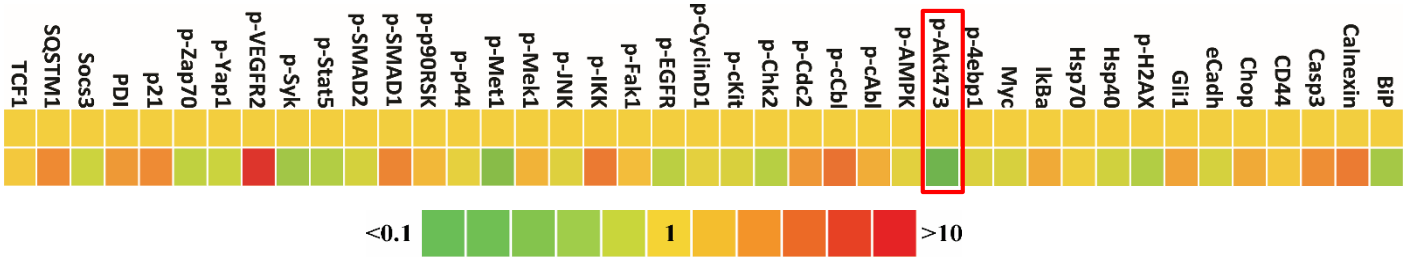
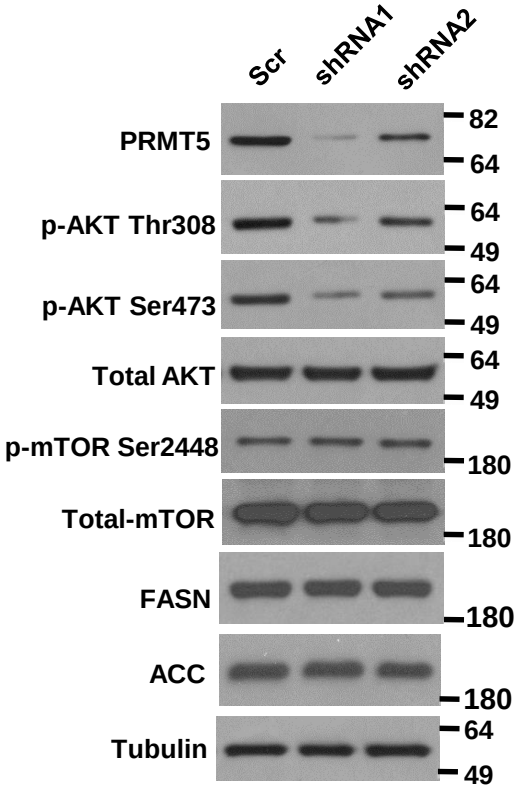
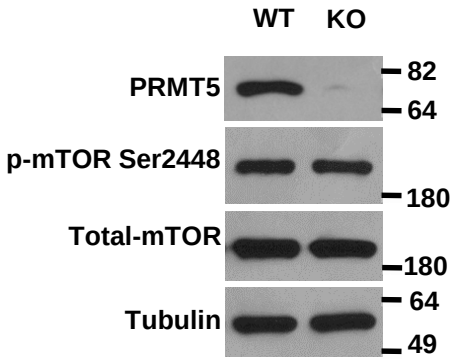
Supplemental Figure 1



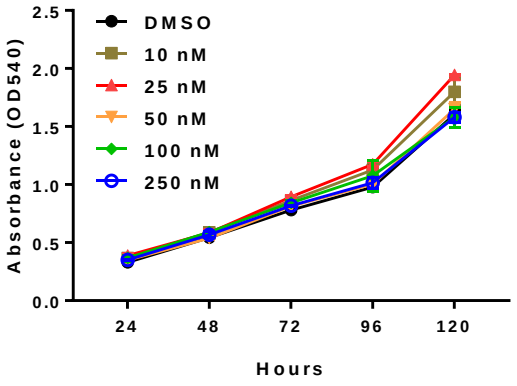
Supplemental Figure 2



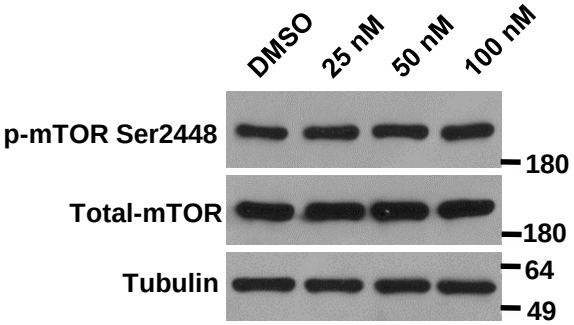
Supplemental Figure 3



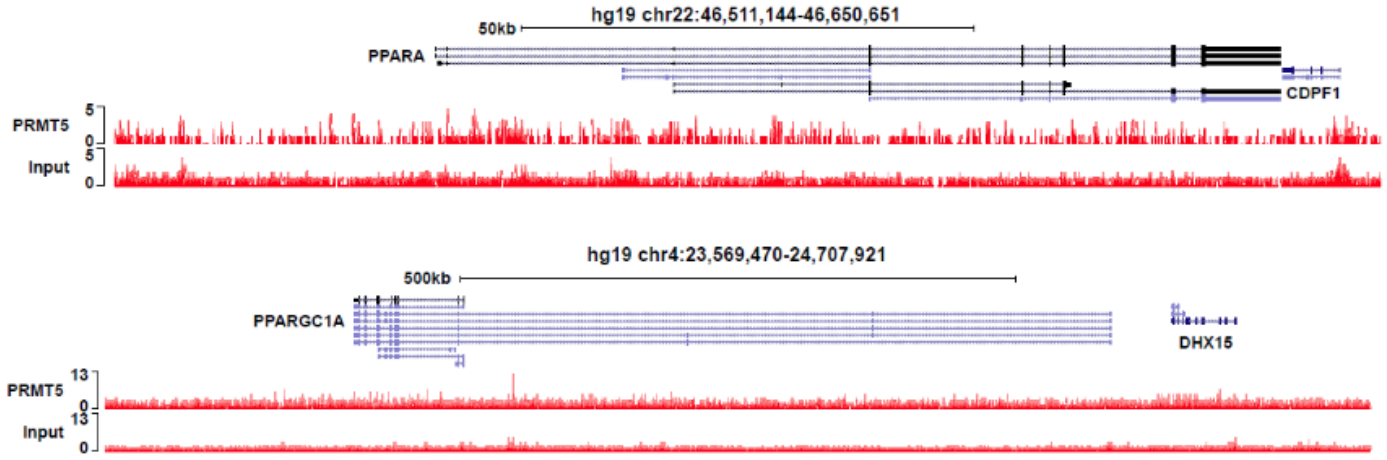
Supplemental Figure 4



Supplemental Figure 5



Supplemental Figure 6



Supplemental Figure 1. Global signaling pathway analysis in PRMT5 knockdown hepatocytes. Activsignal analysis of key protein expression profile in AML12 scramble and shPRMT5 cells. The value was presented as fold changes over scramble. The heatmap was constructed in excel.

Supplemental Figure 2. PRMT5 knockdown does not affect mTOR phosphorylation and de novo fatty acid synthesis pathways. In AML12 scramble and shPRMT5 cells, protein levels of PRMT5, phosphor-AKT Thr308 and Ser473, phospho-mTOR, ACC and FASN were surveyed. Total AKT, total mTOR and tubulin were used as loading controls.

Supplemental Figure 3. Loss of PRMT5 has no effect on mTOR phosphorylation. The expression of PRMT5 and phosphor-mTOR was examined in PRMT5 $^{flox/flox}$ wild type or knockout MEF cells with sample loading normalized by the protein levels of total mTOR and tubulin.

Supplemental Figure 4. PRMT5 inhibitor EPZ015666 has no effect on hepatocyte proliferation. AML12 cells were treated with DMSO or increasing doses of EPZ015666 for 8 weeks. Three thousands of cells from each treated group were seeded in 96-well plate. Cell proliferation was measured in 24 hours interval by adding 10 μL MTT solution (final concentration 5 μg/mL) to each well and incubated for 4 hours. After removal of the media, the plate was air-dried and 100 μL DMSO were added. The plate was incubated at room temperature for 30 min with gentle shaking. Absorbance was measured at OD540 in a Synergy H4 Hybrid microplate reader.

Supplemental Figure 5. EPZ015666 treatment does not change phospho-mTOR levels in hepatocytes. AML12 cells were treated with DMSO or increasing doses of EPZ015666 for 4 weeks. Cells were harvested and total protein was extracted and analyzed for phospho-mTOR levels by Western blotting. Total mTOR and tubulin levels were used as loading controls.

Supplemental Figure 6. Snapshot of PRMT5 ChIP-seq data viewed in UCSC genome browser. PRMT5 binding was aligned to input DNA at gene loci of PPARα and PGC-1α.