# Stearoyl-CoA desaturase 1 blockade promotes immunogenic clearance of tumors

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## Abstract

Metabolic reprogramming plays a critical role in carcinogenesis, in part due its ability to promote immune suppressive properties within tumors. Agents that specifically target crucial metabolic enzymes utilized by cancer are been actively investigated. However, it is unclear whether inhibition of fatty acid metabolism in tumors affects their immunogenicity. Here, we show for the first time that inhibition of stearoyl-CoA desaturase 1 (SCD1), a key enzyme involved in fatty-acid synthesis and a potential prognostic marker for human cancers, increases the immunogenicity of poorly immunogenic tumors. The enhanced immune activation is accompanied by upregulated endoplasmic reticulum (ER) stress and is dependent on the translocation of ER protein calreticulin to the tumor cell surface. Inhibition of SCD1 increased both recruitment and activation of immune cells *in vivo*, which when combined with PD-1 blockade resulted in potent and durable anti-tumor T cell responses in models of HER2-overexpressing breast cancer. Together, our results indicate that inhibition of tumorigenic *de novo* lipogenesis represents a novel approach to enhance T cell based cancer immunotherapy.

## Figure 1

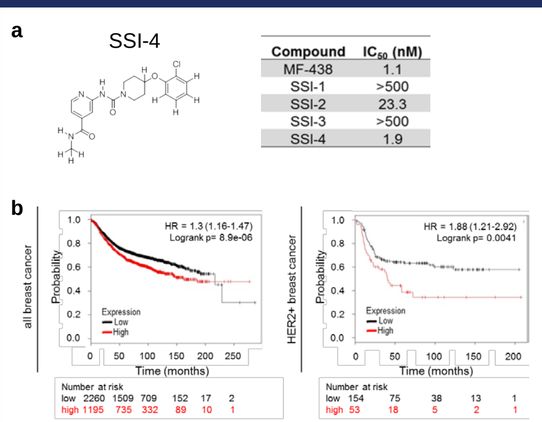


Figure 1. Patient outcome negatively correlates with SCD1 expression. a. SSI-4 is a novel, orally bioavailable inhibitor of SCD1. Shown are SSI-4 chemical structure and $IC_{50}$ determined by LC/MS. b. High SCD1 mRNA expression negatively correlates with patient outcome in all breast cancer, and is markedly enhanced in patients with HER2-enriched tumors.

## Figure 2

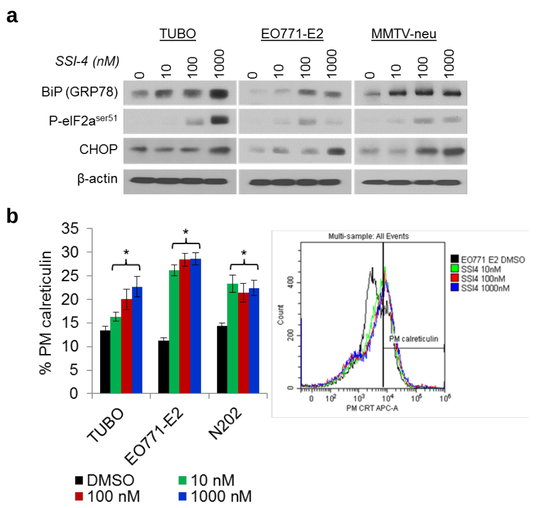


Figure 2. SSI-4 triggers ER stress, resulting in plasma membrane (PM) calreticulin translocation. a. SSI-4 induces activation of the PERK arm of the unfolded stress response. b. SSI-4 promotes PM calreticulin expression, as measured by flow cytometry (FC)

## Figure 3

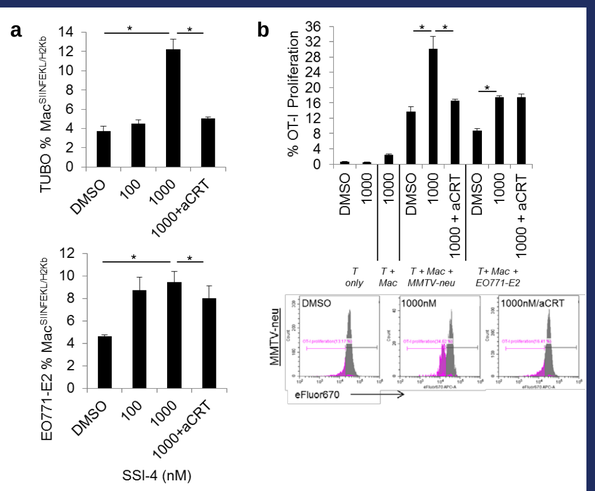


Figure 3. SSI-4 treatment activates the adaptive immune response *in vitro*. a. Increased antigen detection is observed in bone-marrow derived macrophages (BMD) when exposed to cOVA-expressing tumor cells treated with SSI-4. b. CD8 T cell proliferation is observed in OT-I T cells co-cultured with BMD and cOVA tumor cells treated with SSI-4.

## Figure 4

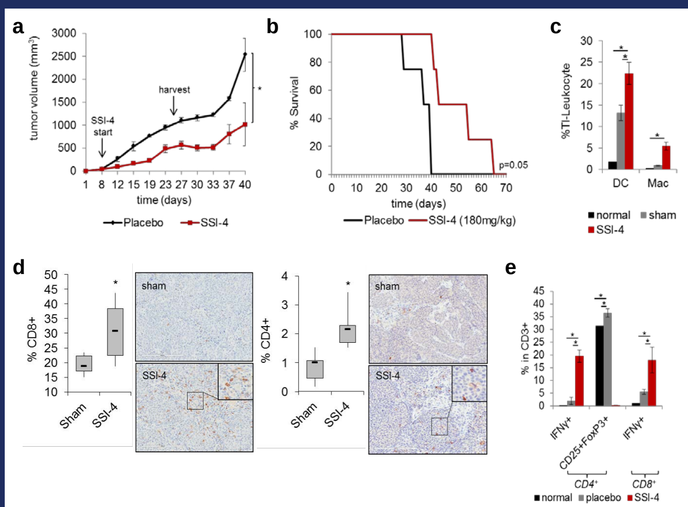


Figure 4. SSI-4 monotherapy promotes intratumor effector T cell recruitment. a-b. SSI-4 monotherapy delays tumor progression and enhances survival of TUBO-bearing immunocompetent BALB/c mice. c. SSI-4 increases the number of intratumor dendritic cells (DC) and macrophages (Mac). d-e. SSI-4 increases intratumor levels of effector CD4 and CD8 T cells, and decreases CD4 T-regulatory population.

## Figure 5

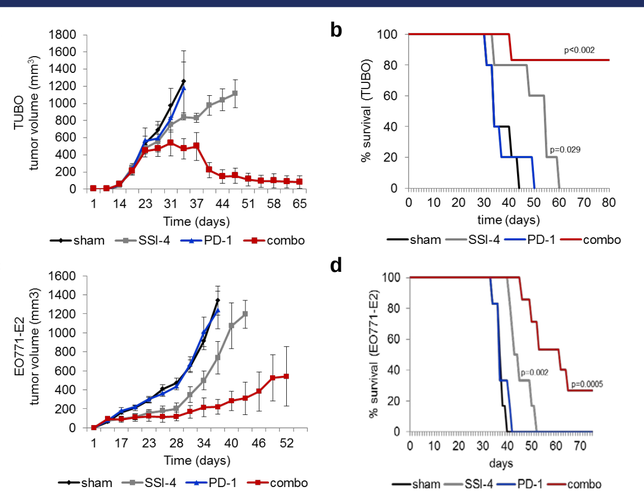


Figure 5. Combination SSI-4 treatment with anti-PD-1 checkpoint blockade produces complete tumor regression in preclinical models of HER2-enriched breast cancer. Tumor growth and survival assessment of either a-b) TUBO-bearing immunocompetent BALB/c mice or c-d) EO771-E2-bearing immunocompetent C57BL/6 mice reveal a synergistic anti-tumor response with combination therapy.

## Discussion

- SCD1 is a broad spectrum anti-cancer target that is overexpressed in numerous aggressive malignancies including breast, renal, lung, ovarian, prostate, thyroid, and colon cancer
- SSI-4 treatment demonstrates activation of the adaptive immune response *in vitro* and *in vivo*
- SSI-4 treatment synergizes with anti-PD-1 checkpoint blockade resulting in complete tumor regression, where SSI-4 monotherapy delays tumor progression and anti-PD-1 monotherapy demonstrates no anti-tumor activity

## Conclusions

- Aberrant *de novo* lipogenesis is linked to tumor immunogenicity
- SCD1 inhibitors such as SSI-4 are immunosensitizing agents, and prime the tumor microenvironment towards a pro-inflammatory phenotype
- SSI-4 may be used as an adjuvant therapy with other immunotherapies including checkpoint blockade

## References

1. Christina von Roemeling, Thomas R. Caulfield et al. Accelerated bottom-up drug discovery platform enables the design of novel stearoyl CoA desaturase 1 inhibitors for cancer therapy. under review (2017) .
2. Florian Rohrig and Almut Schulze. The multifaceted roles of fatty acid synthesis in cancer. Nature Reviews (2016).
3. RA Igal. New insights into a central regulator of cancer metabolism. Biochim Biophys Acta (2016).
4. Peter Sava, Roberto Salgado, et. al. Clinical relevance of host immunity in breast cancer: from TILs to the clinic. Nature Reviews (2016).
5. Lorenzo Galluzzi, Aitziber Buque' et al. Immunogenic cell death in cancer and infectious disease. Nature Reviews (2017)
6. Lucillia Bezu, Ligia C. Gomes-da-Silva, et al. Combinatorial strategies for the induction of immunogenic cell death. Frontiers in Immunology (2015).