First-in-class small molecule inhibitor for treatment and prevention of H. pylori infections

LEAD INVENTOR: Vern L. Schramm

INFECTIOUS DISEASE & ANTIMICROBIAL

BACKGROUND/UNMET NEED

H. pylori is implicated in the development of duodenal or gastric ulcers, early gastric cancer, and gastric mucosa-associated lymphoid tissue Lympho mas. Eradication of this pathogen is recommended. The increasing prevalence of antibiotic-resistant strains of H. pylori and/or suboptimal patient compliance has led to reduced success with traditional treatments, including proton pump inhibitor triple therapies. There is an urgent need for novel new treatments to be developed.

SOLUTION

Dr. Vern Schramm, an expert in enzyme transition state at the Albert Einstein College of Medicine, USA in close collaboration with the Ferrier Research Institute, New Zealand have developed potent selective small molecule inhibitors that prevent H. Pylori infection. The underlying invention is based on the discovery of a novel pathway of menaquinone (vitamin K2) synthesis in H. pylori. The nutrient is essential for growth and survival of H. pylori and is absent in humans and in other human gut microbiota. This has led to development of novel, potent and selective transition state analogue inhibitors of a H. pylori-specific 5'-methyladenosine nucleosidase (HpMTAN). Suitable candidates are capable of tightly binding to the MTAN target, as well as having the ability to penetrate the complex cell membrane found in Gram-negative H. pylori. These potent, selective inhibitors are hard on menaquinone pathway leading to specific targeting of H. pylori infection, while sparing the normal gut flora. These small molecule drugs could be a crucial tool for patients in their fight against the prevalent antibiotic-resistant strain of H. pylori and in face of failure to standard of care treatments.

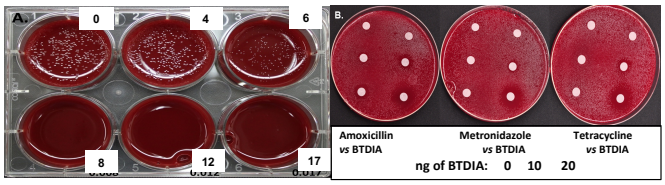

Figure: The effects of BuT-DADMe-ImmA on *H. pylori* growth. **A**. The effects of increasing the concentration of BuT-DADMe-ImmA (ng/ml) on growth on blood agar (one of five experiments in triplicate). **B**. The inhibitory effects of BuT-DADMe-ImmA are compared with amoxicillin, metronidazole and tetracyclin in zone of inhibition studies. Drug quantities per disk were: 0 (top disc), 10 ng (middle disc) or 20 ng (bottom disc). Each specified antibiotic was applied to the disc in the same manner. Small zones of inhibition were seen with 10 ng BuT-DADMe-ImmA (middle right), and large zones at 20 ng (lower right).

APPLICATIONS

- Treatment for H. Pylori infection
- Combination therapy with other antibiotics

ADVANTAGES

- Targets a novel pathway unique to H. pylori
- First-in-class small molecule inhibitor
- Selective and potent inhibitor
- Less harmful side effects as it spares the normal git microbiome
- Mitigates the risk of developing antibiotic resistance in off-target species
- Potentiates bactericidal effects when used in combination therapy
- Efficacy data on mouse model of infection is available

STAGE OF DEVELOPMENT

- Preclinical stage
- Proof of concept studies completed *in vitro*
- Lead optimized
- In vivo data on efficacy is avaiable

RELEVANT LITERATURE

- Wang et al., *Biochemistry* (2012)

INTELLECTUAL PROPERTY

Issued US Patents:

- PCT/US2013/053885

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