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MEP Pathway: A Novel Pathway for New Antibiotics

Prabagaran Narayanasamy*

Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

In recent times the World Health Organization estimated that around 1/3rd of human population has latent *Mycobacterial tuberculosis* (TB). Among them 8 million develop active disease and 3 million expire every year. Out of that, around 20% of cases are multiple drug resistant tuberculosis (MDR-TB), resistant to the main first-line drugs like isoniazid and rifampin, and 2% are extensively drug resistant tuberculosis (XDR-TB), resistant to isoniazid, rifampin, fluoroquinolones and at least one of three second-line drugs (amikacin, kanamycin, or capreomycin). However, no new classes of anti-TB drugs or drug formulations have been introduced clinically since the 1980's and it is very important to explore new opportunity [1].

In addition human immunodeficiency virus (HIV) is a global infectious disease causing significant morbidities and mortality in human. Further complicating disease outcomes are combined HIV and TB co-infections. Over and above the frequent occurrence of HIV-TB co-infection can enhance development of MDR-TB and XDR-TB. Therefore, improvements in drug discovery through novel pathway are needed immediately. In this context, the design and development of novel inhibitors of methyl erythritol phosphate (MEP) pathway is of great interest. This MEP pathway is unique to pathogens and therefore it will not create any toxicity to humans.

Furthermore, Gram-negative bacteria also cause intra-abdominal infections, urinary tract infections, nosocomial pneumonia, and bacteremia. *Escherichia coli, Acinetobacter baumannii* and *Pseudomonas aeruginosa* are important pathogens in the hospital setting, accounting for 37% of all pathogens and 65% of all Gram-negative pathogens causing healthcare-associated infections. Also, the Gram-negative bacteria could easily develop resistance and are resistant to multiple drugs and are increasingly resistant to most available antibiotics. These bacteria have abilities to mutate and find new ways to be resistant and they are capable to pass along genetic materials that allow other bacteria to become drug-resistant as well. Nowadays antibiotic-resistant infections pose critical challenges to clinicians in relation to diagnosis, treatment, and infection control. The estimates of the healthcare costs to the world economy for antibiotic-resistant infections have risen as high as $40 billion. But the treatment options to meet this resistant challenge are increasingly limited. There is an important need for non-traditional antibiotics and new class to meet the needs of patients.

To date two different biosynthetic pathways have been revealed leading to isopentenyl diphosphate, the universal precursor of isoprenoids. The mevalonate pathway is observed in animals whereas the non-mevalonate or MEP pathway is observed in many bacteria, some protozoa and plants. Since the MEP pathway is not found in mammalian cells, it is considered a fascinating target for the development of antimicrobials, antimalarial and herbicidal agents a theorem that is being explored by an increasing number of researchers. In MEP pathway Dxs is used to synthesis Dxp [2]. Followed by IspC to synthesize MEP by reducto isomerization. Then IspD transfers cytidyl to synthesize cytidine di phosphate methyl erythritol (CDPME) [3]. Subsequently, IspE is used to phosphorylate CDPME [4] to form cytidine di phosphate methyl erythritol di phosphate (CDPME2P) [1], followed by cyclization to methyl erythritol cyclo diphosphate (MECPP) [5] by IspF. Consequently, IspG ring opens MECPP to form 1-hydroxy-2-methyl-2-*E*-butenyl 4-diphosphate (HMBPP). Finally, IspH catalyzes HMBPP to form isopentenyl di phosphate. Therefore Dxs, IspC, IspD, IspE, IspF, IspG, and IspH have a great potential to be a chemotherapeutic drug target. HIV-TB, MDR-TB, XDR-TB and drug resistant bacteria can be checked by this mechanistic study and kept in control. This area of research could be more useful to contain the bioterrorism and infectious diseases in future by understanding its growth and modification in its biosynthesis.

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***Corresponding author:** Prabagaran Narayanasamy, Department of Pathology and Microbiology, College of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, 68198, USA, Tel: 402-559-9120; Fax: 402-559-6018; E-mail: p.narayanasamy@unmc.edu

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