The First Step in a Synthesis of Antibiotic Moenomycin

This report features the work of Rey-Ting Guo, Eric Oldfield, and their co-workers published in Angew. Chem. Int. Ed. ***51****, 4157 (2012).*

Moenomycin is a highly potent antibiotic and the only one targeting transglycosylase.[1] The first member of this family, meonomycin A, was described in 1965. Because of its suboptimal pharmacokinetic properties, an excessive half-life and minimal oral bioavailability, it is used commercially only in animals as a feed additive. The outer membrane of gram-negative bacteria also hinders the entrance of meonomycin, and makes it less effective than on gram-positive bacteria. A growing clinical crisis of antibiotic resistance makes meonomycin a new hope to combat human infection.

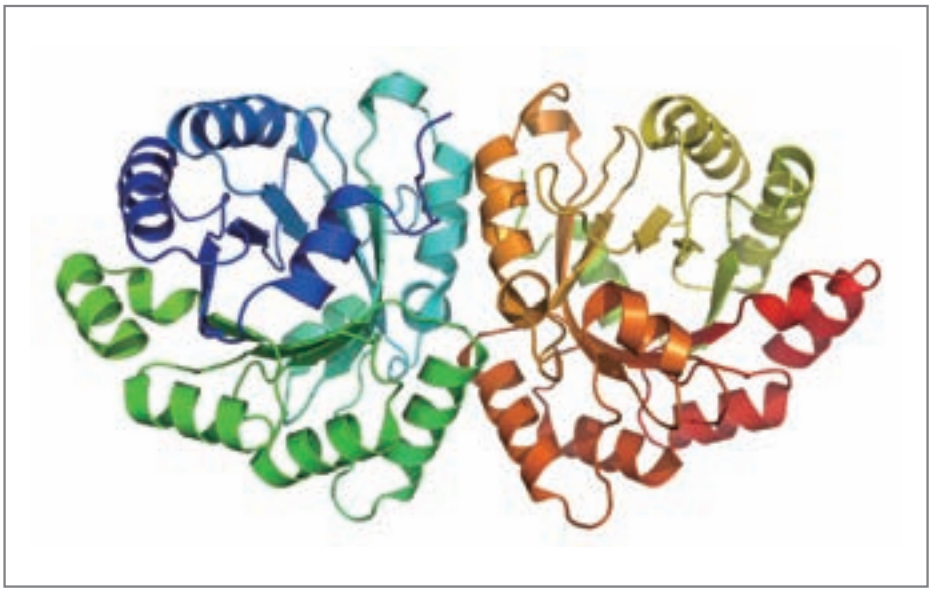

Fig. 1: Overall structures of MoeO5 dimer with TIM-barrel fold. Unlike other homologs in this family, one protomer of MoeO5 dimer is related to the other by 180 degree rotation along X-axis. Active site sits in the middle of TIM-barrel.

Members of the meonomycin family contain a core tetrasaccharide attached to the meonocinol-phosphoglycerate moiety. An additional sugar is attached to this tetrasaccharide in some members, with additional modifications of these sugars. A total synthesis of moenomycin finally succeeded after decades of effort.[2] It was a formidable task because of the complicated functional groups in this chemical compound. Many analogues of moenomycin have been synthesized in the mean time as candidates for new antibiotics.

A biosynthesis of moenomycin provides an alternative method to produce this antibiotic and might open a door to generate new varieties of moenomycin analogues. More than ten genes are involved in a moenomycin synthesis; they are in the vicinity of a *moe* cluster. It takes 17 steps to synthesize moenomycin. The first step is the formation of *cis*-farnesyl-3-PG (FPG) from 3-phosphoglycerate (3PG) and *trans*-farnesyl pyrophosphate (FPP) catalyzed by MoeO5. To understand its functionality, Dr. Guo and Dr. Oldfield lead a group from Tianjin Institute of Industrial Biotechnology, Academia Sinica and University of Illinois Urbana-Champaign to solve the structure of MoeO5 with product FPG.[3] Their work used beamlines **13B1** and **13C1** at NSRRC.

The structure of MoeO5 is a dimer of TIM-barrel of which one protomer is inverted (Fig. 1). Unlike its homolog PcrB, which synthesizes heptaprenylglyceryl phosphate with an all-*trans* configuration (the PcrB structure in complex with FsPP and G1P substrates was solved recently),[4] the product of MoeO5 has a *trans*-to-*cis* isomerization at the C2 = C3 double bond. The C_{15} tail moiety of FPG shows a U-turn in the crystal structure at the C8 = C9 bond (Fig. 2). Such bending is not seen in GGGPS, and MoeO5 can accommodate the tail of only C_{15}, not a longer or a shorter one. The precise positioning of this U-turn on the C_{15} tail might thus be important for a *trans*-to-*cis* conversion of the MoeO5 product. Doud *et al.* recently proposed a synthetic mechanism for TIM-barrel prenyltransferases.[5] MoeO5 might produce an intermediate nerolidyl pyrophosphate (NPP) or (*Z,E*)-FPP during *trans*-to-*cis* conversion. Thus, *trans*-FPP, NPP and (*Z,E*)-FPP are all substrates of MoeO5. The authors of this work propose another mechanism, based on their structures, that the essen-

tial His97 might facilitate the *trans*-to-*cis* isomerization through bound water. Their work makes a foundation for further investigation of the synthesis of this important antibiotic.

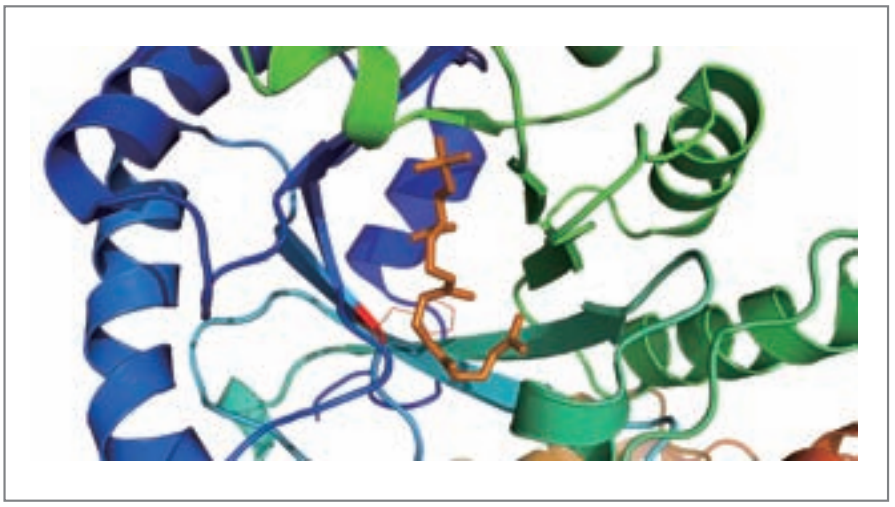

Fig. 2 : *cis*-farnesyl-3-PG (orange) in the binding pocket of MoeO5 shows a U-turn at C8 = C9 double bond. This arrangement is important to position the C2 = C3 double bond at the right place for *trans*-to-*cis* isomerization. His97 depicted as red stick may facilitate the isomerization.

References

1. B. Ostash and S. Walker, Nat. Prod. Rep. **27**, 1594 (2010).
2. J. Taylor, X. Li, M. Oberthür, W. Zhu, and D. Kahne, J. Am. Chem. Soc. **128**, 15084 (2006).
3. F. Ren, T.-P. Ko, X. Feng, C.-H. Huang, H.-C. Chan, Y. Hu, K. Wang, Y. Ma, P.-H. Liang, A. H.-J. Wang, E. Oldfield, and R.-T. Guo, Angew. Chem. Int. Ed. **51**, 4157 (2012).
4. F. Ren, X. Feng, T.-P. Ko, C.-H. Huang, Y. Hu, H.-C. Chan, Y.-L. Liu, K. Wang, C.-C. Chen, X. Pang, M. He, Y. Li, E. Oldfield, and R.-T. Guo, ChemBioChem **14**, 195 (2013).
5. E. Doud, D. Perlstein, M. Wolpert, D. Cane, and S. Walker, J. Am. Chem. Soc. **133**, 1270 (2011).