Background
The expression and function of signal-regulatory protein alpha (SIRPα; also known as PTPNS1, SHPS-1, CD172a, and P84) is well characterized in myeloid effector cells (e.g.: monocytes, macrophages, neutrophils, dendritic cells and microglia).\(^1,3\) where it contributes to tissue homeostasis and regulation of erythrocyte, platelet, and hematopoietic stem cells (HSC). In addition, it regulates synaptic pruning during neuronal development.\(^4-7\) Another important feature of SIRPα is that, upon engagement by cluster of differentiation 47 (CD47), a trans-membrane protein ubiquitously expressed on all cells and overexpressed on tumor cells,\(^4\) it activates ITIM and ITSM domains to recruit the SH2-domain-containing protein tyrosine phosphatases SHP-1 and SHP-2, thereby inhibiting phagocytosis of tumor cells by myeloid effector cells.\(^3,9\)

Based on its anti-phagocytic property, CD47 is well recognized as a “don’t eat me” signal,\(^10\) together with other anti-phagocytic surface proteins, including programmed cell death ligand 1 (PD-L1),\(^1,5\) beta2 micro-globulin subunit of the major histocompatibility class I complex (B2M)\(^12\) and CD24.\(^13\) Therapeutic blockade of the CD47-SIRPα pathway has therefore become a promising strategy to enhance innate immune clearance of tumor cells and subsequent invigoration of anti-tumor immunity.

Methods
Experimental Procedures
Our analysis using publicly available datasets published in Human Protein Atlas\(^21\) and the Cancer Cell Line Encyclopedia\(^13\) confirmed that SIRPα is expressed in human melanoma and renal cell carcinoma.\(^16\) To explore the role of tumor SIRPα, we designed gRNAs to CRISPR out the SIRPα region that interacts with CD47. Our study using SIRPα-knockout (hereinafter, SIRPα-KO) B16 melanoma cells show that SIRPα-KO B16 cells proliferate comparably to the control SIRPα-wild type (WT) B16 cells in vitro; however, upon implantation in immune-competent (C57Bl/6); B6) mice, but not immune-deficient (i.e., RAGnull) mice, SIRPα-KO B16 tumors grow significantly slower than the control SIRPα-WT B16 tumors. Intriguingly, SIRPα-KO B16 tumors exhibit significantly more activated infiltrating lymphocytes (e.g., CD8+ T cells and macrophages) than SIRPα-WT B16 tumors as evidenced by flow cytometry analysis, immunohistochemistry (IHC) and our single cell RNA-sequencing (scRNA-seq) data analysis. Analysis of our bulk RNA-seq of unstimulated, cultured SIRPα-WT and SIRPα-KO B16 cells allows us to identify Cxcl10, Ccl5 and several other genes and pathways that potentially contribute to the observed growth inhibition of SIRPα-KO B16 tumors in immune competent mice.

Results
Our recent work characterized a novel role of tumor SIRPα in suppressing the anti-tumor adaptive immunity.

Conclusions
SIRPα expression on tumor cells confer resistance to anti-tumor immunity.

REFERENCES