tion techniques such as Molecular Beam Epitaxy and Metal Organic Vapour Phase Epitaxy. He described the growth of heterostructures like AlGaAs/GaAs, AlGaAs/InGaAs/GaAs and InGaAs/GaAs multiquantum well structures. These multilayers have been characterized by him using high-resolution X-ray and high-resolution transmission electron microscopy, and photoluminescence and some of their device characteristics explained.

T. P. Pareek, Max Planck Institute, Germany described spin transport in a two-dimensional electron gas. 'Physics on a quantum cascade laser' was a talk given by Tapash Chakraborty, Institute of Mathematical Sciences, Chennai. The quantum cascade laser could be used for quantum engineering of new laser materials and light sources. It is a new nanostructured light source in the mid-infrared range. Anand P. Pathak described the ion beam irradiation effects on the strains in GaAs/InGaAs multilayers of semiconductors. Strained layer superlattices have potential device applications. Ion irradiation can induce lattice strains, with the strains produced depending on the extent of lattice mismatch and layer thickness. The induced strain can be used to engineer devices by tailoring the band structure of interest to materials scientists for varied applications.

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RESEARCH NEWS

Mevalonate-independent pathway of isoprenoids synthesis: A potential target in some human pathogens

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The rapidly increasing resistance of many human pathogens to all currently available drugs has become a serious health problem around the globe. Among these pathogens, *Mycobacterium tuberculosis* still poses a major human threat causing tuberculosis in the lung, and is responsible for more than one-quarter of all preventable adult deaths in the world[1]. In addition, the emergence of various multidrug resistance mycobacterial strains, generates an urgent demand for novel therapeutic approaches. Another leading human pathogen, *Plasmodium falciparum* causing malaria, also accounts for one of the world's worst health problems leading to 1.5 to 2.7 million deaths annually. These deaths are primarily among the children and pregnant women[2]. *Helicobacter pylori*, a human gastric pathogen, is an etiologic agent of chronic active gastritis, peptic ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma; 70 to 90% of the population in developing countries carries this pathogen[3]. Therefore, it has become more important to understand the operation of various metabolic pathways existing in these pathogens, to find a suitable target that can be used in developing drugs against them. One such metabolic process occurring in these microorganisms is that they all utilize the same common mevalonate-independent (non-MVA) pathway of isoprenoids synthesis that was first discovered by Rohmer and coworkers in the early nineties, while studying the biosynthesis of hopanoids (a pentacyclic triterpenic sterol surrogates) from different bacterial species[4].

All isoprenoids in various systems are synthesized through the two common precursors, isopentenyl diphosphate (IPP; C_5 unit) and its isomer dimethylallyl diphosphate (DMAPP; C_5 unit)[5,6] (Figure 1). Among the various systems, plants contain majority of isoprenoids, e.g. mono-, sesqui- and diterpenes and carotenoids. Major isoprenoids found in several bacteria are various quinone derivatives having prenyl side-chains such as ubiquinones and menaquinones, along with polyprenol (bactoprenols) molecules, while in the human system cholesterol, various steroid hormones and bile acids are synthesized via a common precursor, squalene – a triterpene. All these isoprenoids and their derived components in various systems have several known physiological and biological functions as well[5,6]. More recently, the long accepted common view that all isoprenoids are synthesized through the acetate–mevalonate pathway is being questioned[7–10], and the whole story has been changed after the discovery of the non-MVA pathway for biosynthesis of certain class of isoprenoids in several bacteria, green algae and various plant species[11–14]. The synthesis of IPP and DMAPP via non-MVA pathway starts with the formation of 1-deoxy-D-xylulose-5-phosphate (DOXP) by two glycolytic intermediates, pyruvate and glyceraldehyde-3-phosphate. DOXP is also known to be used as precursor in the biosynthesis of thiamine (vitamin B1) and pyridoxol (vitamin B6)[15,16] (Figure 2).

In recent years, using *E. coli* as a model system, extensive efforts have been made to elucidate the sequential steps involved in this novel non-MVA pathway, and various genes, enzymes and their reaction mechanisms along with all possible intermediates have been discovered[5,14,17] (Figure 2). A bioinformatics approach has been used to identify various non-MVA-route genes in *E. coli*[18–20], and orthologous sets of genes in various other organisms, including some human pathogens[21,22] such as *M. tuberculosis*, *P. falciparum*, and *H. pylori*. Whole genome sequence comparisons

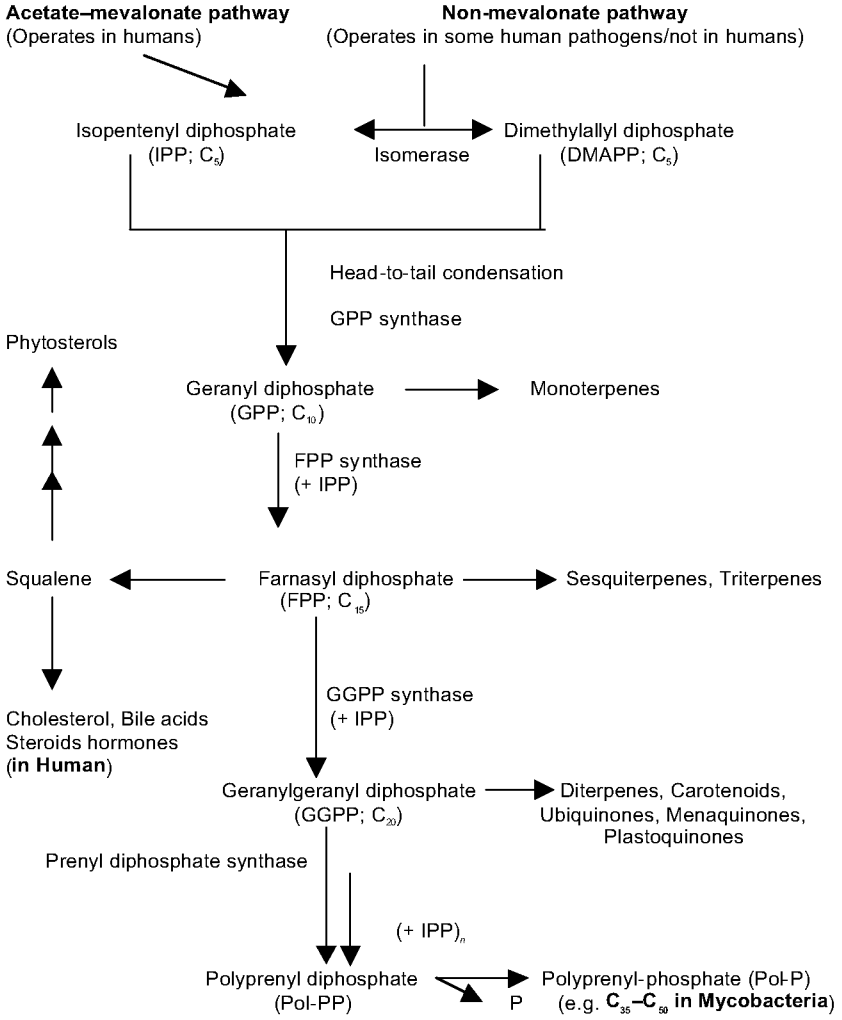

Figure 1. General diagram elucidating the biosynthesis of various classes of natural compounds of isoprenoid origin found in various systems. Difference between IPP and DMAPP (precursors of all isoprenoids) generating pathways is also depicted, e.g. one exists in humans and the other is exclusively found in some human pathogens.

retrieved putative non-MVA pathway genes in *M. tuberculosis*[14,22]. All essential genes (*dxs*, *dxr* or *ispC*, *ispD*, *ispE*, *ispF*, *ispG* and *ispH*; annotated as and studied in detail in *E. coli*)[5,14,23] encoding for different enzymes involved and various sequential steps (I to VII) are shown in Figure 2.

Mycobacterial species contain polyprenyl phosphate (Pol-P) molecules synthesized from various isoprene (as IPP) units, and are presumably known to be involved in the cell-wall biosynthesis. Pol-P is typically synthesized by enzymes that catalyse the head-to-tail condensation of IPP with various allylic prenyl diphosphates, generating longer and physiologically appropriate allylic prenyl diphosphates, which then further dephosphorylate to form the appropriate Pol-P molecules[24] (Figure 1). The availability of Pol-P is reported to be rate-limiting for several aspects of cell-wall synthesis in other organisms, such as in *Staphylococcus*[25] and *Bacillus*[26] species and in *E. coli*[26]. *M. smegmatis* is known to have two forms of Pol-P molecules, heptaprenyl(C_{35})- and decaprenyl(C_{50})-phosphate, while *M. tuberculosis* contains only one form, decaprenyl phosphate[24], and these Pol-P molecules are reported to covalently link with mannose during the mycobacterial cell-wall synthesis[27]. Since both forms of Pol-P in *M. smegmatis* are found glycosylated, it was therefore suggested that both could be involved in various stages of cell-wall biosynthesis in mycobacterial species[24], as mature mycolic acid (a very long chain C_{60}–C_{90} fatty acid) is reported to be formed via precursors while attached to a heptaprenyl-P molecule[28]. Decaprenyl-P-arabinose is also known as a precursor of the arabinan portions of arabinogalactan, arabinomannan and lipoarabinomannan[29], the components of mycobacterial cell-wall complex[30]. A polyprenyl diphosphate (Pol-PP) carrier lipid has also been implicated in the synthesis of the linker unit of galactan, and in the synthesis of linear forms of lipoarabinomannan in mycobacterial species[31,32]. All the above reports indicate the exclusive role of Pol-P molecules in the formation of mycobacterial cell wall, as rate limiting factor in bacterial growth and essential for the viability of mycobacteria. It is also worth mentioning here that all mycobacterial species are susceptible to antibiotic bacitracin, which specifically binds prenyl diphosphate intermediates in Pol-P synthesis[33].

In view of the crucial role of Pol-P in mycobacterial cell-wall biosynthesis, the synthetic steps involved in its formation could be used as a potential target, and molecular genetic approaches such as knockout strategy for some of the genes of non-MVA route, that generate the initial chain-building unit (IPP) could be exploited, and that may be further used for drug targeting against such enzymes encoded by these knockout genes. However, the enzymes are involved in polyprenylation steps (i.e. prenyl diphosphate synthase), could possibly have some significant similarity with the mammalian enzymes; therefore, they may not be suitable for knockout and drug targeting strategies. In mycobacteria, IPP is synthesized exclusively via the non-MVA pathway[34]; therefore the intermediate enzymes of this novel pathway could be a suitable target. Moreover, a similar pathway does not exist in humans. Thus disruption of some of the crucial gene(s) from the non-MVA pathway in *M. tuberculosis* may generate a mutant(s) that might be defective in IPP synthesis as well as in the synthesis of Pol-P in this organism. Alternatively, the crystallographic structures of expressed protein(s) from mycobacterial enzyme(s) of the non-MVA route might also provide some valuable information to look into the appropriate inhibitors for these enzymes and thus to prevent the synthesis of IPP and/or Pol-P molecules. The crystal structure for some of the intermediate enzymes of this pathway from *E. coli* has recently been studied[35–40].

Like *M. tuberculosis*, the other two human pathogens, *P. falciparum* and *H.*

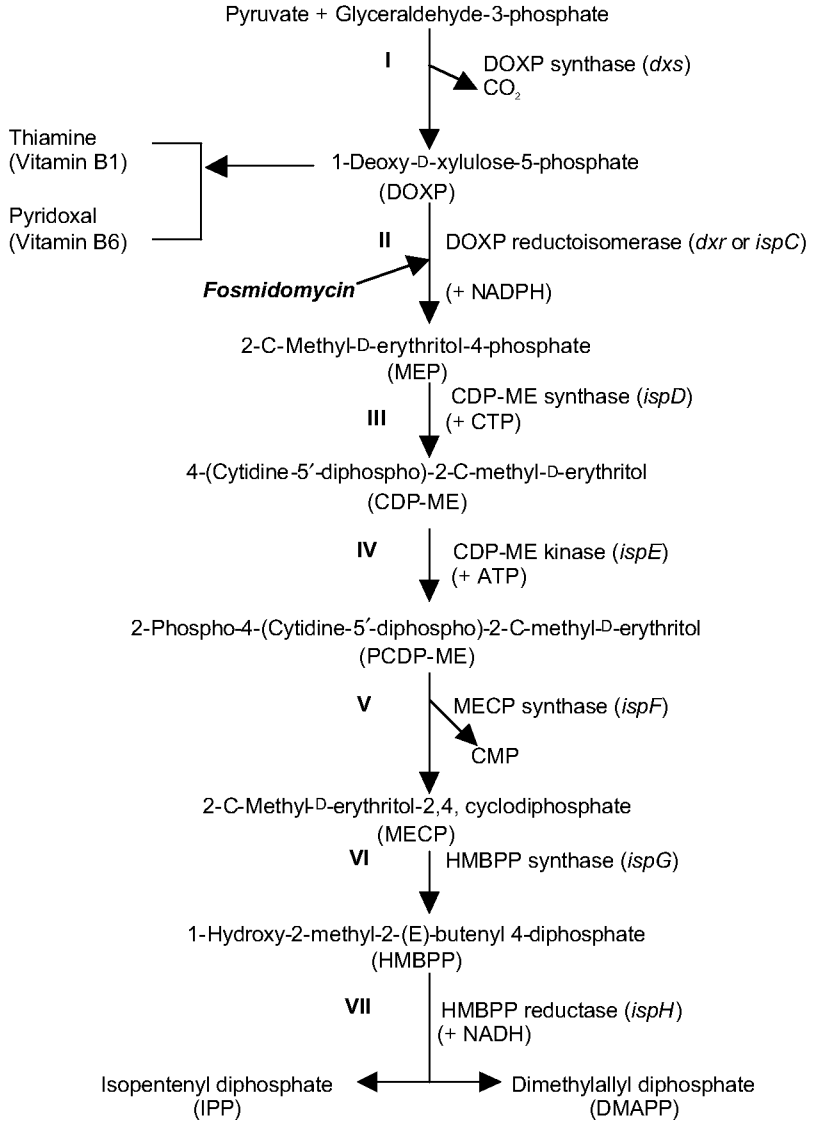

Figure 2. Genes, enzymes and intermediates involved in various sequential steps of mevalonate-independent pathway leading to synthesis of IPP and DMAPP. Genes (as annotated and studied in *E. coli*) for each enzyme are given as italics in parenthesis. CMP, CDP, CTP and ATP, are mono-, di-, and triphosphates of cytidine and adenosine respectively. Fosmidomycin inhibiting step-II of this pathway is also shown.

pylori also utilize the same non-MVA pathway, as predicted by their genetic analysis[21,22]. However, the synthesis of such class of isoprenoid-derived components from this pathway has not yet been characterized in these two organisms[2,3]. Genome sequence analyses from both organisms could provide a better understanding of the biology of these pathogens, although the *P. falciparum* genome has been partially sequenced. Furthermore, since the non-MVA pathway does not occur in mammals, the enzymatic steps involved in this pathway are being sought as potential drug targets against these pathogens. One such effort has already been made when *P. falciparum* was found to be sensitive to the inhibition of this alternative non-MVA isoprenoid biosynthetic pathway by fosmidomycin[21], an antibiotic also used as herbicide[41], that inhibited one of the key regulatory enzymes, DOXP reductoisomerase[42,43] of this novel pathway. Although this compound was found unsuitable as a drug in the human system, due to its short half-life in serum, nevertheless, the following studies have drawn attention to the enzymes in the non-MVA pathway as exciting targets for the development of novel antimicrobial compounds[44,45]. Furthermore, structural genomic studies on enzymes of this non-MVA pathway exclusively from these human pathogens could provide some additional information, leading to the development of drugs that would eventually save more human lives from diseases caused by these deadly organisms.

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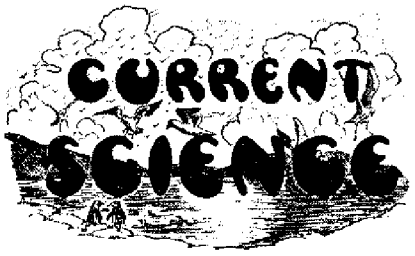

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Tuberculosis in India

The *Indian Medical Gazette* has for the third year in succession published a special tuberculosis number, The editor, Dr L. E. Napier, sums up the reasons for this departure from the usual practice of the *Gazette*, which is a journal for the general practitioner in India and in no sense a specialist journal. He points out that a special effort is being made by the whole nation to tackle the tuberculosis problem and he feels that everyone should join in and support Lady Linlithgow's movement. The second reason is to show the practitioner in India what is being done, both in this country and abroad, for the tuberculous patient, to impress upon him that a very great deal can be done and that practically no case is hopeless, so that he in turn will pass on the information and will counteract a spirit of hopelessness which would be fatal to the movement.

He writes, 'A perhaps not unnatural reaction to the enthusiasm of the early days of the launching of the appeal is now appearing and the people who helped to raise the fund are asking how the problem is going to be tackled, some in an interested and helpful spirit, others querulously and with a suggestion of hopelessness. 'What is the good', the latter say, 'of pointing to the successful campaigns in other countries, countries that are able and prepared to spend hundreds of pounds per tuberculosis death in sanatoria and tuberculosis hospitals, when we cannot afford as many pice for this special purpose?' But we shall not tackle the problem on the lines that they are doing it in Western countries and we should not do so even if we had the necessary resources; we shall devise means suited not only to our limited resources but to the special conditions of the country. Whilst the balance is certainly in favour of the richer Western countries, we have some factors that work in our favour, the sun, for example, and the relatively small proportion of our children that live under the conditions comparable to those of the grinding poverty and squalor of the overcrowded, sunless slums of many large European cities'.

He continues, 'The control of the disease is so closely associated with the treatment of the existing cases that one cannot dissociate the two ideas. The anti-tuberculosis programme will of course include the building of sanatoria, up-to-date and well-equipped dispensaries, and after-care settlements, to act as models and to show what can be achieved under the most favourable conditions, but in such institutions, as with the funds available we could hope to found, scarcely one per cent of our patients could be accommodated, and we shall certainly not be content to leave matters there: something must be done for the remaining 99 percent and tuberculosis dispensaries, conducted on more modest, but still we hope up-to-data lines, will have to be established, not only in every province and district but eventually in every *thana* or *taluk* in the country'.