P33 Studies of the Non-Mevalonate Pathway

I. Biosynthesis of Menaquinone-7 in Bacillus subtilis

II. Synthesis of Analogs of Fosmidomycin as Potential Antibacterial Agents

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The non-mevalonate pathway is a newly discovered isoprenoid biosynthetic pathway in some bacteria, cyanobacteria, algae and plants [1-3]. Because isoprenoid metabolites (ubiquinone, menaquinone, undecaprenol) are essential for bacterial growth, this pathway may represent a novel target for antibacterial agents. Antibiotics with a unique mechanism of action are needed to combat the risk of antibiotic resistance that is a current worldwide problem. In order to study this pathway as viable target, it was necessary to verify use of the pathway in our model system, the bacterium *Bacillus subtilis*. Incubation experiments with [6,6-$^2H_2$]-D-glucose and [1-$^2H_3$]-deoxy-D-xylulose were conducted to provide labeled menaquinone-7 (MK-7), the most abundant isoprenoid in *B. subtilis*. ^{2}H-NMR analysis of the MK-7 revealed labeling patterns that strongly support utilization of the non-mevalonate pathway. Another approach to study the pathway is by structure activity relationships of proposed inhibitors of the pathway. Fosmidomycin is a phosphonic acid with antibacterial activity known to inhibit isoprenoid biosynthesis in susceptible bacteria and may act by inhibiting the non-mevalonate pathway. Fosmidomycin and an N-methyl analog were synthesized[4-6] and tested for antibacterial activity. Fosmidomycin was active against *Escherichia coli* and *B. subtilis*, while N-formyl-N-methyl-3-amino-propylphosphonic acid was inactive.