The Function of *orf13* and *orf16*, Genes Involved in the Biosynthesis of Rifamycin B by *Amycolatopsis mediterranei* S699

Chang-Joon Kim[1,2], Feng Xu Ma[1], Taifo mahmud[2,3], Heinz G Floss[2], and Sung Bae Kim[1]

[1]Department of Chemical & Biological Engineering, Gyeongsang National University, Jinju 660-701, Korea,

[2]Department of Chemistry, University of Washington, Box 351700, Seattle, WA 98195-1700, USA,

[3]Department of Pharmaceutical Sciences, College of Pharmacy, Oregon State University, Corvallis, OR 97331-3507, USA

Tel:+82-55-751-5391, FAX: +82-55-753-1806

Synthetically modified derivatives from rifamycin, such as rifampicin, rifabutin, and rifapentine are principal chemotherapeutic agents used for combating tuberculosis, leprosy and AIDS-related mycobacterial infections. Recently, as with many other antibiotics, the incidence of resistance of *Mycobacterium tuberculosis*, the causative agent of tuberculosis, to rifamycin is continuing increase over time, due largely to mutational alterations of the target molecule. This issued the search for improved new drug candidates. Despite the preparation of a large number of rifamycin derivatives by semi-synthetic approaches, the structural modifications have been limited primarily to one of the region of the molecule, the C3- or C4- positions of the aromatic core unit. Hence there is a need for alternative, biological method of structural modifications. To this end, we investigated the reactions involved in rifamycin B biosynthesis in *A. mediteranei S699* by inactivation of orf13 or orf16, showing strong similarity to bacterial cytochrom P450, in rifamycin biosynthetic gene cluster. The conversion of rifamycin SV to rifamycin B was almost stopped by the *orf16*-disrupted mutants. Rifamycin B was still produced by the *orf13*-disrupted mutants with lowered productivity compared with wild-type cells.

References

1. **August, P. R., Tang, L., Yoon, Y. J. *et al.* (1998)**. Biosynthesis of the ansamycin antibiotic rifamycin: deductions from the molecular analysis of the rif biosynthetic gene cluster of *Amycolatopsis mediterranei* S699. *Chem. Biol.* **5**, 69-79.
2. **Floss, H. G., and Yu, T.-W. (2005)**. Rifamycin - mode of action, resistance and biosynthesis. *Chem. Rev.* **105**, 621-632.
3. **Ghisalba, O., Ross, R., Schupp, T. and Nuesch, J. (1982)**. Transformation of rifamycin S into rifamycin B and L. A revision of the current biosynthetic hypothesis. *J. Antibiot.* **30**, 487-491.