COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Penems: Orally Available, Shelf Stable, Broad Spectrum Antibiotics

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Beta-lactams are the most widely used antibiotic class in the treatment of bacterial infections in humans. Among these, carbapenems are the most potent, broad-spectrum FDA-approved compounds on the market, and as such are utilized as the last line of defense against complex multi-drug resistant (MDR) bacterial infections. Carbapenems, however, are administered intravenously, requiring a clinical setting during the entire course of antibiotic treatment. These antibiotics are also inherently fragile to heat, moisture, and often times difficult to purchase during times of shortage due to their synthetic production process, which relies on overseas outsourcing of advanced synthetic intermediates. The penems are a class of beta-lactams that retain the potency of carbapenems but have improved stability due to the presence of a sulfur atom in the heterocycle. Some penem candidates have advanced to Phase III clinical trials, however these do not contain the 2-aminoethylthio sidechain structure that attributes increased potency in the carbapenems. The Johns Hopkins University (JHU) has developed a new series of penem structures that retain those structural features for the treatment of mycobacterial infection, and has shown unprecedented efficacy against the increasingly problematic Mycobacteroides abscessus (M. abscessus). In previous work, these compounds have shown promising pharmacokinetic properties for beta-lactams and were effective in mice against mycobacterial infection, including tuberculosis and M. abscessus.

Additional drugs for the treatment of complex bacterial infections are needed for warfighters as well as the general population. Battlefield applications require broad-spectrum solutions that can be used outside of the clinical setting. Fluoroquinolines, despite their harsh side effects, remain the broad-spectrum antibiotic of choice against most complicated infections1,2 and more options are required in the inevitable emergence of fluoroquinolone-resistant strains.

The Johns Hopkins University Applied Physics Laboratory (JHUAPL) identified these penems as potential orally available, shelf stable, broad-spectrum antibiotics. JHUAPL has tested novel, orally administrable, penem antibiotics against a large variety of bacterial agents for their minimum inhibitory concentration (MIC) values and has found that in comparison to currently used therapeutics, these compounds have similar broad-spectrum activity to carbapenems and improved activity in most cases to fluoroquinolones and other commonly prescribed antibiotics. Alone, these compounds have activity in MDR strains of 4/6 ESKAPEs, a set of highly virulent and antibiotic resistant pathogens common to nosocomial infection.

1. Joint Trauma System Clinical Practice Guideline (JTS CPG): Infection Prevention in Combat-related Injuries (CPG ID:24), 2021.

2. Joint Trauma System Clinical Practice Guideline (JTS CPG): Acute Traumatic Wound Management in the Prolonged Field Care Setting (CPG ID:62), 2017.

Antibiotics were designed, synthesized and provided by the Craig Townsend laboratory at the Johns Hopkins University and experiments were guided by recommendations and procedures provided by Eric Nuermberger and Gyanu Lamichhane at the Johns Hopkins Medical Institute.