

Prenyltransferases as Targets for the Discovery of New Antibiotics

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Prenyltransferases are involved in the biosynthesis of isoprenoids through the condensation of C₅-diphosphates to form the compounds used in cell membrane, cell wall, terpene biosynthesis, electron transfer, and in many eukaryotes, cell signaling pathways (Ras, Rho, Rap, Rac). Therefore, there has been considerable interest in developing specific inhibitors as new drugs for various diseases associated with these pathways.

Through our structural analysis efforts, we have studied the product chain length determinants of several *trans*-type prenyltransferases, including geranylgeranyl pyrophosphate synthase (GGPPS), hexaprenyl pyrophosphate synthase (HexPPS), and octaprenyl pyrophosphate synthase (OPPS). The specificities were determined by the size and depth of the activity site cavity. Large amino acids, such as Tyr¹⁰⁷/His¹³⁹ for GGPPS, Leu¹⁶⁴ for HexPPS, and Phe¹³² for OPPS, form the floor to block product further elongation (1). In addition, we solved the structures of yeast GGPPS complexed with several bisphosphonate inhibitors (2).

Undecaprenyl diphosphate synthase (UPPS), a *cis*-prenyltransferase, produces mixed (*E,Z*) long-chain C₅₅-undecaprenyl diphosphate (UPP) via *cis* double-bond addition. It has been considered as a new target for anti-microbial therapy because UPP is used to form the lipid-I and lipid-II species needed for peptidoglycan cell-wall biosynthesis in bacteria. Here, bisphosphonates were tested as inhibitors of UPPS, with the most active one having an IC₅₀ of < 600 nM. In the UPPS-inhibitor complexes, four distinct binding sites were observed (2), in contrast to the observation of only one bisphosphonate-binding site in farnesyl diphosphate synthase (FPPS). The availability of these structures opens up new avenues for the design of novel inhibitors.

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Another prenyltransferase called dehydrosqualene synthase (CrtM) from *Staphylococcus aureus*, uses the head-to-head condensation of two farnesyl diphosphate (FPP) molecules to produce the presqualene diphosphate C₃₀ molecule, resembling the human squalene biosynthesis. Interestingly, the C₃₀ - presqualene diphosphate is the precursor for the biosynthesis of staphyloxanthin, the golden carotenoid pigment which promotes resistance of the bacteria to reactive oxygen species and host neutrophil-based killing. CrtM, therefore, has been tested as the target to treat the hospital- and community-acquired infections produced by methicillin-resistant *S. aureus* (MRSA). Based on the structural similarity between CrtM and human squalene synthase (SQS), SQS inhibitors for cholesterol-lowering activity in humans also can be bound to CrtM through blocking the biosynthesis of staphyloxanthin *in vitro* (median inhibitory concentration ~100 nM), resulting in colorless bacteria with increased susceptibility to killing by human blood and to innate immune clearance in a mouse infection model (3).

1. Chang TH et al. Crystal structure of type-III geranylgeranyl pyrophosphate synthase from *S. cerevisiae* and the mechanism of product chain length determination. *J Biol Chem* 281:14991-5000 (2006).
2. Guo RT et al. Bisphosphonates target multiple sites in both cis- and trans-prenyltransferases. *Proc Natl Acad Sci USA* 104:10022-7 (2007).
3. Liu CI et al. A cholesterol biosynthesis inhibitor blocks *Staphylococcus aureus* virulence. *Science* 319:1391-4 (2008).

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