EPS-3903, a Potent Inhibitor of STAT6, Exhibits Preferential Lung and Alveolar Macrophage Distribution With Low Drug–Drug Interaction Potential for the Treatment of Asthma

Lisha Xu, Yang Li, Tianzhu Zang, Daniel Leonard, Jonathan Kibel, Meng Huang, Joshua Klaene, Shucha Zhang, Khanh Hoang, Siu-Lung Chan, Sean Rafferty, Sourav Ghorai, William Cassels, Samuel Bartlett, Yat Sun Or, Li-Juan Jiang

Enanta Pharmaceuticals, Inc., Watertown, MA 02472, USA

Poster #75

Enanta Pharmaceuticals

BACKGROUND

Dysregulated macrophage polarization, particularly toward the M2 phenotype (alternative macrophage activation), is a hallmark of severe asthma that contributes to type 2 inflammation and pathogenic airway remodeling. The Signal Transducer and Activator of Transcription 6 (STAT6) is a master regulator of this macrophage activation pathway and its downstream signaling is critical for initiating allergic inflammation. Consequently, inhibiting STAT6 in macrophages and airway epithelial cells presents a compelling strategy for asthma treatment. Here, we characterize EPS-3903, a novel, potent, and orally bioavailable small-molecule STAT6 inhibitor which demonstrates a favorable pharmacokinetic profile with low drug-drug interaction (DDI) potential.

METHODS

- Intracellular uptake of EPS-3903 was assessed in lung epithelial cells and macrophages across multiple species (mice, rats, and humans).
- EPS-3903 was administered orally at 25 mg/kg to mice and rats. Drug concentrations in plasma, brain, lungs, and alveolar macrophages (AMs) were quantified by LC/MS/MS.
- Drug-drug interaction (DDI) potential was screened using standard *in vitro* assays for transporter inhibition, cytochrome P450 (CYP) enzyme inhibition, and pregnane X receptor (PXR) activation.

RESULTS

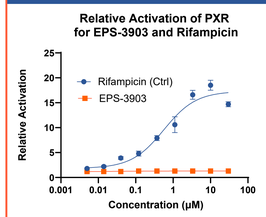
EPS-3903: No Inhibition Across Major Human Cytochrome P450 (CYP) Isoforms

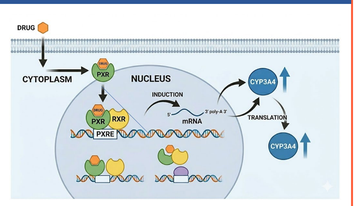
IC_{50} (μM)	1A2	2B6	2C8	2C9	2C19	2D6	3A4/5
DI	>100	>100	49.2	40.6	>100	>100	>100
TDI	>100	>100	49.5	48.6	>100	>100	>100

DI: Direct Inhibition; TDI: Time-Dependent Inhibition

- IC_{50} for different CYP isoforms were greater than 40 μM.

EPS-3903: Negligible Induction Potential With No Activation of the Pregnane X Receptor (PXR)

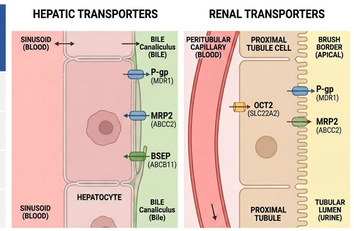




RESULTS

EPS-3903: Low Drug-Drug Interaction Potential

Transporter Inhibition	IC_{50} (μM)
Pg-P[1]	> 20
MRP2[2]	> 20
BSEP[3]	> 20
OCT2[4]	> 20



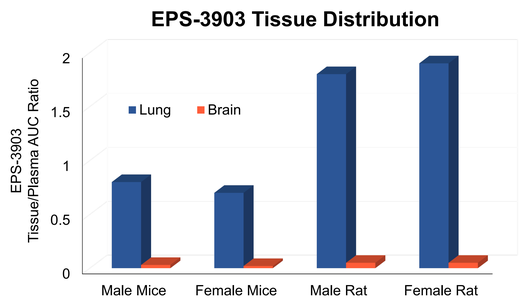
1. P-gp overexpressed in MDCK-MDR1 Cell line; 2. Membrane-bound vesicles made from human embryonic kidney (HEK293) cells; 3.Inverted HEK293-derived human BSEP vesicles; 4. Human embryonic kidney (HEK293) cells stably expressing OCT2; SLC (Solute Carrier); ABC (ATP-Binding Cassette)

- EPS-3903 did not inhibit major renal and hepatic transporters.
- Low potential for bilirubin elevation due to lack of MRP2 and BSEP inhibitions.

EPS-3903: Preferential Lung Distribution With Minimal Brain Penetration

EPS-3903 Tissue / Plasma AUC Ratio				
Tissue	Mice		Rats	
	Male	Female	Male	Female
Lung	0.8	0.7	1.8	1.9
Brain	0.03	0.02	0.05	0.05

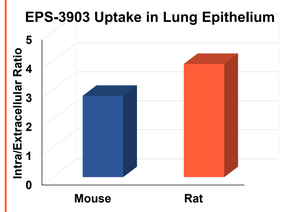
Single Dose PK; p.o. 25 mg/kg for CD-1 mice and SD Rats; AUC: area under the curve.



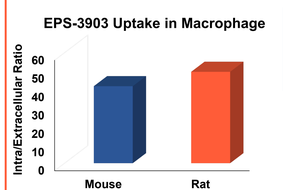
- Brain to Plasma Ratio of < 0.1 indicates no brain penetration.
- No gender differences were observed in tissue distributions.

RESULTS

EPS-3903: Excellent Intracellular Uptake Across Species in Lung Epithelial Cells and Macrophages



Lung Epithelium	EPS-3903 Intra / Extracellular Ratio
Mouse	2.8
Rat	3.9

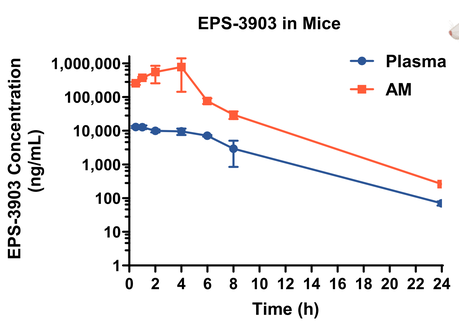


Macrophages	EPS-3903 Intra / Extracellular Ratio
Mouse	41.8
Rat	49.6

EPS-3903: Strong Correlation of *In Vitro* and *In Vivo* Tissue and Macrophage Penetration in Rat and Mouse

EPS-3903	Lung / Plasma Ratio		AM / Plasma Ratio
	Rat	Mouse	Mouse
In Vitro	3.9	2.8	41.8
In Vivo	1.9	0.8	35.1

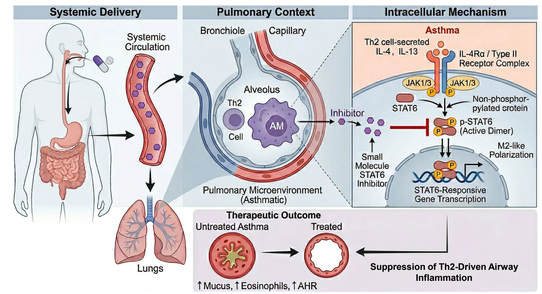
In vitro ratios were calculated based on intracellular and extracellular concentration; *In vivo* ratios were calculated based on drug exposure (area under the curve from 0-24 hours: $AUC_{0\text{-}24}$). AM: alveolar macrophage



Single Dose PK; p.o. 25 mg/kg, male CD-1 mice (Data points were obtained in triplicate)

RESULTS

EPS-3903: Excellent Intracellular Uptake in Human Lung Epithelial Cells and Macrophages



Human Cell Type	EPS-3903 Intra / Extracellular Ratio
Lung Epithelium	5.4
Macrophages	52.6

- EPS-3903 is projected to have excellent target tissue (lungs) penetration for the best efficacy in asthma.

CONCLUSIONS

- Preferential accumulation of EPS-3903 in target tissues (lung and AMs) supports development in asthma.
- No off-target distribution (brain) minimizes the adverse side effects.
- Low DDI potential for EPS-3903 derisks adverse events and hospitalization.
- The favorable profile of EPS-3903 enables co-administration with standard asthma treatments, broadening its utility across diverse patient populations.

REFERENCES

1. Macrophage polarization has been heavily associated with development of asthma. Transl. Res. 2017 Oct 7;191:1–14.
2. Macrophages with reduced expressions of classical M1 and M2 surface markers in human bronchoalveolar lavage fluid exhibit pro-inflammatory gene signatures. Sc Rep. 2021 Apr 15;11:8282.
3. Transcription factors STAT6 and KLF4 implement macrophage polarization via the dual catalytic powers of MCPIP. J. Immunol. 2015 May 1;194(12):6011–6023.