Hereditary angioedema (HAE) is a genetic disorder that causes recurrent episodes of tissue swelling in the skin and mucosal membranes. Studies have implicated uncontrolled plasma contact system activation as a primary cause of attacks. Contact system activation generates bradykinin, which increases vascular permeability and inflammation. FXIIa inhibition may provide a novel therapeutic target to prevent the activation and amplification of the contact system in HAE.

This study evaluates the effects of FXII gene knockout and the FXIIa inhibitor KV998083 on angiotensin converting enzyme (ACE) inhibitor captopril-induced vascular permeability and bradykinin-mediated vascular leakage in mice.

Captopril-induced vascular permeability in mice: A carotid is inserted in the right jugular vein and connected to a 100µl Hamilton syringe. Captopril is infused at 2.5 mg/kg followed by Evans blue dye at 30 mg/kg. After 30 minutes of circulation time, the mouse is sacrificed and larynx, trachea and colon are collected.

Evans blue assay: Tissues are weighed and incubated in formamide at 72°C. Samples are scanned at 740 nm for absorbance on a plate reader. Evans blue concentration is calculated by a standard curve and normalized by dry weight of the tissue (ng/mg tissue).

Ex vivo DXS-induced angioedema assay: Citrated blood was collected from WT mice at 30 minutes after IV infusion of captopril at 2.5 mg/kg or vehicle. HK protein levels are measured as above.

Captopril-induced leakage in colon:

Effect of Icatibant upon captopril-induced Evans blue leakage in colon:

- Icatibant is potent and selective inhibitor of Factor XIIa.

- KV998083 Selectivity:

- KV998083 at 1 mg/kg I.V. protects HK from cleavage in mouse plasma exposed to DXS.

- HK levels in mouse plasma are reduced following captopril infusion at 30 minutes.

- Decrease in plasma HK levels indicates that captopril-induced vascular leakage is mediated by bradykinin 2 receptor.

- Administration of KV998083 inhibits captopril-induced leakage in a dose responsive manner.

- Factor XII KO mice were protected against captopril-induced bradykinin-mediated vascular leakage.

- KV998083 administration suppressed captopril-induced leakage in a dose responsive manner (0.3, 1, and 3 mg/kg).

- Captopril-induced leakage with KV998083 administration at 3 mg/kg was not different from FXII KO levels.

- KV998083 achieves protection of HK in plasma.

- FXIIa inhibition may provide prophylactic prevention of bradykinin-induced angioedema.

Conclusion: Factor XII KO mice were protected against captopril-induced bradykinin-mediated vascular leakage. KV998083 administration suppressed captopril-induced leakage in a dose responsive manner (0.3, 1, and 3 mg/kg). Captopril-induced leakage with KV998083 administration at 3 mg/kg was not different from FXII KO levels. KV998083 achieves protection of HK in plasma. FXIIa inhibition may provide prophylactic prevention of bradykinin-induced angioedema.