

LuCap PDX Tumor CT-1107 Sensitivity

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Introduction



Prevalence

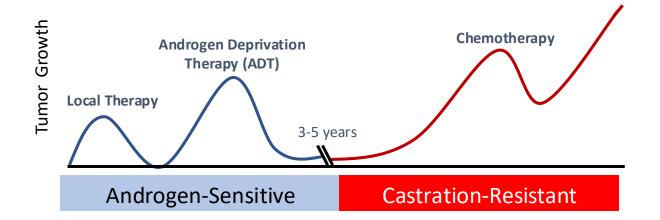
- Prostate cancer (PCa) is 2nd most commonly diagnosed cancer type in US (~299,010 in 2023)
- Incidence increases with age (~60% of all PCa diagnosed in men ≥ 65)
- ~35,250 men died of advanced prostate cancer in 2023 as tumors metastasize and develop resistance to standard of care

Unmet needs

• Metastatic castration-resistant prostate cancer (mCRPC)

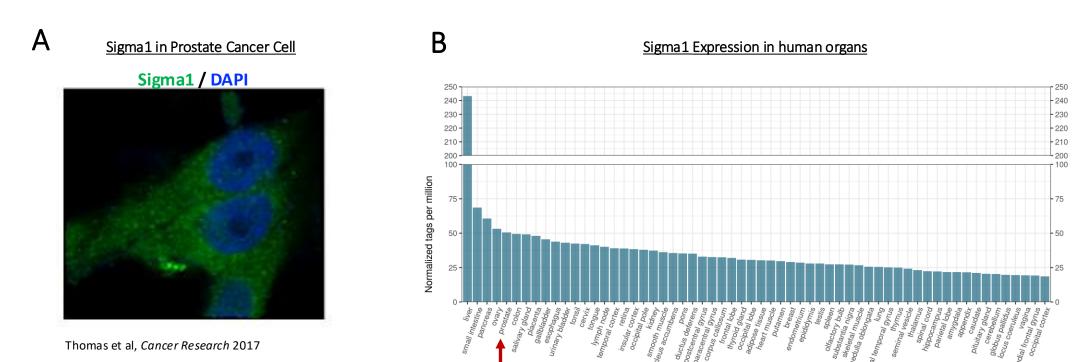
Research aims

• Study the novel drug-like compound, CT-1107, that inhibits Sigma1 as a potential treatment for PCa



Sigma1/SIGMAR1 – What is it?



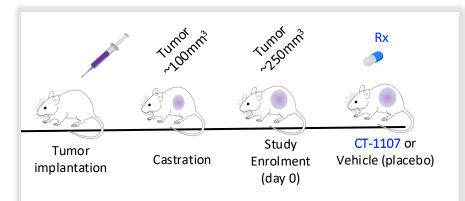


Sigma1 is an endoplasmic reticulum (ER) resident integral membrane ligand-operated scaffolding or chaperone protein.

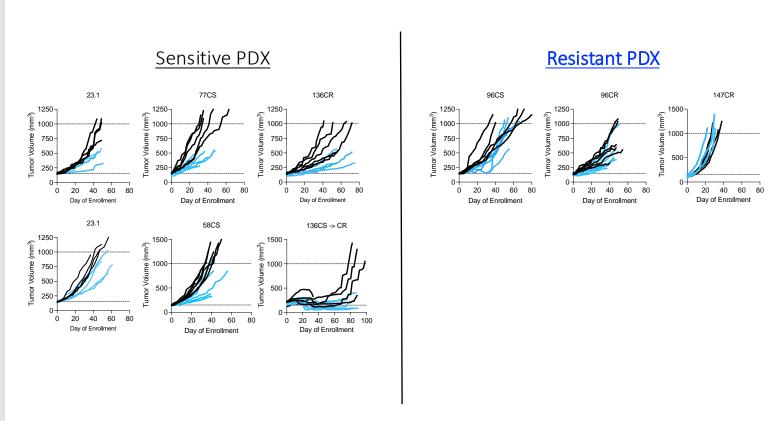
- A. Sigma1 is present in the ER membrane, throughout the cytoplasm of cancer cells (LNCaP prostate cancer cell shown, Sigma1 in green)
- B. Sigma1 is present in high level across human organs, including liver and prostate

CT-1107 selectively blocks growth of castration resistant prostate cancer (CRPC) patient derived human tumors implanted into mice





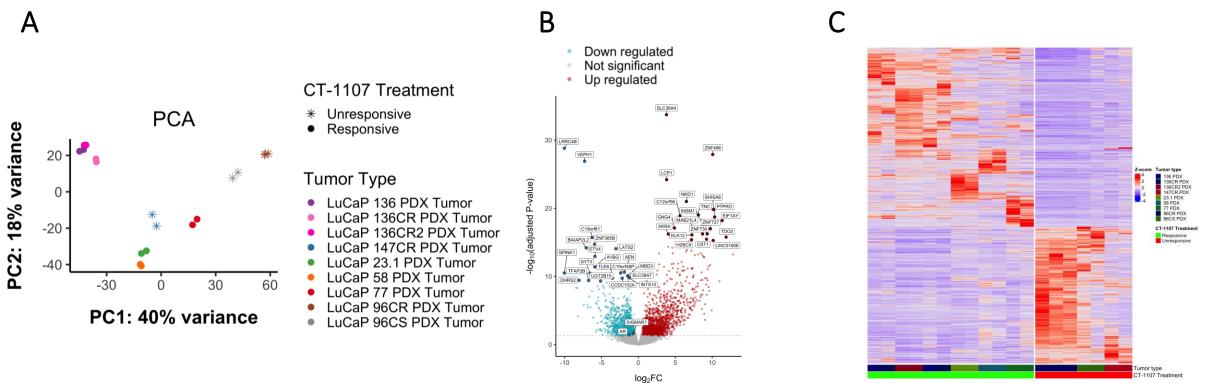
- LuCap patient derived xenograft (PDX) models.
- Myc-amplified, aggressive prostate tumor models that are minimally responsive to chemotherapy
- Vehicle treated animals have unchecked tumor growth while Sigma1i treated tumors have slowed growth in some PDX tumors



What makes a tumor sensitive to Sigmar1 inhibition?

Resistant vs Sensitive Models to CT-1107



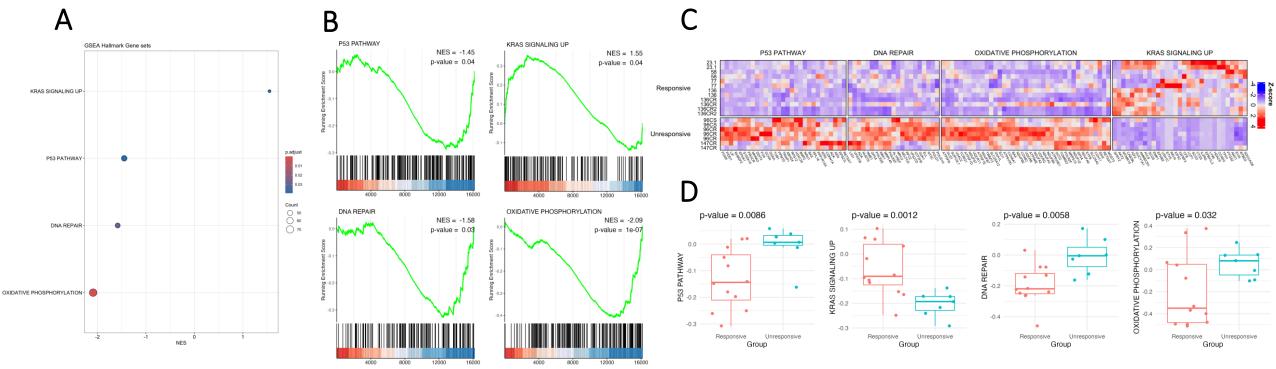


Comparing the gene expression of LuCap PDX tumors that are CT-1107 resistant to sensitive models.

- A. Principal Component Analysis (PCA)
- B. Volcano plot of Differentially expressed (DE) genes
- C. Expression heatmap of significant DE genes

Resistant vs Sensitive Models to CT-1107



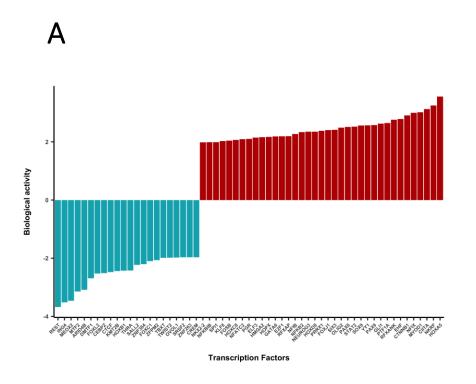


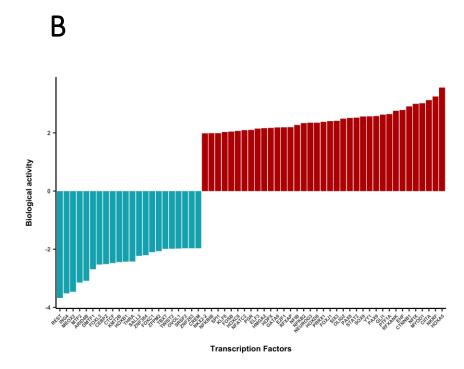
Sensitive PDX tumors have suppression of key oncogenic signaling pathways and induction of tumor apoptotic pathways

- A. Gene set enrichment analysis (GSEA) significantly enriched pathways
- B. Enrichment plots of significant pathways
- C. Expression heatmap of leading genes in significant pathways
- D. Gene set variation analysis (GSVA)

Transcription Factor (TF) analysis







Significant TFs identified by TF analyses

- A. Significantly enriched TF activities inferred with a univariate linear model of target gene weights using the CollecTRI network
- B. Significantly enriched upstream regulators computed with Ternary Dot Product Scoring statistics on the STRINGdb biological network