CAT-5571 is a novel fatty acid cysteine conjugate that can synergistically activate autophagy through the simultaneous inhibition of transglutaminase and activation of AMPK.

**RESULTS SUMMARY**

CAT-5571 is orally bioavailable in the mouse, rat and dog. When mice (n = 16) were dosed orally with CAT-5571 (100 mg/kg, BID) for 3.5 days, autophagy was activated in lung tissues.

**Summary:** CAT-5571 mediates its anti-inflammatory effects through enhancing autophagy in epithelial cells. Studies to develop CAT-5571 for in vivo administration demonstrate CAT-5571 is effective in vivo at enhancing autophagy in lung tissues.

**Application:** Since patients with CF not only have inflammation, but they are also chronically colonized with bacteria, pre-clinical studies were designed to demonstrate the anti-inflammatory potential of CAT-5571 and the overall impact on Pseudomonas aeruginosa colonization. The murine model of CF in which the Cfr gene is either knocked out or dysfunctional can provide a consistent and reproducible model in which to measure the differences in the CF host's inflammatory response to pathogens relative to controls with functional Cfr providing an ideal window for studying anti-inflammatory drugs in the context of ongoing chronic infection.

**Model Specifics:** We used the Cfr gut corrected mouse B6.129(Crfrtm1Kth)Tg(FABPCFTR)1Jaw/Cwr (gut corrected F508del) and controls. For each species (WT and Cfr deficient) there were at least two groups: Pseudomonas aeruginosa infected 10^9 viable CFUs embedded into agarose beads shown in A. The time line of dosing post infection is shown in B.

**I. In Vitro and In Vivo Development of CAT-5571**

**II. In Vivo Therapeutic Testing of CAT-5571 in the Murine Model of CF Infection and Inflammation**

**CONCLUSIONS:**

- CAT-5571 activates autophagy in human colon and human primary bronchial epithelial cells.
- CAT-5571 is bioactive in vivo post-administration into mice, rats and dogs. The end-point of autophagy could be measured in all cases.
- The impact of CAT-5571 appears to be through decreasing intracellular colonization of Pseudomonas aeruginosa.
- In the murine model of CF lung infection and inflammation, CAT-5571 decreased bacterial load and lung neutrophils consistent with improved outcomes in the CF murine model.

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**REFERENCES:**