Repurposing Non-Antibiotic Drugs for Tuberculosis Treatment Through Host Modulation

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Technology description

A novel technology treating mycobacterial infections (Mycobacterium), especially M. tuberculosis using a PARP inhibitor.
The use of poly ADP ribose polymerase (PARP) inhibitors (preferably, low toxicity PARP inhibitors such as veliparib, among others) in the treatment of tuberculosis, especially pyrazinamide-resistant diseases, provides more effective alternatives to pyrazinamide. Pyrazinamide, a potent antituberculosis agent acts through inhibition of the host enzyme PARP. Using structurally unrelated PARP inhibitors in place of PZA could prevent antagonisms caused by isoniazid and increase the effects of combination drug regimens in the treatment of tuberculosis.

Background

Pyrazinamide (PZA) is a significant drug, with its powerful sterilizing activity, in fighting tuberculosis, a disease caused by mycobacteria that affects mammals. The most accepted explanation of PZA activity is intracellular acidification and proton gradient uncoupling by pyrazinoic acid (POA) diffusion across the cell wall. POA is a potent inhibitor of PARP at levels that are readily achieved during conventional PZA therapy. When PZA is activated into POA by the tuberculosis enzyme pyrazinamidase, the macrophage poly ADP ribose polymerase (PARP) is inhibited, which contributes to pyrazinamide’ s antimycobacterial activity and prevention of depletion and necrosis. However, an interference in this process occurs in mutations of PZA, which results in the inability for host PARP inhibition to occur. PARP inhibitors such as veliparib are not involved in the trapping of PARP at DNA breakage sites and have much lower side effects in both animal models and clinical studies. Antagonisms may also occur between PARP and another tuberculosis drug called isoniazid, as well as with its metabolites that may activate PARP in response to interactions. Structurally unrelated PARP inhibitors instead of PZA could prevent antagonism caused by ГNH, and maximize the effects of combination drug regimens in TB and MDR-TB.

Technology Description

Researchers at the University of New Mexico have developed a novel technology treating mycobacterial infections (Mycobacterium), especially M. tuberculosis using a PARP inhibitor. The use of

PARP inhibitors (preferably, low toxicity PARP inhibitors such as veliparib, among others) in the treatment of tuberculosis, especially pyrazinamide-resistant diseases, provides more effective alternatives to pyrazinamide. Pyrazinamide, a potent antituberculosis agent acts through inhibition of the host enzyme PARP. Using structurally unrelated PARP inhibitors in place of PZA could prevent antagonisms caused by isoniazid and increase the effects of combination drug regimens in the treatment of tuberculosis.

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Application area

Maximize effects of combination drug regimens in treating tuberculosis and MDR-TB
Resolves a host-directed target of pyrazinamide activity
Treat PZA resistance and prevent PZA-INH antagonism
Inhaled PARP inhibitors to treat tuberculosis
Has multiple roles in cellular responses to genotoxic and oxidative insult
PARP-1 functions as a DNA damage sensor
PARP inhibition screens to discover new tuberculosis drugs
Measurements of host PARP activity to determine optimal therapy for tuberculosis

Institution

The University of New Mexico

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