A novel polymer-conjugated methionine aminopeptidase 2 (MetAP2) inhibitor SDX-7320 inhibited the growth of EO771 mammary gland tumors and ameliorated the immunosuppressive tumor immune micro-environment (TIME)

Poster #1226

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Introduction

Cancer patients who are obese face a greater risk of dying from certain cancers compared to non-obese patients (Calle, 2003). Obesity may contribute to cancer progression via multiple mechanisms: increased leptin, decreased adiponectin, increased adipose tissue estrogen, elevated insulin (secondary to peripheral insulin resistance), and alteration of the tumor immune microenvironment (TIME) which suppresses host anti-tumor immune responses (Quail, 2019).

Small molecule inhibitors of methionine aminopeptidase type 2 (MetAP2) have previously demonstrated clinical activity both as anti-tumor agents (Kudelka, 1998; Herbst, 2002) and against obesity/type 2 diabetes (Hughes, 2013; Kim, 2015). However, clinical development of some small molecule, fumagillin-based MetAP2 inhibitors has been hampered by CNS toxicity (Bhargava, 1999).

SDX-7320 is a copolymer-drug conjugate of a novel fumagillin-derived MetAP2 inhibitor (SDX-7539) attached via a cleavable amino acid linker to a hydroxypropylmethacrylamide (HPMA) backbone, designed to limit CNS penetration and therefore reduce CNS toxicity.

To evaluate the efficacy of SDX-7320 we utilized a syngeneic model of obesity-accelerated breast cancer, using the mouse mammary gland tumor line, EO771. Anti-tumor efficacy of SDX-7320 was evaluated +/- 5-FU, and the impact of SDX-7320 on the tumor immune microenvironment (TIME) was also assessed.

Now nearing completion of Phase I (NCT02743637), SDX-7320 is being developed to treat cancers whose growth is affected by metabolic hormones such as leptin, insulin, and adiponectin (termed "metabo-oncology"). Further clinical trials with SDX-7320 are planned for 2019, specifically combination studies of SDX-7320 with standard-of-care therapies in patients whose tumors are affected by metabolic hormones.

Materials & Methods

Female C57Bl/6 mice were surgically ovariectomized at six weeks of age (Jackson Lab) and following recovery were placed on a 60% high fat diet (D12492), or a 10% low fat diet (D12450J). EO771 cells (50,000; from CH3 Biosystems) were injected into the fourth mammary gland and followed until tumors reached approximately 50 mm^3 at which time treatment with SDX-7320 (s.c., Q4D, total of four doses) or 5-FU (10 mg/kg, i.p. injection every other day) was initiated.

Fifteen days after initiating dosing, animals were euthanized, plasma was collected and tumors dissected. Three tumors from each group were placed into tissue culture medium at 4^0C and shipped to KCAS Bioanalytical (Shawnee, KS), where the tissue was dissociated and analyzed for MDSC/neutrophil content (CD11b+/GR-1+ cells). Biomarkers were measured in plasma obtained at day 15 using ELISAs (leptin, adiponectin, estradiol) or a multiplexed cytokine array. Tumor samples were fixed in 4% buffered formalin (24 h) then transferred to 70% ethanol prior to embedding in paraffin, sectioning and staining with the indicated antibodies (Wax-It Histology Services, Vancouver, BC).

References

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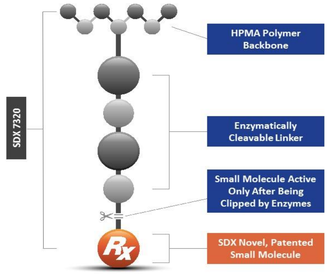
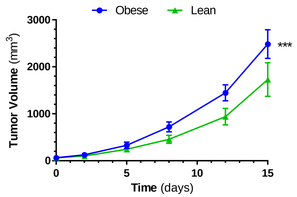
Structure of SDX-7320

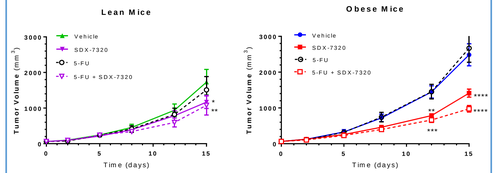


Obesity Stimulated the Growth of EO771 Mammary Gland Tumors



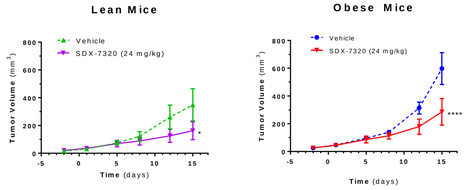
***p < 0.005 two-way ANOVA with multiple comparisons

SDX-7320 +/- 5-FU Inhibited the Growth of EO771 Mammary Gland Tumors



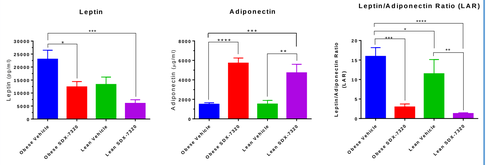
*p < 0.5, **p < 0.01, ***p < 0.005, ****p < 0.001 two-way ANOVA with multiple comparisons

SDX-7320 Inhibited the Growth of EO771 Mammary Gland Tumors in Lean and Obese Mice



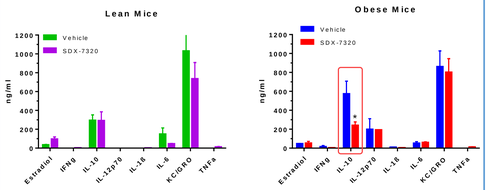
*p < 0.05, ****p < 0.001 two-way ANOVA with multiple comparisons

SDX-7320 Lowered Leptin, Increased Adiponectin, and Decreased the Leptin/Adiponectin Ratio (LAR)



*p < 0.5, **p < 0.01, ***p < 0.005, ****p < 0.001 one-way ANOVA with multiple comparisons

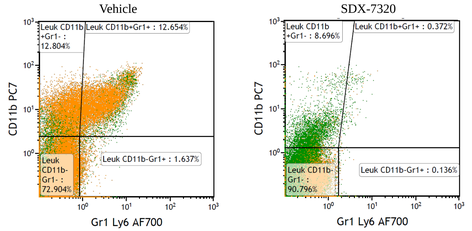
SDX-7320 Decreased Plasma IL-10 in Obese Mice



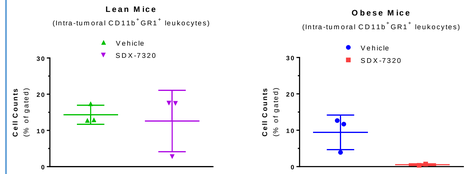
*p < 0.05, one-way ANOVA with multiple comparisons

SDX-7320 Altered the Tumor Immune Microenvironment (TIME)

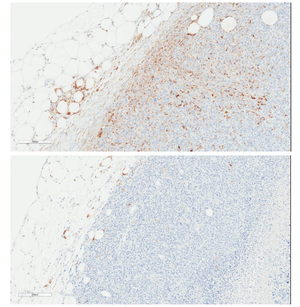
SDX-7320 Eliminated Intra-Tumoral Myeloid-Derived Suppressor Cells (MDSCs)/Neutrophils in Obese Mice



SDX-7320 Eliminated Intra-Tumoral Myeloid-Derived Suppressor Cells (MDSCs)/Neutrophils in Obese, but not Lean Mice

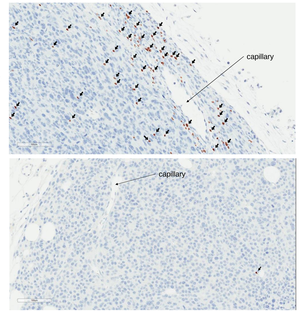


SDX-7320 Decreased Arginase1 in EO771 Tumors from Obese Mice



SDX-7320 Altered the Tumor Immune Microenvironment (TIME)

SDX-7320 Reduced FoxP3 Staining in Tumors from Obese Mice



Summary and Conclusions

- **The MetAP2 inhibitor SDX-7320 significantly retarded tumor growth in a syngeneic model of obesity-accelerated breast cancer.**
- **SDX-7320 exhibited combinatorial efficacy with 5-FU to reduce the growth of EO771 tumors, especially in obese mice.**
- **Favorable changes in circulating adipokines (leptin, adiponectin, LAR) potentially contributed to reductions in tumor growth.**
- **SDX-7320 attenuated the immunosuppressive EO771 TIME:**
  - **Reduction in staining for Arg1 and FoxP3 in the tumor**
  - **Reduction in intra-tumoral CD11b+/GR-1+ cells (MDSC/neutrophils)**
  - **Reduction in plasma IL-10 levels**
- **SDX-7320 may be effective in combination with 5-FU or with immune-modulators whose activity is muted by an immuno-suppressive TIME in patients with obesity/metabolic dysfunction.**
- **SDX-7320 is progressing to Phase 2 clinical trials in cancer patients whose disease may be affected by metabolic hormones.**

Acknowledgements

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