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

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Introduction
Cancer patients who are obese face a greater risk of dying from cancer compared to non-obese patients (Ekbom, 2003). Excess visceral adipose is believed to contribute to metastasis and progression of cancer via multiple mechanisms including increased secretion of the adipocyte hormone leptin, increased secretion of adiponectin, increased production of estrogen in adipose tissues, and increased levels of cytokines in perilipid membrane as well as the local effects of inflammatory processes (Olshansky, 2010). Small molecules inhibitors of leptin and/or adiponectin (2-MetAP2) have previously demonstrated clinical activity in cancer patients (Kudoh, 1999; Wohler, 2004) as well as in obesity (Brueggeman 3-jb, 2011; Xie, 2015). However, development of small molecules MetAP2 inhibitors has been hampered by CNS toxicity (Boursier, 1999). SDX-7320 is a copolymer drug company of a novel fumagillin-derived MetAP2 inhibitor (SDX-7320), structurally similar to a classically studied and lethal hypophosphorylatable (Bupine) baculovirus, aimed at normalizing CNS inflammation and therefore reduce CNS toxicity (SDX-7320) currently being evaluated in a Phase 1 trial of patients with solid tumors (NCT0274367).

Materials & Methods
Binding of test articles to recombinant human MetAP2 was measured using a custom ELISA, based on a previously published example (Brotman, 2008). The assay was modified slightly by the use of competing MetAP2 inhibitors in the ELISA. Leptin/adiponectin ratio (LAR) was measured using human LAR kit. 

Results

Structure of SDX-7320

In Vitro MetAP2 Binding

Efficacy of SDX-7320 in Lean and Obese Mice with E0771 Mammary Gland Tumors

Effect of SDX-7320 on E0771 Tumor Growth in Lean and Obese Mice

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

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

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

Effect of SDX-7320 on Phospho-STAT3 in E0771 Mammary Gland Tumors from Obese Mice

Effect of SDX-7320 on Phospho-STAT3 in E0771 Mammary Gland Tumors from Obese Mice

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 E0771 tumors (a model of post-metastasized breast cancer).

• SDX-7320 reduced the level of active (phosphorylated) STAT3 in E0771 mammary gland tumors.

• SDX-7320 attenuated the growth of subcutaneous B16F10 melanoma, decreased lung metastasis (tumors), and significantly improved survival.

• SDX-7320 significantly decreased adipose tissue mass (a source of tumor-promoting hormones), and also reduced glucose levels in obese, metaphase resistant mice after a glucose challenge (IPGTT).

• SDX-7320 is currently being evaluated in a Phase 1 clinical trial in patients with solid tumors (NCT0274367).

Acknowledgements
We acknowledge Deirdre Slate and Raphael Nir of SBH Life Sciences (Natick, MA) for conducting ELISA assays and Andrew J. Dannenberg (Weill Cornell Medical College, NYC) for advice. We also thank John L. Herbst, 2015). 

References