MONASH University

MONASH INNOVATION

REDUCING REINFECTION RATES FOR VIRULENT FORMS OF *Clostridium difficile*

Novel combination of first-in-line treatment with off-patent compounds that inhibit *Clostridium difficile* sporulation infections, resulting in a reduction in the rates of reinfection and offering improved, cost-effective outcomes for patients.

- **Demonstrated anti-sporulation activity**
- **Anticipated combination therapy using off-patent drugs**
- **Demonstrated reduction in recurrence rates of reinfection**

THE CHALLENGE

Clostridium difficile is a spore-forming bacterium and the leading cause of antibiotic-associated nosocomial diarrhoea worldwide. It results in 250,000 infections and 14,000 deaths each year in the US, at an estimated medical cost of US$1billion (US Centers for Disease Control and Prevention - CDC).[1]

Patient susceptibility to *C. difficile* results from antibiotic treatment for an unrelated condition. Disruption of the natural gut microbiota allows this bacterium to colonise and flourish.[2]

Antibiotics are used to treat most *C. difficile* cases, but are not very effective at managing recurrent or severe disease and there are no vaccines available. There is therefore an urgent need to develop alternative therapies targeting this bacterium.[2]

C. difficile produces spores which are generated in large numbers in the host gut. The Lyras laboratory at Monash University has shown that *C. difficile* spores play a very important role in virulence, causing disease recurrence and increasing disease severity (unpublished data).

Strategies preventing or reducing spore production from *C. difficile* would be invaluable for infection control and disease reduction purposes; however, none are available.

To date, there are no reported molecular targets for the inhibition of sporulation in *C. difficile* nor have any specific inhibitors of sporulation been identified.

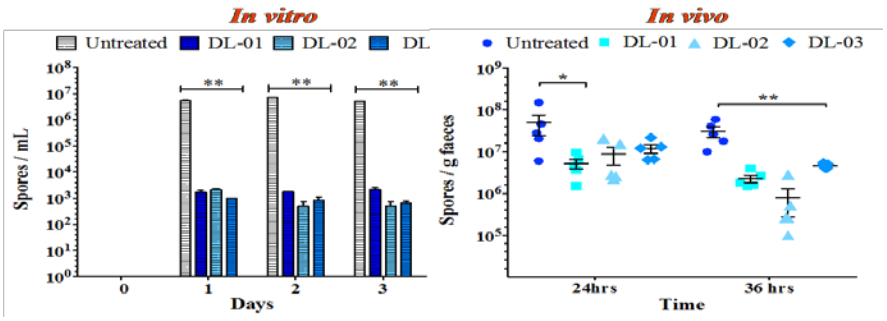

Figure 1. Effect of DL-01*, DL-02*, 03* on *C difficile* sporulation *in vitro* and DL- and *in vivo.* *Generic compounds used in these studies.

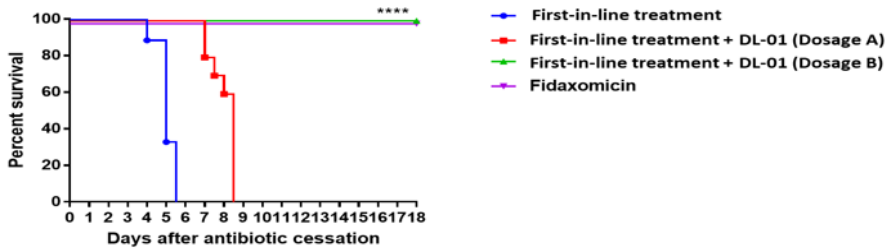

Figure 2. Effect of combination therapy with DL-01* on recurrence rates of *C difficile* infections *in vivo*.

THE TECHNOLOGY

Researchers in the Lyras laboratory have developed novel sporulation blocking strategies. We have identified off-patent compounds that inhibit current virulent forms of *C. difficile* sporulation; no such compounds are available for any spore-forming bacteria.

In vitro studies demonstrate significant decreases in spore survival. Using our mouse infection model;[3] the *in vivo* results are highly significant, with a 13-40 fold reduction in sporulation compared with the generic compounds identified.

We have also identified the molecule targets for these compounds and performed genetic and biochemical DNA structural studies with them.

Excitingly, the team has demonstrated *in vivo* that the combination therapy with current standard-of-care reduces recurrence, transmission and disease severity at level comparable to Fidaxomicin.

Intellectual property: Australian Provisional patent application 2017903760.

THE OPPORTUNITY

We seek a partner to support commercialization of a novel drug combination using current generic drugs, for the treatment of virulent forms of *C. difficile* that result in lower rates of reinfection than is currently achievable.

References

1. Antibiotic Resistance Threats in the USA, 2013. *US Dept Health Centers for Disease Control.*
2. Smits, W (2016). *Clostridium difficile* infection. *Nature Reviews Disease Primers.* Apr 7; 2:16020.
3. Carter, G (2015). Severe intestinal and systemic *Clostridium difficile* disease is associated with Toxin B. *MBio.* 6(3):e00551.

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