure 8



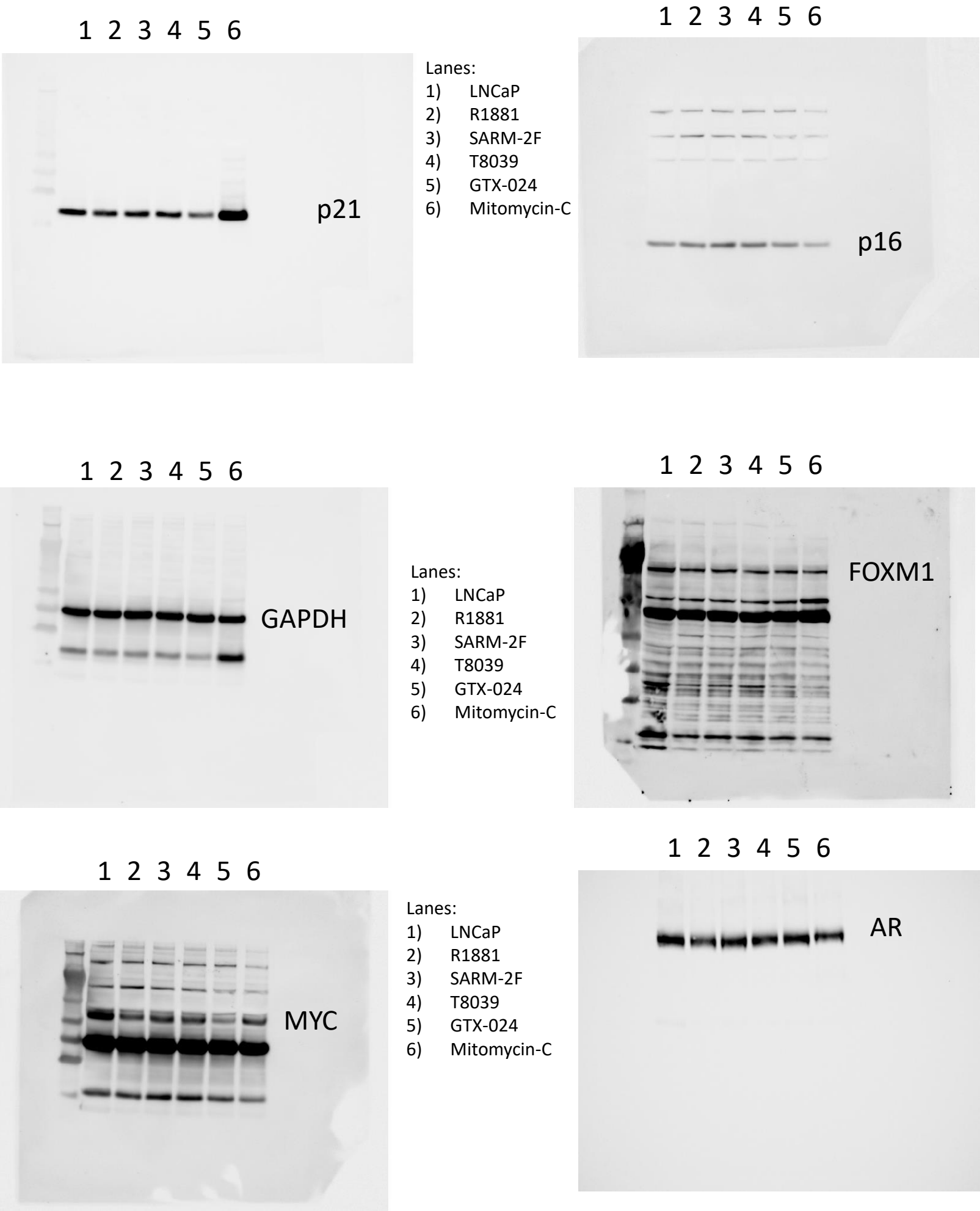
Supplemental Figure 8. Analyses of SARM induced AR cofactor binding. A) MARCONI modulation Index (MI = $\log_{10}(\text{DHT signal} / \text{DMSO signal})$) values of nuclear receptor cofactors for DHT agonized AR-LBD (n=3). **B)** Heat map comparing SARM agonized and DHT agonized cofactor binding MI values. **C)** DHT-ranked plot of MARCONI MI values. **D)** Gene Ontology annotation of proteins bound to AR in both SARM-2F and R1881 samples as detected by RIME.

Supplemental Figure 9

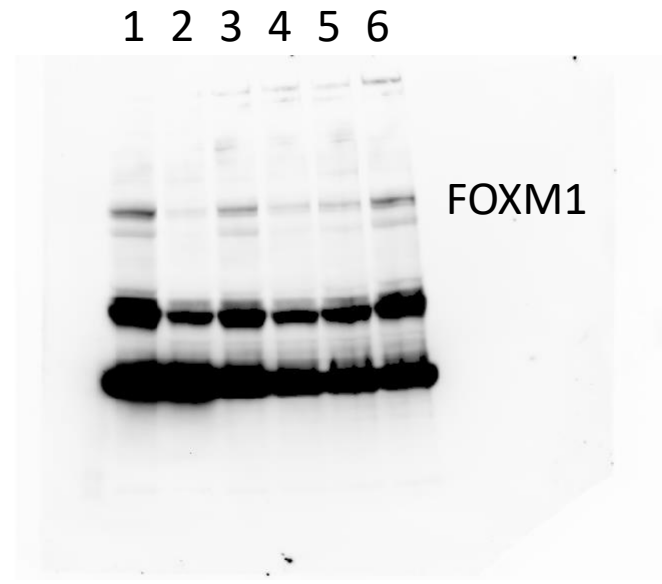
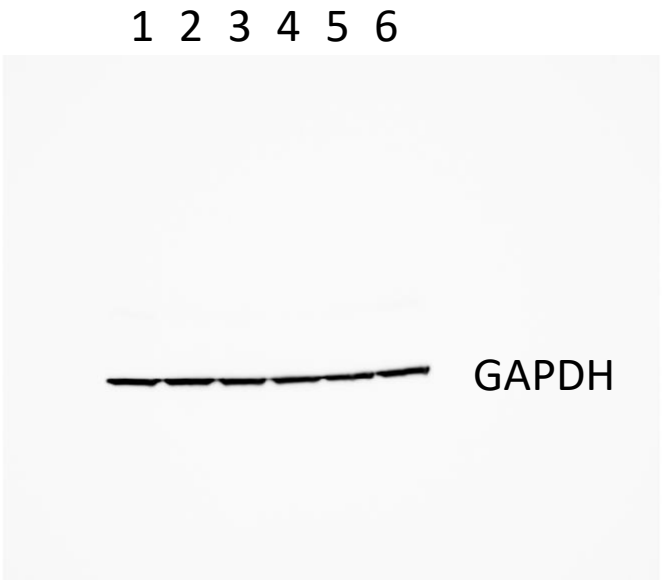
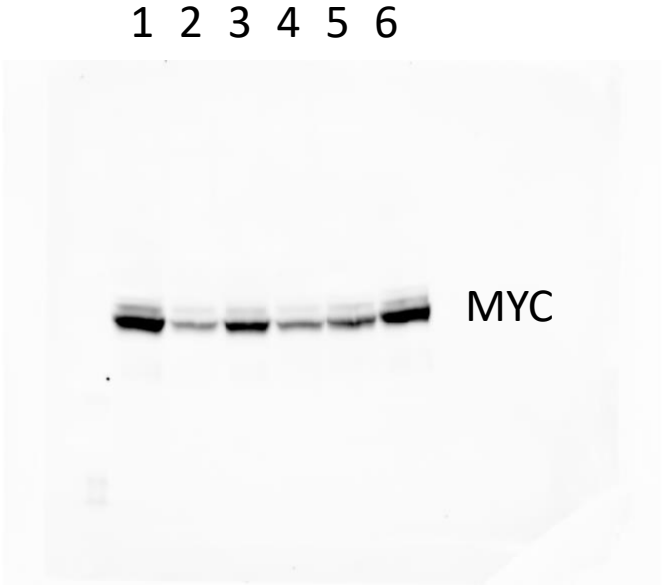
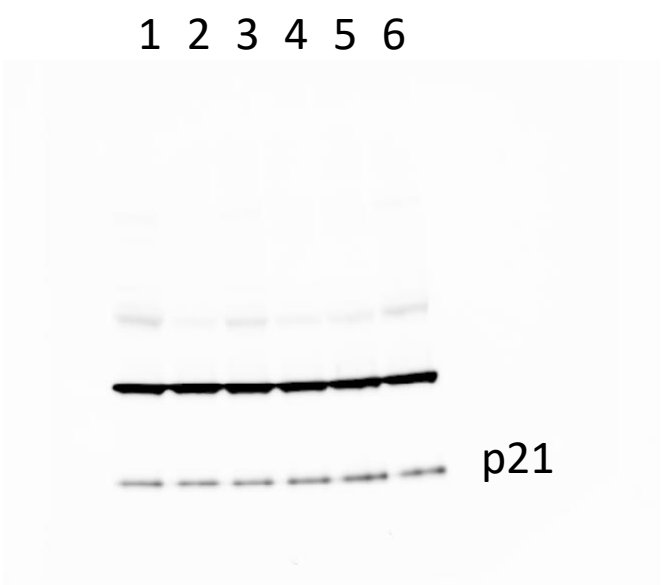


Supplemental Figure 9. AR target gene expression in SARM-treated 22PC-EP, PC3-AR, and LuCaP35CR PDX. qRT-PCR analyses were performed on 22PC-EP treated for 48 hours at the indicated doses of SARMs under normal growth conditions for: **A)** AR activated gene FKBP5, and **B)** AR repressed gene UGT2B17. (n=3)(* = $p < 0.05$) (Data represent mean $\pm$ SD). qRT-PCR analyses were performed for FKBP5 on PC3 cells engineered to express **C)** wild-type AR or **D)** AR-H874Y and treated for 48 hours at the indicated doses of SARMs under normal growth conditions (n=4)(* = $p < 0.05$). qRT-PCR on RNA extracted 48 hours after PDX model LuCaP 35CR was treated with the indicated doses of SARMs, orally, or an IM injection of 40mg/kg testosterone for: **E)** KLK3 and **F)** FKBP5. Each dose is represented by two tumors analyzed separately by qRT-PCR then combined to graph (n=3+3) (* = $p < 0.05$ one-way ANOVA Dunnett's multiple comparisons test) (Data represent mean $\pm$ SD).

Full unedited gels for Figure 2E

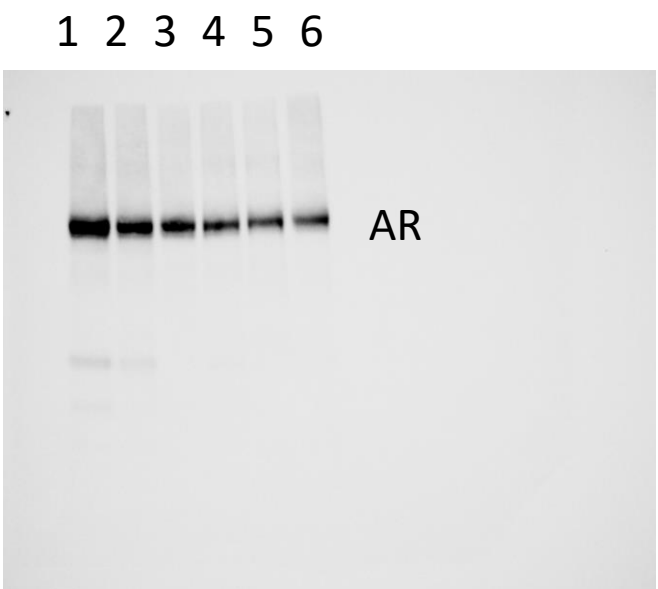
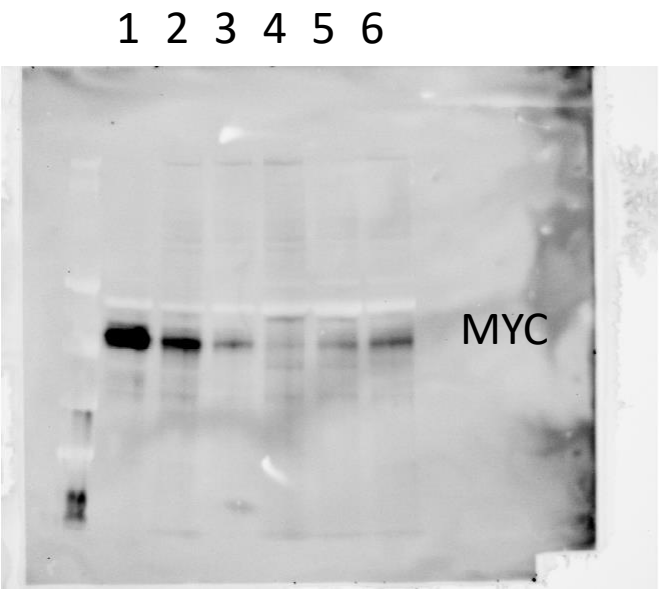
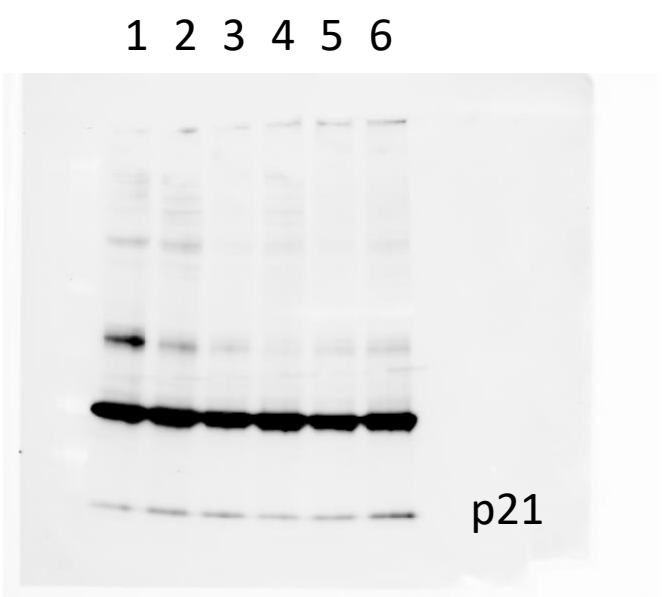
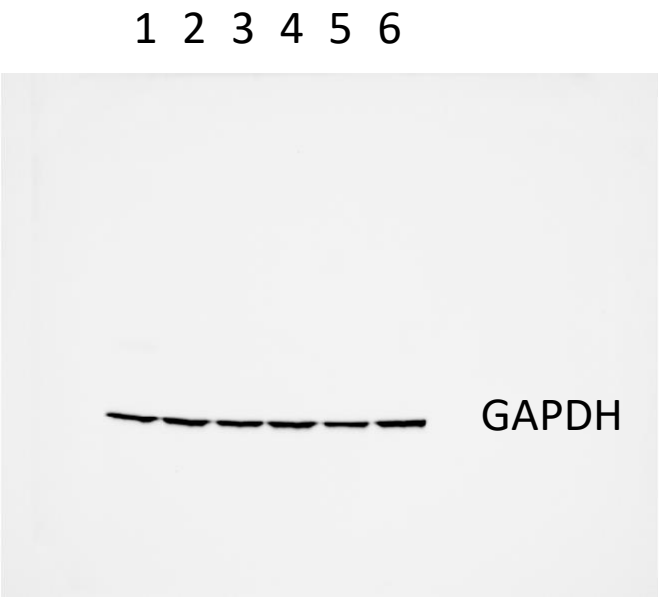


Full unedited gels for Figure 3B



- Lanes:
- 1) DMSO
 - 2) R1881 1nM
 - 3) ENZ 10uM
 - 4) Cpd26 1uM
 - 5) Cpd26 1nM
 - 6) Cpd16 1pM

Full unedited gels for Figure 7G



- Lanes:
- 1) Vehicle
 - 2) Testosterone
 - 3) 15 mg/kg T8039
 - 4) 30mg/kg T8039
 - 5) 100mg/kg SARM-2F
 - 6) 200mg.kg SARM-2F