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Discovery of a Potent and Selective KIT Inhibitor for the Treatment of Mast Cell-Mediated Diseases

Tessa Cressey*, Shu-Fan Chou*, Miranda Crepeau, Archie Reyes, Yaohui Nie, Shucha Zhang, Lijuan Jiang, Jiajun Zhang, YukMing Siu, Scott Mitchell, Michael Vaine, Yat Sun Or, Manuel Roqueta-Rivera

Enanta Pharmaceuticals, Inc., Watertown, MA

BACKGROUND

- Mast cell-mediated inflammation has been associated with serious inflammatory and autoimmune disorders with significant unmet need, such as chronic spontaneous urticaria (CSU).
- KIT is a well-characterized receptor tyrosine kinase that provides critical survival, differentiation, proliferation, and activation signals for mast cells.
- In CSU, KIT activation can lead to rapid mast cell degranulation and release of pro-inflammatory tryptases, histamine, and cytokines.
- Inhibition of KIT signaling results in inhibition of mast cell degranulation and in mast cell depletion, representing a promising therapeutic approach for CSU.
- EDP-978 is an oral, small molecule compound that selectively inhibits the tyrosine kinase activity of wild-type KIT for treating mast cell-mediated diseases.

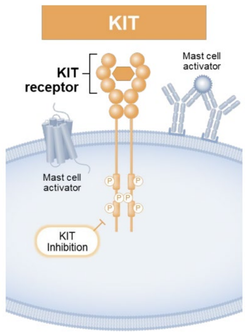


Figure 1. KIT signaling in mast cells

METHODS

- Phosphorylation of KIT in response to stem cell factor (SCF) signaling was assessed in M-07e cells.
- Cellular proliferation assays to assess potency were performed in UT-7 cells and engineered Ba/F3 KIT expressing cells.
- Mast cell (MC) degranulation was measured by β-hexosaminidase release in primary human CD34+ derived MC and primary mouse bone marrow derived MC.
- Selectivity was broadly assessed utilizing a KINOMEscan to screen 468 non-mutant kinases.
- Selectivity against KIT family kinases: CSF1R, PDGFRα, and PDGFRβ, were determined by cellular proliferation assays in engineered Ba/F3 cells expressing the relevant kinase.
- *In vivo* MC depletion after 1 week of oral EDP-978 treatment was measured in the skin (toluidine blue staining) and peritoneal lavage (flow cytometry) of mice.
- *In vivo* KIT potency was assessed in an SCF challenge study with a plasma histamine readout in mice.

RESULTS

EDP-978 is a potent inhibitor of wild-type KIT

Assay	EDP-978 EC_{50} (nM)
KIT K_d	0.3 (K_d)
Phosphorylated KIT M-07e - Cellular	1.6
Endogenous KIT UT-7 - Cellular Proliferation	2.8
Engineered KIT Ba/F3 - Cellular Proliferation	3.3
Primary Human CD34+ Derived Mast Cell Degranulation	3.4
Primary Mouse Bone Marrow-Derived Mast Cell Degranulation	7

Table 1. Potency of EDP-978 in biophysical and cellular assays. Mast cell degranulation measured by β-hexosaminidase. K_d determined by DiscoverX KdELECT. EC_{50}, half-maximal effective concentration. K_d, dissociation constant.

EDP-978 is a selective kinase inhibitor

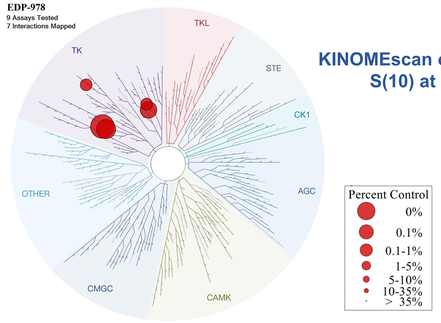


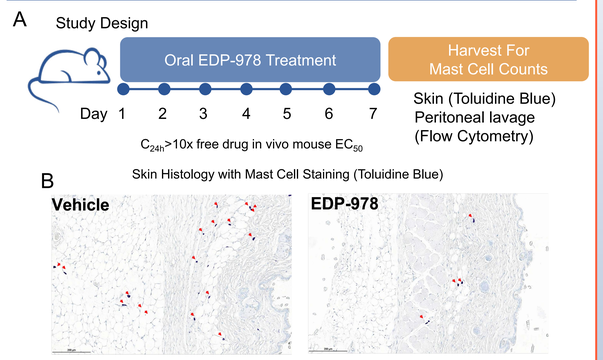
Figure 2. KINOMEscan panel S(10) visualization of EDP-978 at 1 µM. Kinome selectivity assessed at 1 µM EDP-978 against 468 kinases using the DiscoverX KINOMEscan. S(10) = (number of non-mutant kinases interactions within 10% of positive control ligand)/(number of non-mutant kinases tested).

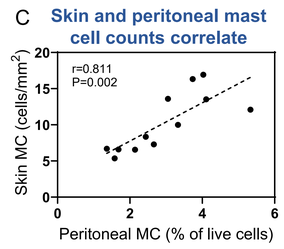
Assay	EDP-978
S(10) at 1 µM, Kinase Selectivity	0.02
CSF1R Selectivity	223x*
PDGFRα Selectivity	930x*
PDGFRβ Selectivity	840x*
FLT3 Selectivity	>30,000x^

Table 2. Selectivity of EDP-978 in biophysical and cellular assays. K_d and S(10) determined by DiscoverX KdELECT and KINOMEscan.
*Based on Ba/F3 proliferation data and relative to Ba/F3 KIT. ^Based on K_d.

RESULTS

EDP-978 depletes mast cells in mice





EDP-978 Depletes 98% of peritoneal mast cells with high expression of the high-affinity IgE receptor (FcεRI)

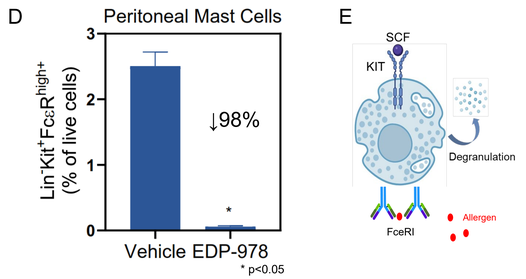


Figure 3. Depletion of mast cells in BALB/c mice with treatment of EDP-978. (A) Male BALB/c mice were treated with EDP-978 or vehicle for 7 days. Mast cell counts determined by toluidine blue staining (skin) and flow cytometry (peritoneal lavage). (B) Skin mast cell toluidine blue staining. (C) Correlation of skin and peritoneal mast cells. (D) Mast cells in peritoneal lavage with high FcεRI expression. (E) Schematic of mast cell degranulation generated using Biorender.

RESULTS

EDP-978 inhibits SCF-mediated histamine release in mice

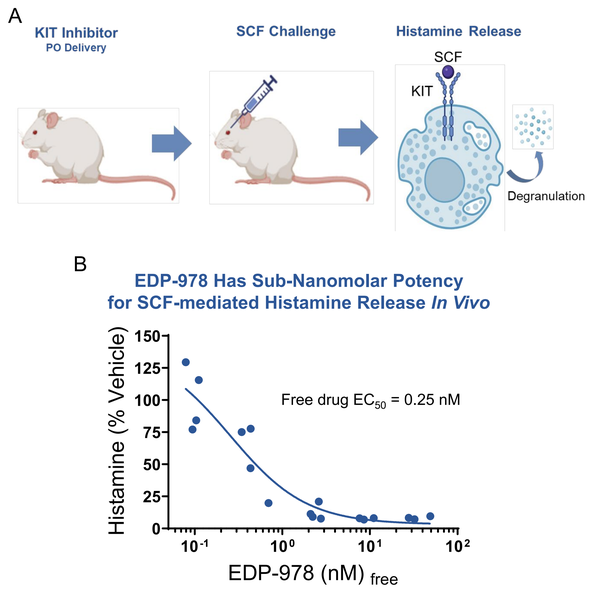


Figure 4. Inhibition of SCF-mediated histamine release in mice treated with EDP-978. (A) Mice were dosed with EDP-978, challenged with SCF, and histamine release into plasma was measured. Biorender generated. (B) Free drug EC_{50} of EDP-978. SCF, stem cell factor.

CONCLUSION

EDP-978 is a potent and selective wild-type KIT inhibitor, which inhibits mast cell degranulation *in vitro* and *in vivo* and depletes mast cells *in vivo*. EDP-978 depletes 98% of peritoneal mast cells with high expression of FcεRI in 7 days. EDP-978 may have therapeutic potential for treating mast cell-mediated diseases.

Disclosure

All authors are either current or former employees of Enanta Pharmaceuticals, Inc. and received salary and stock compensation.

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