**Abstract**

- **Background:** In an murine IP sepsis model, comparing with vehicle control 9 hr post infection, FG-630 (60 mg/kg) showed favorable PK parameters in mice with CL of 15.8 mL/min/Kg; Vd of 3.9 L/Kg, T1/2 over 12 hr, rendering a 55% oral bioavailability in urine.

- **UTIs are one of the most common infections worldwide.**

- **LpxC** is a human homologue and its inhibition is cidal to most GN bacteria. The vast majority of LpxC inhibitors reported over the past 20 years utilize a hydroxamic acid metal binding pharmacophore which is a less than optimal therapeutic moiety due to known liabilities, with 50% of FBS, 2.0 mM glucose in drinking water.

- **Introduction**

  - The rise of drug-resistant Gram-negative (GN) infections caused by the ESKAPE pathogens *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacteriaceae* species is an increasing danger to worldwide healthcare.

- **UTIs are one of the most common infections worldwide.** *Enterobacteriaceae* are the main organisms associated with UTIs with *Escherichia coli* responsible for 60-80% of said infections.

- **Fluoroquinolones (FQs) have been used as a mainstay for UTI treatment due to their oral bioavailability and deposition in the urinary tract tissues.** However, there is a clear unmet need for novel oral antimicrobial agents due to the increasing levels of resistance to FQs and other antibiotics used to treat UTIs.

- **FG-630 demonstrated in vitro antibacterial activity against WT and MDR Entero**

- **FG-630 demonstrated in vivo antibacterial activity against GN bacteria, including clinical isolates harboring plasmids containing the resistance genes mer-, EBL, KPC, and NDM. FG-630 showed MIC of >128 mg/L against S. aureus.**

- **In murine IP sepsis model, comparing with vehicle control 9 hr post infection, FG-630 showed 5.34 **and** 5.88, respectively, the bladder by 3.8 and 2.4, respectively, and the urine by 1.44 and 3.92, respectively.**

- **Conclusion:** FG-630 demonstrated in vivo antibacterial activity against WT and MDR Enterobacteriaceae and favorable PK properties in mice. FG-630 significantly reduced CFU burden in the kidneys, bladder and urine of mice in models of MDR IP sepsis and UTI.

**Method and Materials**

- **MICS:** Determined by CLSI M7-A10

- **Strains:** A wide range of clinical and culture collection isolates recovered from worldwide sources including MDR strains expressing mer-, EBL, KPC, and NDM, resistance to antimicrobials and virulence factors.

- **UTI model:**
  - **Preconditioning:** 5 days 5% glucose in drinking water
  - **Mouse Strain:** C57/Bl6 female 20-25g (8 mice per group)
  - **Infection:** Transurethral infection with ~3.9x10^8 CFU/mouse, E. coli UTI199
  - **Treatment:** Insulin post-infection 5, 15, or 60mg/kg IV FG-630 q24h for 3 days. Ciprofloxacin 10mg/kg/day q12h for 3 days

- **Endpoints:** Urine, bladder and kidney were harvested at 24h (pre-treatment group) and 9th post infection and 9th post infection.

**IP Sepsis study**

- **Mice: ICR (CDI) male 25-30g (8 mice per group)

- **Infection:** Bacterial suspension administered IP in 5% hog mucin ~3.7×10^9 CFU/mouse, E. coli ATCC BAA 2469

- **Pain Relief:** Buprenorphine 0.03mg/kg SC

- **Treatment:** Administered IV 1h and 9th post infection, vehicle, FG-630 60mg/kg, or Tigecycline 20mg/kg

- **Endpoints:** IP sepsis score at 1h (pre-treatment group) and 9th post infection quantitatively cultured.

**Summary and Conclusions**

- **FG-630 demonstrated in vitro activity and spectrum against a variety of Gram-negative bacteria, including clinical isolates harboring plasmids containing the resistance genes mer-, EBL, KPC, and NDM.**

- **FG-630 was rapidly distributed into lung, liver and kidney upon dosed at 5 mg/kg, and displayed sustained level of exposure into urine upon dosed at 60 mg/kg to mice.**

- **In the mouse IP sepsis model, FG-630 reduced MDR E. coli biomass, CFU/mL counts in the kidney by 5.55 and 5.88, respectively.**

- **We continue to optimize FG-630 for antibacterial spectrum and physiochemical properties with the aim of developing the first new class of Gram-negative antibiotic in decades.**

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