In cell culture, SSI-4 demonstrates anti-proliferative synergy with desaturase (SCD1), a key mediator of fatty acid (FA) biosynthesis and rate-limiting in biosynthesis and desaturation is required for HCC survival. Targeting these may prove the critical need for more effective therapeutic strategies. Recent studies indicate lipid chemoresistance associated with HCC. In so doing, we evaluated a novel lead SCD1 inhibitor lipogenic tumor survival mechanism mediated by SCD1 as a means to combat the chemoresistance associated with HCC. In so doing, we evaluated a novel lead SCD1 inhibitor lipogenic tumor survival mechanism mediated by SCD1 as a means to combat the chemoresistance associated with HCC.

**Objectives:** Objectives include demonstration antitumor activity of the lead SCD1 inhibitor. The lead SCD1 inhibitor, is used as a comparator. SSI-1 and SSI-3 IC50 values were >1 uM and mouse weight were monitored over time. ER stress is attenuated in response to SSI-4 inhibition. ER stress is attenuated in response to SSI-4 inhibition.

**Results:** We identified elevated SCD1 mRNA and protein in HCC tissues. SSI-4 dose-dependently inhibits cell proliferation in HCC cell lines with specificity for inhibition of HCC cells and tumors led to endoplasmic reticulum (ER) stress followed by cleaved caspase 3 and ER stress (BIP upregulation), as well as attenuation of Wnt regulated genes based upon signal intensity (0–3) and mouse weight were monitored over time. ER stress is attenuated in response to SSI-4 inhibition. ER stress is attenuated in response to SSI-4 inhibition.

**Conclusions:** Targeting a novel lipid metabolic pathway in HCC may provide antitumor synergy with SCD1 inhibitors.

**Methods:** Paraffin-embedded patient HCC tissue samples were evaluated for SCD1 expression. Western analysis showed that survivin and cMyc were elevated in concert with SCD1 expression in cell lines. As such, we therapeutically targeted a novel epiphenomenon survival mechanism by SCD1 as a means to combat the chemo-resistance associated with HCC. We examined for synergy with FDA approved drugs for HCC such as sorafenib.

**Results:** We identified elevated SCD1 mRNA and protein in HCC tissues. SSI-4 dose-dependently inhibits cell proliferation in HCC cell lines with specificity for inhibition of HCC cells and tumors led to endoplasmic reticulum (ER) stress followed by cleaved caspase 3 and ER stress (BIP upregulation), as well as attenuation of Wnt regulated genes based upon signal intensity (0–3) and mouse weight were monitored over time. ER stress is attenuated in response to SSI-4 inhibition. ER stress is attenuated in response to SSI-4 inhibition.

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**References & Acknowledgements**