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carbonic anhydrase leads for treatment of bacterial infections

Novel, orally bioavailable carbonic anhydrase inhibitors effectively treat drug-resistant Enterococcus and Neisseria gonorrhoeae while preserving the gut microbiome, offering a superior therapeutic alternative to current antibiotics.

Enterococcus

Antimicrobial resistance (AMR) is one of the leading causes of death worldwide and poses a large problem to public health. Enterococcus faecium and Enterococcus faecalis are each responsible for between 100k-250k AMR-related deaths globally, with most infections occurring in acute care facilities. Enterococcus is normally found in the human gastrointestinal (GI) tract, but when the GI microbiome becomes imbalanced, Enterococcus can grow rapidly and cause infections, particularly in healthcare facilities. Enterococcus was previously treated with the antibiotic vancomycin, but this resulted in vancomycin-resistant enterococci (VRE) and required the development of new antibiotics such as linezolid, which are already starting to become less effective against Enterococcus strains. Thus, there is a need to develop novel antibiotics with new modes of action that can be used to treat enterococcal pathogens. Previous work from this group showed that carbonic anhydrase inhibitors have potent responses against VRE. They designed analogs based on the 1,3,4-thiadiazole acetazolamide inhibitor scaffold to target enterococcal pathogens, and in this technology, they developed a drug discovery pipeline to find more efficacious molecules for treatment of Enterococcus. Their lead compounds show comparable results to linezolid in treatment of multiple enterococcal pathogens with improved overall survival of mice models with respect to vehicle and reduced VRE load in peritoneal tissues. Importantly, the inhibitors are narrow-spectrum with no effect on the GIT microbiome, an innovative and critical feature of the class. Further development of the lead compound could result in an efficacious treatment for human VRE infections.

Neisseria gonorrhoeae

Gonorrhea is a sexually transmitted infection caused by the bacteria, Neisseria gonorrhoeae, and it was estimated by the World Health

Technology ID

2025-FLAH-71261

Category

Pharmaceuticals/Drug Discovery & Development
Pharmaceuticals/Pharmaceutical Packaging & Delivery Systems
Pharmaceuticals/Computational Drug Delivery & Nanomedicine
Pharmaceuticals/Small Molecule Therapeutics
Pharmaceuticals/Research Tools & Assays

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Organization (WHO) to infect more than 82 million people worldwide in 2020. This number is likely an underestimate since gonorrhoeae can be asymptomatic and thus exacerbates the spread of the infection between people. The current treatment is an intramuscular injection of ceftriaxone, but some Neisseria strains are already developing resistance to this drug. Additionally, the development of an orally bioavailable drug would be preferable as it is easier to give to a patient. There are two bacterial topoisomerase inhibitors currently in phase III clinical trials for treating gonorrhoeae, but there is still a need to develop new therapeutics with alternative mechanisms of action for treatment of gonorrhoeae. Previous work from this group showed that acetazolamide, an FDA-approved carbonic anhydrase inhibitor, shows potent inhibition of N. gonorrhoeae. Researchers at Purdue University have synthesized a large cohort of bacterial carbonic anhydrase inhibitor compounds and investigated them for activity against N. gonorrhoeae, resulting in several lead compounds with significant in vivo efficacy in an infected mouse model. Further development of the lead compounds could result in an efficacious treatment for human gonorrhoeae infections.

Technology Validation:

Enterococcus

-All analogs act as effectively or order of magnitude more effective than the original FDA-approved hit, acetazolamide, at inhibiting carbonic anhydrase enzymes in bacterial strains

-Most lead analogs had robust metabolic stability in mice liver microsome assays with half-lives greater than 120 minutes

-Lead analogs can significantly improve overall survival of mice in septicemic model and significantly reduce bacterial load in peritoneal tissues, comparable to acetazolamide and linezolid

N. gonorrhoeae

-Two analogs have 4-fold and 8-fold increased in potency against N. gonorrhoeae strains compared to the original FDA-approved hit, acetazolamide, and no cellular toxicity against commensal GI tract organisms or healthy human tissue

-Two analogs have plasma stabilities of 86% and 100% after 3 hours

-One analog was evaluated in mouse model and reduced bacterial burden by 1.5-log10 after one day and 1.72-log10 after three days relative to vehicle control, comparable to ceftriaxone results

Advantages

-Oral bioavailability

-Facile synthesis

-No effect on gut microbiome diversity

Applications

-Orally bioavailable drugs for targeting vancomycin-resistant enterococci and Neisseria gonorrhoeae

Related Publications

1.Kaur, J. et al. J Med Chem. 2020 Aug 11;63(17):9540â€“9562.

2.Hewitt, C.S. et al. ACS Infect Dis. 2021 Mar 25;7(7):1969â€“1984.

3.Holly, K. J. et al. J Med Chem. 2025, Aug 29; published online; doi: 10.1021/acs.jmedchem.5c01584

TRL: 3

Intellectual Property:

Provisional-Gov. Funding, 2025-07-21, United States

Keywords: Antimicrobial resistance, VRE treatment, Neisseria gonorrhoeae therapeutics, carbonic anhydrase inhibitors, novel antibiotics, drug discovery pipeline, narrow-spectrum inhibitors, oral bioavailability, acetazolamide analogs, enterococcal pathogens