

Enhancement of Avermectin B_{1a} Production through Vhb Gene Expression and Genome Shuffling Method

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Avermectin (AVM) B_{1a} produced by *Streptomyces avermitilis* as a secondary metabolite via polyketide pathway is an excellent anthelmintic agent in humans and animals. In preliminary experiments, we found that a major factor influencing the biosynthesis of AVM B_{1a} was oxygen availability. In fermentations using 2.5 L bioreactor, AVM B_{1a} production was almost linearly increased according to the increase in DO level. Therefore, we attempted to express *Vitreoscilla* hemoglobin (*Vhb*) gene in the producing strains for more facilitated utilization of DO. A putative *Vhb*-harboring transformant, SSK-1Vhb showed about 40% higher AVM B_{1a} productivity than the corresponding mother strain in 250 ml shake flask cultivations. Currently we are investigating the expression of *Vhb* in the strain of SSK-1Vhb using RT-PCR in 5 L bioreactor cultivations with various DO levels.

In order to enhance AVM B_{1a} production level, we also performed random genome shuffling among five high-yielding mutants. Some of the genome-shuffled regenerants were found to have higher AVM B_{1a} productivity than the corresponding mother strains, demonstrating that this method could be very efficient in the enhancement of production yields and stability of producers.