Evexomostat/SDX-7320 Significantly Enhances the Efficacy of Nintedanib in Models of Bleomycin-Induced Lung Fibrosis

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Introduction

Interstitial lung disease (ILD) includes a group of diseases that lead to progressive lung fibrosis and hypoxia. Therapies for the management of patients with ILD include corticosteroids [1], immuno-suppressants [2], and for patients with idiopathic pulmonary fibrosis (IPF) the recently-approved anti-fibrotic drugs, nintedanib and pirfenidone [3, 4]. Although these agents provide benefit to IPF patients, more effective treatments are urgently needed [5 - 8].

Methionine aminopeptidase type 2 (MetAP2 or p67) is a multi-functional protein that catalyzes the removal of the N-terminal methionine from nascent polypeptides [9]. Prior studies suggest that MetAP2 is a potential target for the treatment of IPF and other fibrotic disorders. Fumagillin, a natural product inhibitor of MetAP2 was shown to suppress experimental lung fibrosis [10]. Additionally, TNP-470, a synthetic analog of fumagillin, was efficacious in models of intra-peritoneal fibrosis [11] as well as liver fibrosis [12]. Despite these encouraging findings the clinical development of TNP-470 was discontinued because of central nervous system toxicity [13]. Given the potential importance of MetAP2 as a therapeutic target we have developed a novel polymer-conjugated MetAP2 inhibitor (evexomostat/SDX-7320) with the goal of improving the therapeutic index (with respect to CNS toxicity). Importantly, in a recent phase 1 clinical trial of evexomostat/SDX-7320 in advanced cancer patients, neurotoxicity was infrequent and generally mild [14, NCT02743637].

Here, we show that MetAP2 is detected in a variety of cell types that are potentially important in the pathogenesis of IPF. Furthermore evexomostat/SDX-7320 attenuated fibrosis and improved lung function in aged male mice with bleomycin-induced lung fibrosis. Interestingly the combination of evexomostat/SDX-7320 with nintedanib was more potent than either agent alone in suppressing experimental lung fibrosis and improving lung function.

Materials & Methods

MetAP2 expression in control versus IPF lungs was evaluated using a publicly available single-cell RNASeq data set. (http://www.ipfcellatlas.com/).

The effect of evexomostat/SDX-7320 on lung fibrosis and lung function was evaluated in two models of bleomycin-induced lung fibrosis: one using young female mice and another using aged male mice.

Young female mice study (performed at SMC Labs)

Eight-week-old female C57BL/6J mice were instilled intratracheally with bleomycin (3.0 mg/kg, in a volume of 50 µL per animal using a Micro-sprayer® (Penn-Century, USA) and one-week later mice were randomized into groups (n=12/group) based on body weight change from baseline. SDX-7320 was administered subcutaneously in the interscapular region at a dose of 8 mg/kg in a volume of 5 mL/kg every 4 days (Days 7, 11, 15 and 19). Nintedanib was administered orally at a dose of 100 mg/kg in a volume of 10 mL/kg once daily. The animals were sacrificed on Day 21 and lungs were harvested and processed for histology.

Aged male mice study (performed at Aragen)

Seventy-two-week-old male C57BL/6J mice were instilled intratracheally with bleomycin (1.5 U/kg, in a volume of 70 µL per animal) and one-week later mice were randomized into groups (n=10/group) based on body weight change from baseline and penH value. SDX-7320 was administered subcutaneously in the interscapular region at a dose of 8 mg/kg in a volume of 5 mL/kg every 4 days (Days 7, 11, 15 and 19). Nintedanib was administered orally at a dose of 50 mg/kg in a volume of 2 mL/kg once daily. Pulmonary functions (blood saturation, pulmonary resistance and elastance) were evaluated on Day 21 (iSTAT and Flexivent), and all animals were sacrificed on Day 21. Lungs were harvested and processed for histology.

For both studies, quantification of fibrosis (% collagen, pulmonary density and % fibrotic foci) was performed using imaging assay Morpho-Quant®-Lung from digitalized scans of picosirius red (PSR)-stained lung sections (Biocellvia).

Figure 1. MetAP2 Expression in Control and IPF Lungs

From Adams, Science Advances; 08 Jul 2020; ipfcellatlas.com

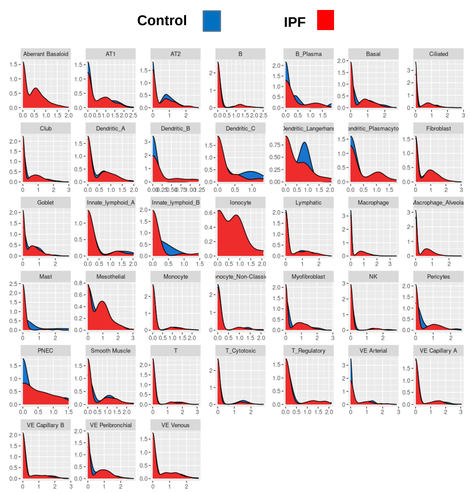


Figure 2. Evexomostat/SDX-7320: A Clinical-Stage, Polymer-Conjugated MetAP2 Inhibitor

Pro-drug of a novel MetAP2 inhibitor (polymer-drug conjugate, PDC)

- *Active component released by lysosomal cathepsins*
- *Designed to limit CNS exposure, avoid toxicity seen with small molecule MetAP2 inhibitors*
- *Improved aqueous solubility relative to small molecule MetAP2 inhibitors*
- *PK properties improved (lower C_{max}, higher AUC, longer $t_{1/2}$) compared to related small molecules*

- ❖ Evexomostat has completed a Phase 1 dose escalation safety study in late-stage cancer patients.
- ❖ Evexomostat is dosed once every 14 days via subcutaneous administration, and was generally well tolerated with only mild to moderate safety findings in the Phase 1 study (NCT02743637).
- ❖ Evexomostat is currently being tested in a study of patients with HR+/Her2- metastatic breast cancer and PIK3CA gene mutation(s) at multiple sites in the US (NCT05455619), and in metastatic triple-negative breast cancer under a research collaboration with Memorial Sloan Kettering Cancer Center in New York.

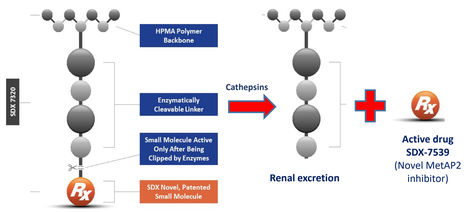
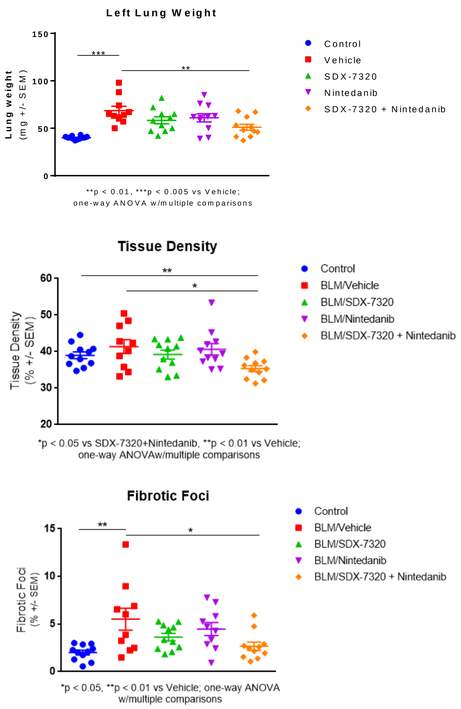


Figure 3. SDX-7320 + Nintedanib Attenuated Lung Edema, Tissue Density and Fibrotic Foci in Young Female Mice



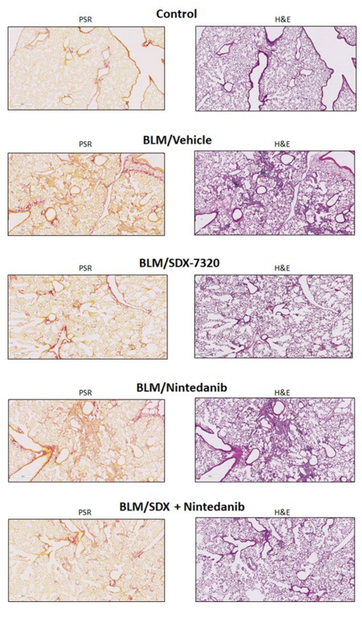
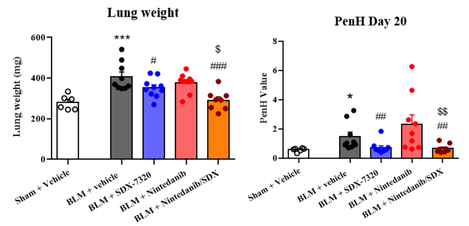
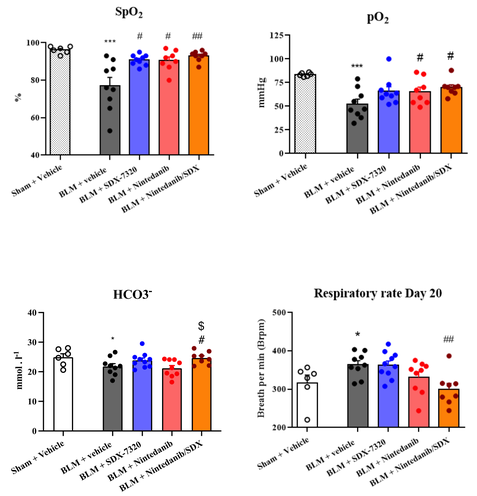


Figure 4. SDX-7320 + Nintedanib Attenuated Lung Edema in Aged Male Mice



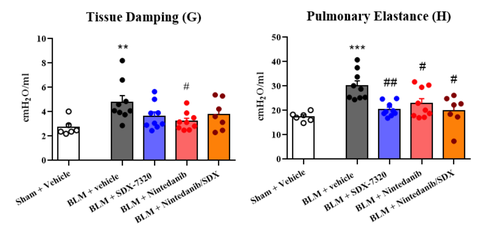
***p < 0.005 vs Sham+Veh; #p < 0.05 vs BLM+Veh; $p < 0.05 vs BLM+Nin; ##p < 0.01 vs BLM+Veh; $$p < 0.01 vs BLM+Nin using one-way ANOVA

Figure 5. SDX-7320 + Nintedanib Improved Blood/gas Exchange Efficiency in Aged Male Mice



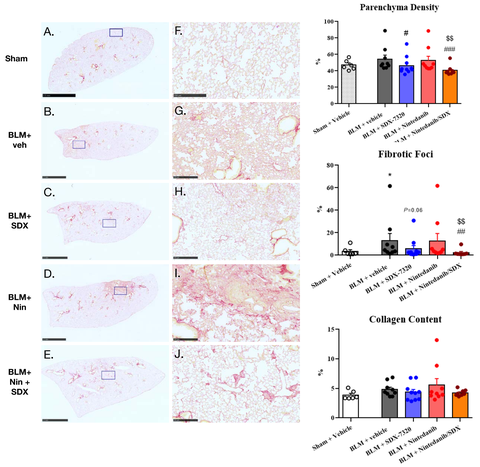
***p < 0.005 vs Sham+Veh; #p < 0.05 vs BLM+Veh; $p < 0.05 vs BLM+Nin; ##p < 0.01 vs BLM+Veh; $$p < 0.01 vs BLM+Nin using one-way ANOVA

Figure 6. SDX-7320 + Nintedanib Improved Pulmonary Resistance in Aged Male Mice



***p < 0.005 vs Sham+Veh; #p < 0.05 vs BLM+Veh; $p < 0.05 vs BLM+Nin; ##p < 0.01 vs BLM+Veh; $$p < 0.01 vs BLM+Nin using one-way ANOVA

Figure 7. SDX-7320 + Nintedanib Attenuated Lung Fibrosis Development in Aged Male Mice



Key Takeaways

- Evexomostat/SDX-7320 alone, and especially when combined with nintedanib, significantly reduced lung edema, improved pulmonary function, reduced fibrotic foci, and improved histological measures of lung fibrosis in bleomycin-treated aged, male mice.
- Evexomostat/SDX-7320 in combination with nintedanib significantly attenuated lung edema and lung fibrosis in young, bleomycin-treated female mice.
- Single-cell RNASeq data from IPF lungs showed significant MetAP2 expression in aberrant basaloid cells, as well as other cell types.

The combination of evexomostat/SDX-7320 with nintedanib may offer unique benefits to patients with IPF.

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