

Introduction

- Aneuploidy is copy-number alterations due to the gain or loss of whole chromosomes or chromosome arms, and a hallmark of cancer present in 90% of solid tumors.
- Aneuploidy creates cellular stress and can impair proliferation in normal cells, but cancer cells can adapt and exploit these altered karyotypes.
- TCGA analysis from our lab show arm-level aneuploidies occur in clear tissue-specific patterns. Some alterations, such as chromosome 3q (chr 3q) gain, are tumor-type specific, frequently occurring in squamous cancers (**Fig. 1**).
- Lung SCC accounts for 25–30% of non-small cell lung cancers (NSCLC) and has limited targeted treatment options compared with lung adenocarcinoma.
- Our lab has developed a CRISPR-Cas9 based approach to induce targeted chromosome arm aneuploidies in human cells (**Fig. 2**).
- Our studies revealed that chr3q gain creates a dependency on the SREBP pathway, a central regulator of cholesterol homeostasis.
- Hypothesis:** Chr3q gain specific aneuploidy rewires cholesterol homeostasis, which produces a specific metabolic vulnerability that can be targeted to inhibit tumor growth of aneuploid tumor cells

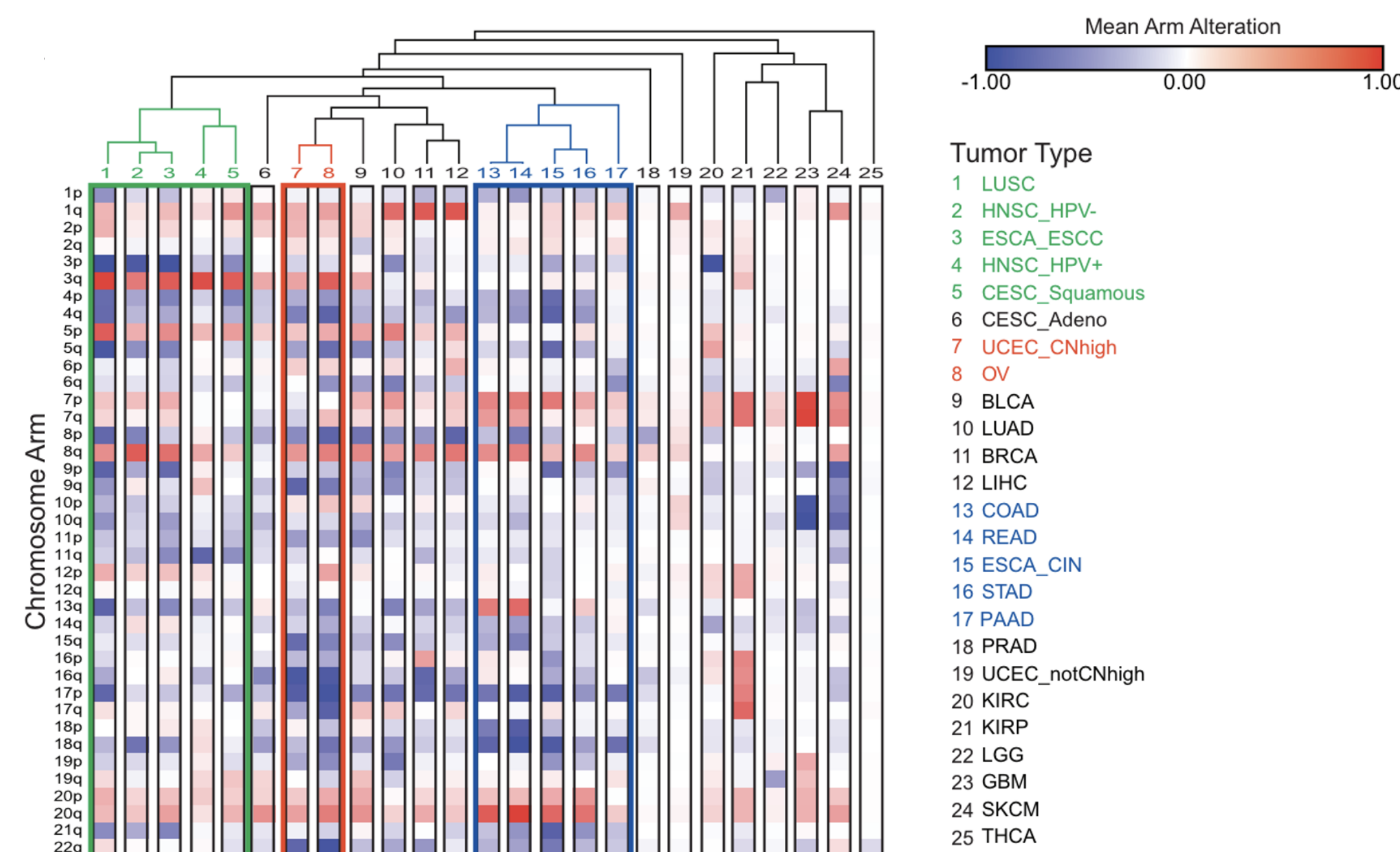


Fig 1. TCGA analysis reveals arm aneuploidies occur in tissue-specific patterns.

Model System

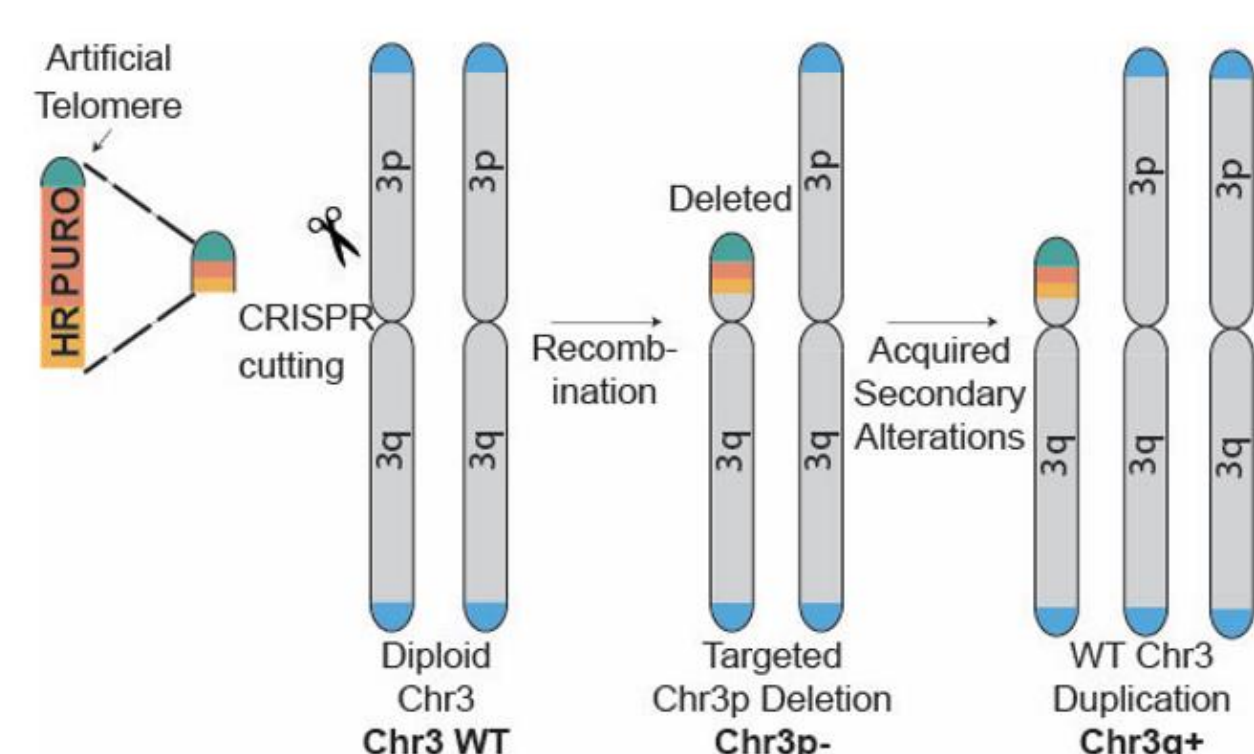


Fig 2. CRISPR-Cas9 approach used to generate targeted chromosome 3p arm deletion and 3q gain in immortalized airway lung epithelial cells (AAELs).

Results

Chr3q gain correlates with SREBF1 genetic dependency

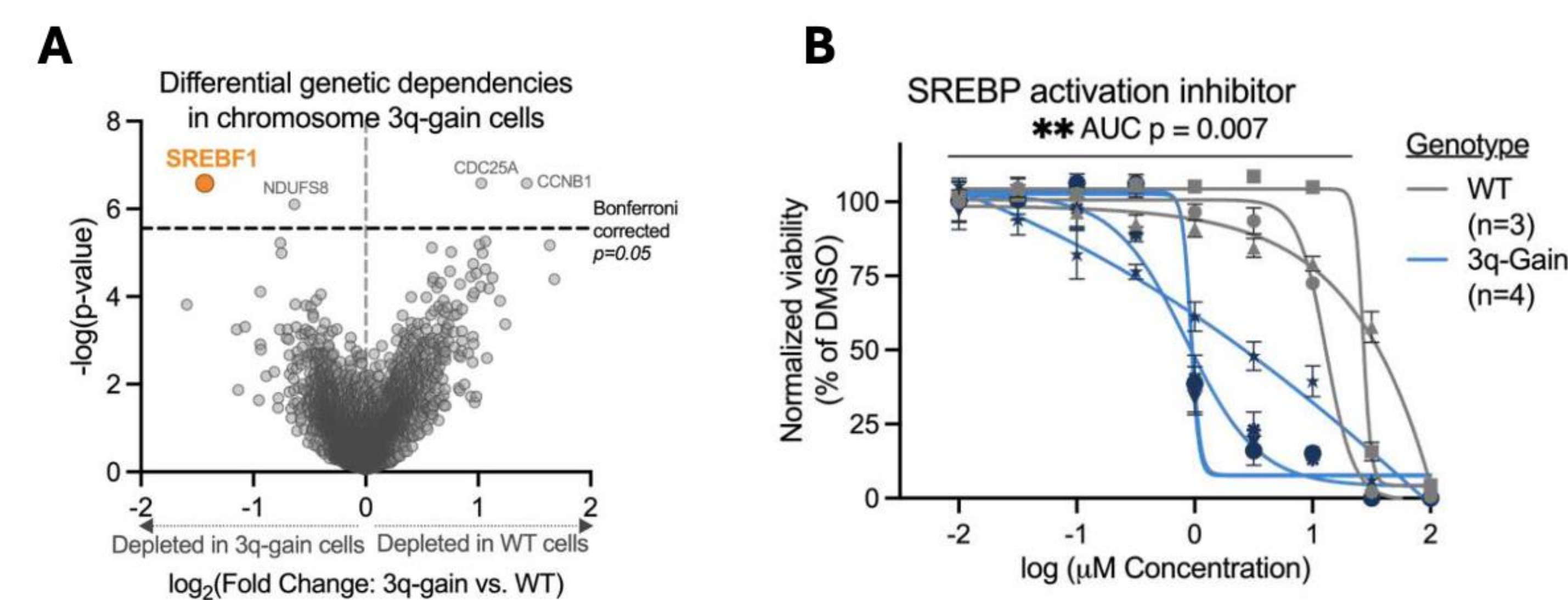


Fig 3. A) Genetic screen demonstrating SREBF1 depletion in chr3q gain. B) SREBP activation inhibitor treatment reduces chr3q gain cell viability.

Chr3q gain correlates with HMGR inhibition sensitivity

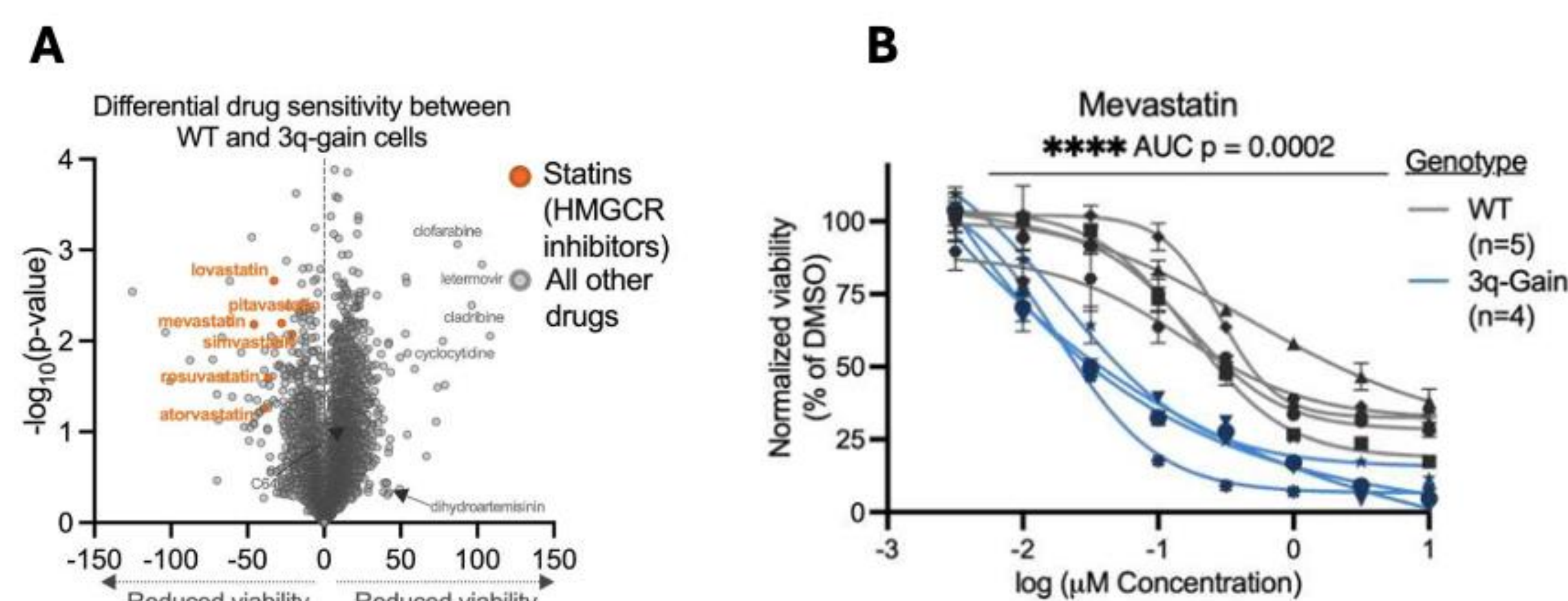


Fig 4. A) Drug sensitivity in WT and 3q gain cells following chemical screen B) CellTiter-Glo dose curve with 72hr mevastatin treatment.

Mevastatin drives chr3q gain cell viability decrease via apoptosis

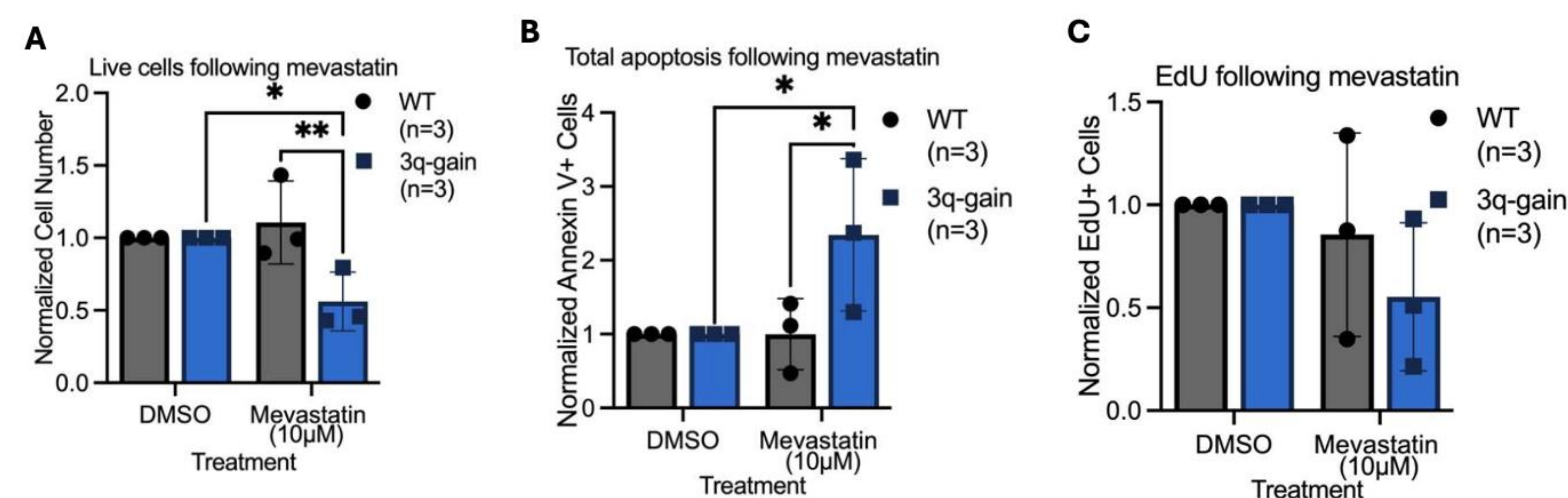


Fig 5. A) Total cell number following 72hr mevastatin treatment B) Apoptosis via Annexin V+ cells following 72hr mevastatin treatment. C) EdU incorporation following 72hr mevastatin treatment.

RNA-seq reveals SREBP pathway depletion in chr3q gain

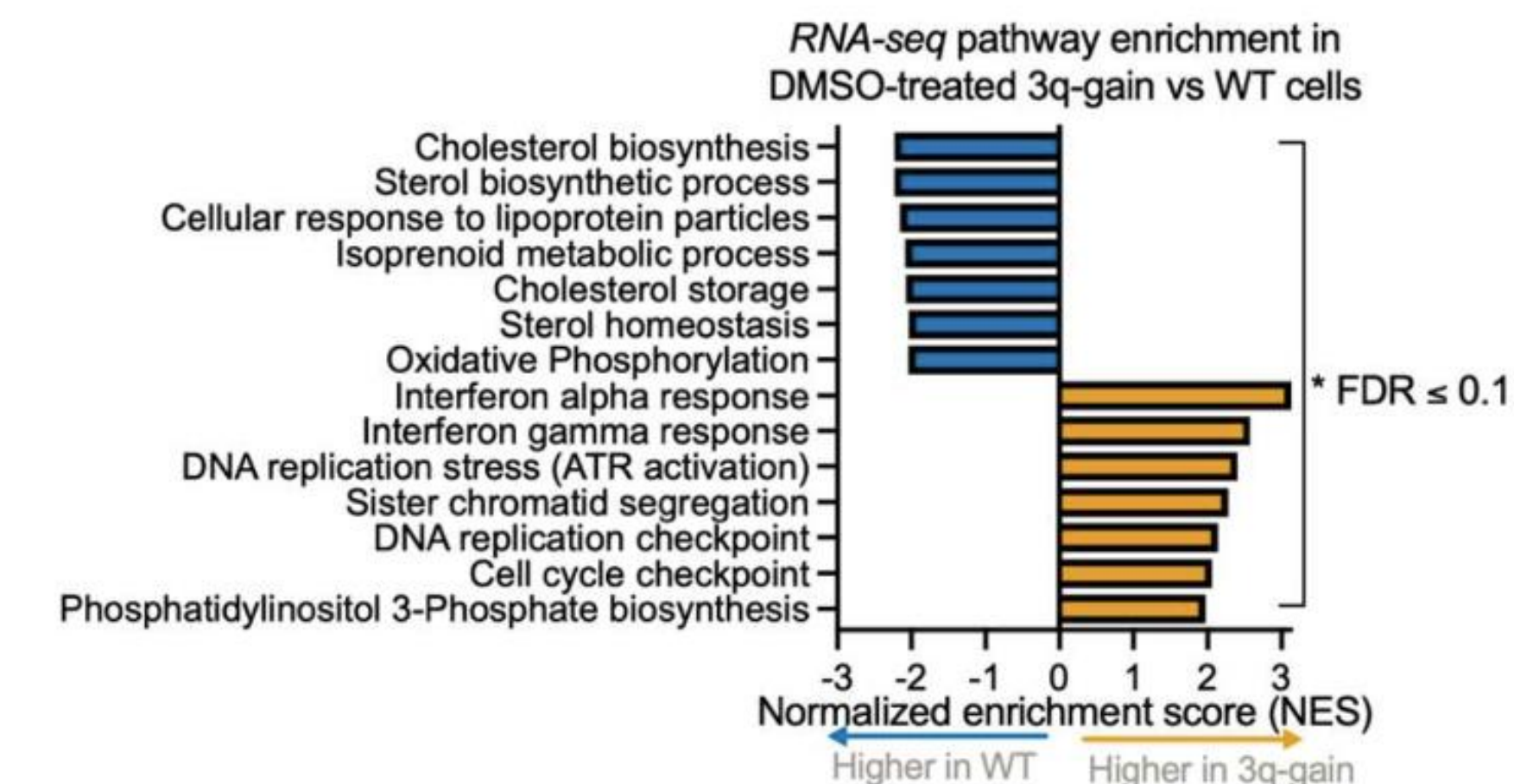


Fig 6. RNA-seq GSEA enrichment analysis in WT vs 3q gain cells.

Mevastatin sensitizes chr3q gain cells to DNA repair gene depletion

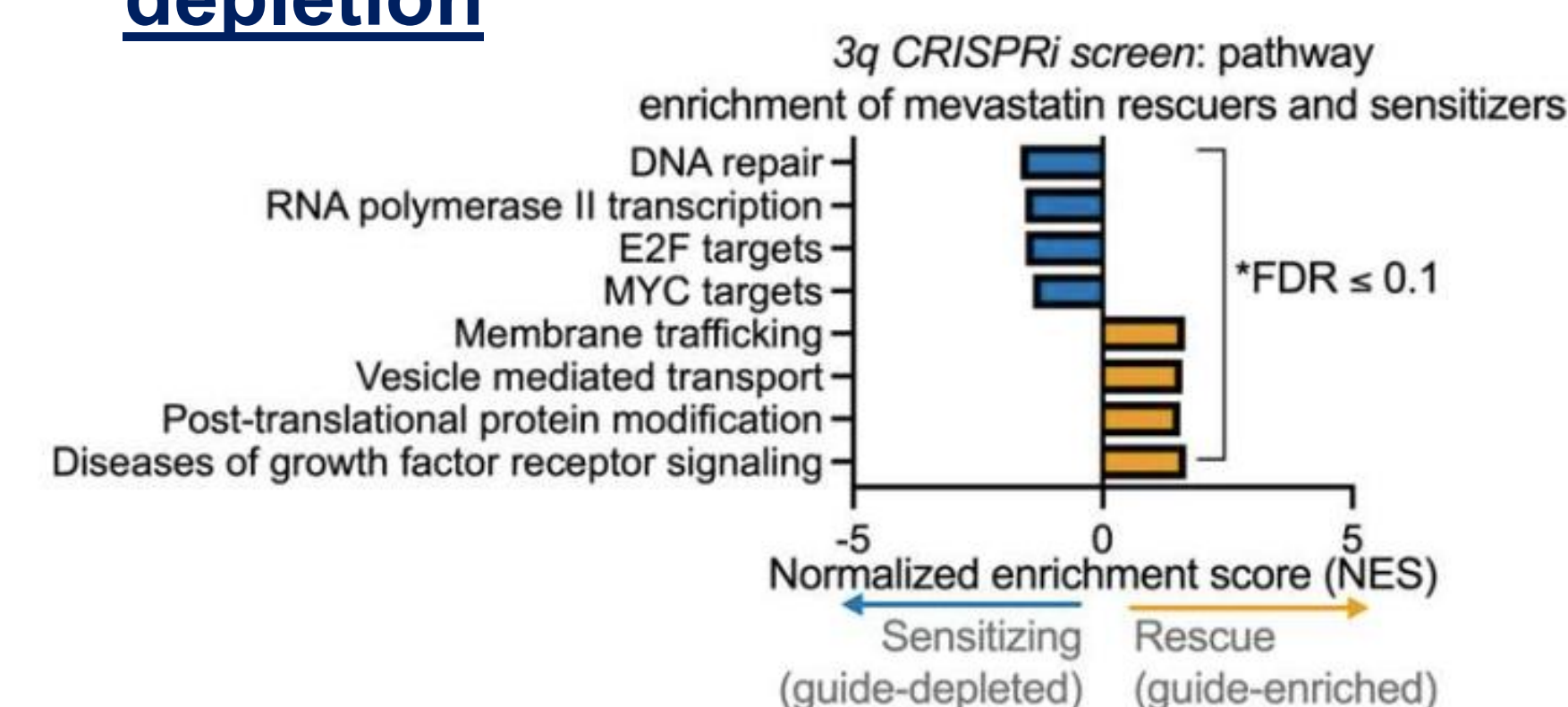


Fig 7. Chr3q CRISPRi screen enrichment analysis in mevastatin treated WT vs 3q gain cells.

Mevastatin treatment modulates chemotherapeutic sensitivity

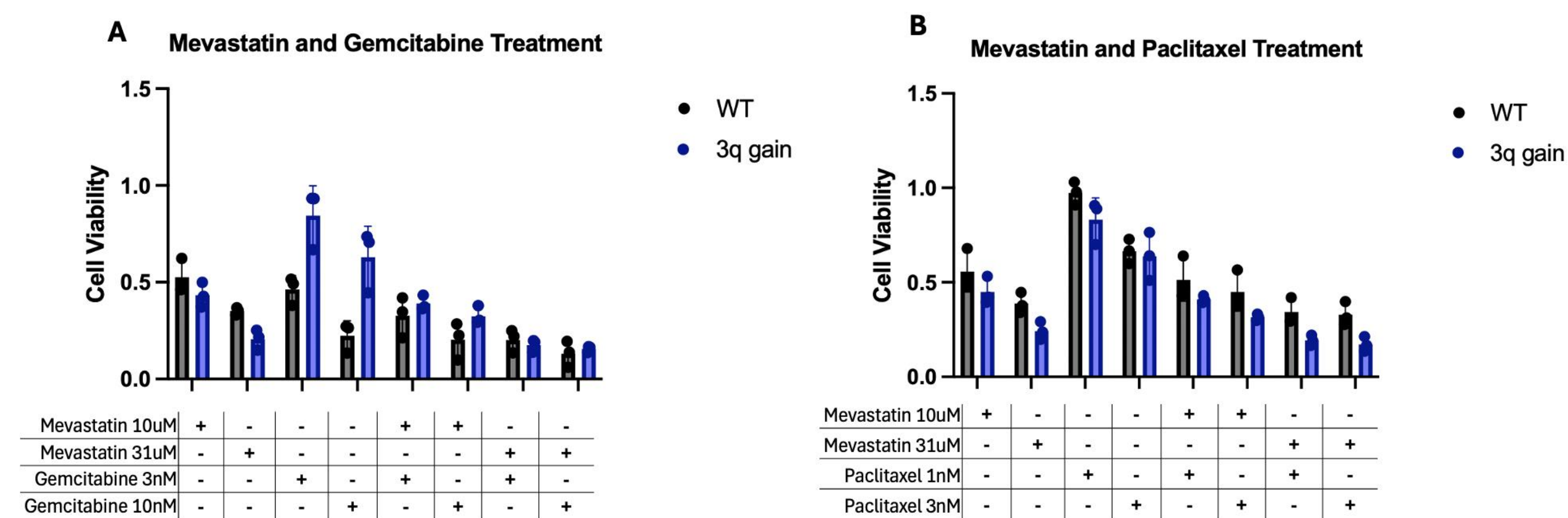


Fig 8. CellTiter-Glo viability of WT and 3q gain cells treated with A) mevastatin and gemcitabine combinations B) mevastatin and paclitaxel combinations.

Conclusions and Future Directions

- Our results show chr3q gain creates a dependency on the SREBP pathway, and correlates with increased genetic dependency on SREBF-1
- RNA-seq and cell cycle studies reveal increased apoptosis with mevastatin treatment, however EdU positive cells were unchanged between conditions suggesting genotype-specific viability differences are due to apoptosis.
- Future experiments include evaluating combination treatments with statins and chemotherapeutics for synergistic effects and determining the metabolic mechanisms underlying this 3q gain dependency.
- Mouse xenograft models will be used to determine effects of tumor volume and growth of statin and chemotherapeutic drug combinations validated *in vitro*.