Preclinical activity of SDX-7320 in mouse models of obesity and obesity-driven cancer

Poster #4919

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Introduction

Cancer patients who are obese face a greater risk of dying from cancer compared to non-obese patients (Calle, 2003). Excess visceral adiposity is believed to contribute to metastasis and progression of cancer via multiple mechanisms: increased secretion of the adipose tissue hormone leptin, decreased secretion of adiponectin, increased production of estrogen in adipose tissue, and elevated insulin (secondary to peripheral insulin resistance) as well as the local effects of inflammatory cytokines (Gucalp, 2016).

Small molecule inhibitors of methionine aminopeptidase type 2 (MetAP2) have previously demonstrated clinical activity in cancer patients (Kudelka, 1998; Herbst, 2002) as well as in obesity/type 2 diabetes (Hughes, 2013; Kim, 2015). However, development of some small molecule 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, intended to limit CNS penetration and therefore reduce CNS toxicity. SDX-7320 is currently being evaluated in a Phase I trial of patients with solid tumors (NCT02743637).

Materials & Methods

Binding of test articles to recombinant, human MetAP2 was measured using a custom ELISA, based on a previously published example (Bernier, 2004). This assay measured the ability of test articles to compete for binding of a custom, biotinylated, fumagillin derivative (SDX-9280) to MetAP2. Proliferation of human umbilical vein endothelial cells (HUVECs) was measured using CellTiter 96® AQ_{ueous} One Solution (Promega) after incubating cells with test compounds for 72 hours in culture medium containing 2% fetal bovine serum.

Male C57Bl/6 mice (Taconic) were made obese by feeding a high-fat diet (60 % calories from fat/21% calories from sucrose) for >12 weeks until their average weight was >40 grams. SDX-7320 or vehicle (5% mannitol/water) was dosed subcutaneously (s.c.) every 4 days (Q4D) for 28 days (total of 8 doses), Intraperitoneal glucose tolerance tests (IPGTT) were carried out in the AM (day 24), after 2 hours of food deprivation by injecting dextrose (1 g/kg) into the intraperitoneal cavity at t = 0. Blood samples were obtained via the sub-mandibular gland at the indicated times for measurement of blood glucose.

B16F10 melanoma cells were injected s.c. into C57Bl/6 mice (Jackson Lab) made obese by feeding a high fat diet (D12451, Research Diets) until their average weight was >40 g, as well as into age-matched lean mice (fed D12450B, Research Diets). Treatment with SDX-7320 (s.c., Q4D, total of six doses) was initiated when tumors reached an approximate volume of 100 mm^3.

Female C57Bl/6 mice were surgically ovariectomized at six weeks of age (Jackson Lab) and following recovery were placed upon either a high-fat or low-fat diet as described above. 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 was initiated (s.c., Q4D, total of four doses).

References

Bernier. (2004), *PNAS*, 10768-73.
Bhargava, P. (1999), *Clinical Cancer Research*, *5*: 1989–1995.
Calle, E. (2003), *New England Journal of Medicine*, *348*: 1625-38.
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Hughes, T. (2013), *Obesity*, *21*: 1782-1788.
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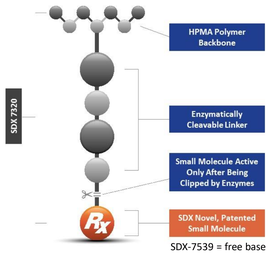
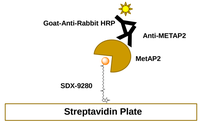
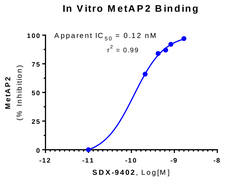
Structure of SDX-7320

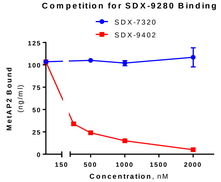


SDX-7539 = free base
SDX-9402 = besylate salt

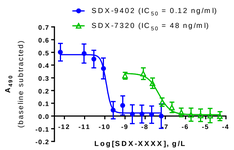
In Vitro MetAP2 Binding





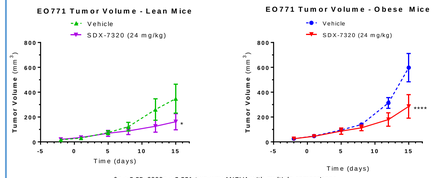


In Vitro HUVEC Proliferation



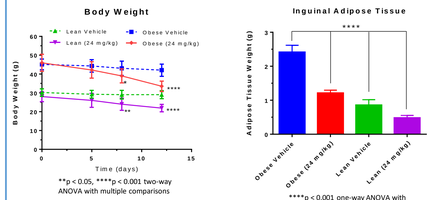
Efficacy of SDX-7320 in Lean and Obese Mice with EO771 Mammary Gland Tumors

Effect of SDX-7320 on EO771 Tumor Growth in Lean and Obese Mice



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

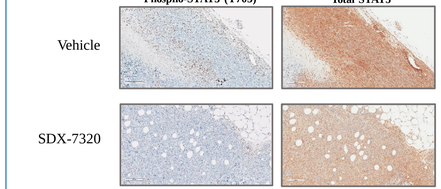
Effect of SDX-7320 on Body Weight and Adipose Tissue Mass



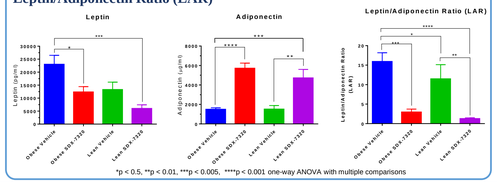
**p < 0.05, ****p < 0.001 two-way ANOVA with multiple comparisons

****p < 0.001 one-way ANOVA with multiple comparisons

Effect of SDX-7320 on Phospho-STAT3 in EO771 Mammary Gland Tumors from Obese Mice



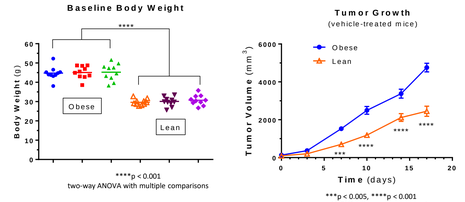
Effect of SDX-7320 on Plasma Leptin, Adiponectin, and the Leptin/Adiponectin Ratio (LAR)



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

Efficacy of SDX-7320 in Lean and Obese Mice with Subcutaneous B16F10 Melanoma

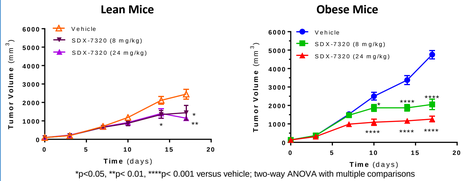
Effect of Obesity on B16F10 Tumor Growth



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

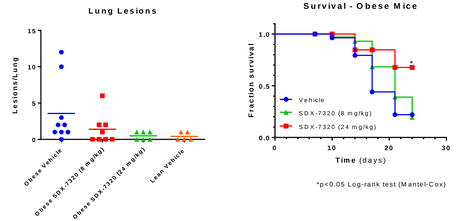
***p < 0.005, ****p < 0.001 two-way ANOVA with multiple comparisons

Effect of SDX-7320 on B16F10 Tumor Growth



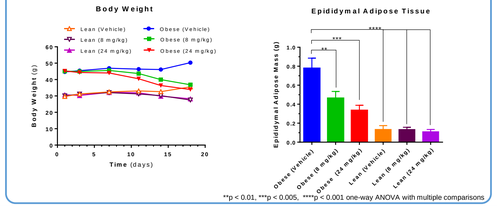
*p<0.05, **p< 0.01, ****p< 0.001 versus vehicle; two-way ANOVA with multiple comparisons

Effect of SDX-7320 on Lung Lesions and Survival in Obese Mice



*p<0.05 Log-rank test (Mantel-Cox)

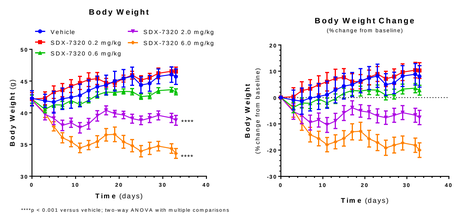
Effect of SDX-7320 on Body Weight and Adipose Tissue Mass



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

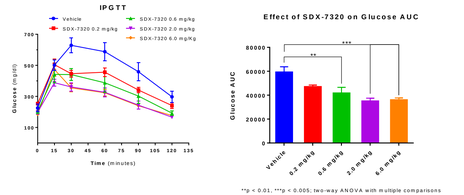
Efficacy of SDX-7320 in Diet-Induced Obese, Insulin-Resistant Mice

Effect of SDX-7320 on Body Weight



****p < 0.001 versus vehicle; two-way ANOVA with multiple comparisons

Anti-Diabetic Efficacy of SDX-7320



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

Summary and Conclusions

- **The MetAP2 inhibitor SDX-7320 significantly retarded tumor growth in two syngeneic models of *obesity-accelerated cancer*.**
- **SDX-7320 normalized plasma leptin and adiponectin levels in mice with EO771 tumors (a model of post-menopausal breast cancer).**
- **SDX-7320 reduced the level of active (phosphorylated) STAT3 in EO771 mammary gland tumors.**
- **SDX-7320 attenuated the growth of subcutaneous B16F10 melanoma, decreased lung metastases (trend, NS) and significantly improved survival.**
- **SDX-7320 significantly decreased adipose tissue mass (a source of tumor-promoting hormones), and also reduced glucose levels in obese, insulin resistant mice after a glucose challenge (IPGTT).**
- **SDX-7320 is currently being evaluated in a Phase I clinical trial in patients with solid tumors (NCT02743637)**

Acknowledgements

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