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Poster abstract submission

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Poster title

Discovery and pre-clinical development of LY256 for the treatment of Clostridioides difficile infection

Poster abstract

Clostridioides difficile infection (CDI) is the leading cause of hospital-associated diarrhoea worldwide, with a high mortality rate among affected patients. The bacterium C. difficile is ranked by the CDC as an 'urgent' threat. Worryingly, rates of CDI in the US and UK have increased in recent years. In 2024, the CDI rate in the UK reached levels previously seen in 2011/2012. The first-line treatment of CDI is antibiotic therapy, either vancomycin or fidaxomicin. However, these antibiotic treatments, particularly vancomycin, disrupt the gut microbiota. Thus, an urgent unmet clinical and market need for new antibiotic treatments remains.

We recently discovered a macrocyclic peptide, LY256 [1] that selectively kills all C. difficile strains tested (MIC = 0.5–1µg/mL) but shown to preserve the protective gut microbiota. We will provide an account of our bulk scale (sub-100g) manufacture of LY256. The toxicokinetic profile of LY256 was determined in rats – when exposed to supratherapeutic oral dose of LY256 at 50mg/kg BID for 5 days, the treatment was well tolerated. Importantly, systemic exposure, i.e. plasma levels, was <10ng/mL for all animals at all time-points.

In the murine model of CDI, LY256 (oral dose 2.5-10mg/kg BID for 5 days) was associated with a significantly greater survival time at the highest dose (compared to vancomycin) and with a significant reduction in spore burden (compared to fidaxomicin). In the in vitro human gut model, LY256 when dosed at 200 mg/L demonstrated a rapid reduction of vegetative C. difficile and a sustained decrease in TcdA/B cytotoxin levels. Toxin levels dropped below the lower limit-of-detection three days post-dosing cessation. Significantly, LY256 had no impact on the microbiota. LY256 is a first-in-class and novel pathogen-specific antimicrobial for the treatment of CDI, with the unique potential to preserve gut microbiota and prevent C. difficile recurrence.

[1] W.C. Chan, S. Genapathy and L. Yang. Antibacterial Compounds (2021) Patent No. US11192888 B2; (2018) EP3596089 B1.

Research topic

Small molecule therapeutics