THE USE OF AI AND ADVANCED COMPUTER SYSTEMS TO DEVELOP DRUGS AGAINST NEW EMERGING THREATS

Development Of A Potent Lpxc Inhibitor From Structural Insights And Machine Learning Analysis For Post-exposure Prophylaxis Treatment Of Antibiotic-resistant Burkholderia Pseudomallei In A Murine Infection Model

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The UDP-3-O-(R-3-hydroxymyristoyl)-N-acetyl-glucosamine deacetylase, LpxC, is an attractive target to create a novel class of small molecule inhibitors as antibacterial agents specific to Gram-negative bacterial pathogens, including the biodefense pathogen B. pseudomallei. Here, we report the development of VB-233 from structural and ligand dynamics insights as well as machine-learning-based safety evaluation. VB-233 displays outstanding antibiotic activity against 30 strains of clinical isolates of B. pseudomallei in vitro. VB-233 shows excellent bioavailability in the lung epithelial lining fluid in B. pseudomallei infected mice when delivered orally (PO) or via intraperitoneal (IP) injection. VB-233 treatments (PO or IP) dose-dependently rescued mice from the lethal B. pseudomallei infection in comparison with the vehicle group ($p < 0.0001$), and the murine survival rates in VB-233 treatment groups at dosing levels of 30 mg/kg q12h or higher (PO or IP) were significantly better than that from the standard-of-care ceftazidime arm (150 mg/kg q6h via subcutaneous injection; p range 0.001-0.05). Importantly, treatment of VB-233 more rapidly reversed the murine body weight loss caused by B. pseudomallei infection than the standard-of-care ceftazidime, suggesting that oral VB-233 developed from structural insights and machine learning algorithms is a more effective and faster acting antibiotic than ceftazidime.

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