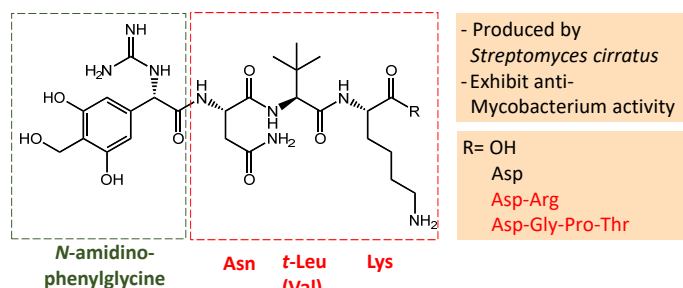


Abstract

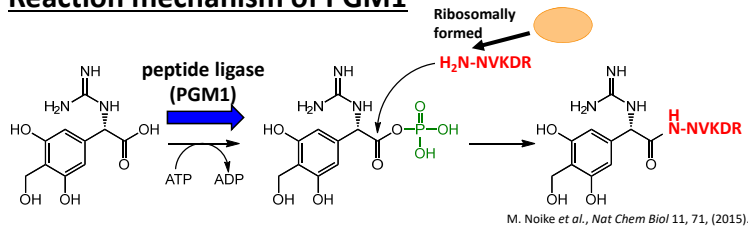
We identified a novel peptide ligase (PGM1) involved in pheganomycins biosynthesis. The enzyme activates a carboxyl group of an *N*-amidino-phenylglycine derivative by phosphorylation in the presence of ATP and catalyzes the amide bond formation between the *N*-amidino-phenylglycine derivative and ribosomally synthesized peptides. This is the first example of an ATP-grasp enzyme catalyzing the amide bond formation with peptides as nucleophiles. We identified gene clusters containing a peptide ligase ortholog in actinobacteria by BLAST analysis. These gene clusters were heterologously expressed in *Streptomyces lividans* and *Streptomyces albus* to probe the function of the orthologs. We detected a specific metabolite in culture broth of the transformant. We also identified a novel ATP-grasp enzyme, which is involved in peptidoglycan biosynthesis and catalyzed ligation between L-Glu and UDP-MurNAc-L-Ala. Besides, a novel epimerase catalyzing the epimerization of the terminal L-Glu of the product was also identified.

Background

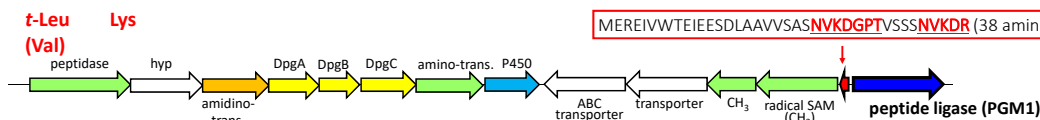
Structure of pheganomycins (PGMs)



Reaction mechanism of PGM1

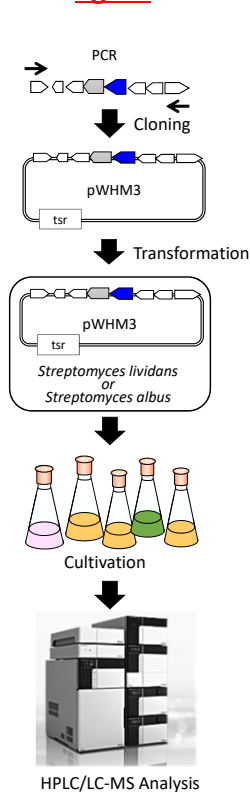


Biosynthetic gene cluster of PGMs

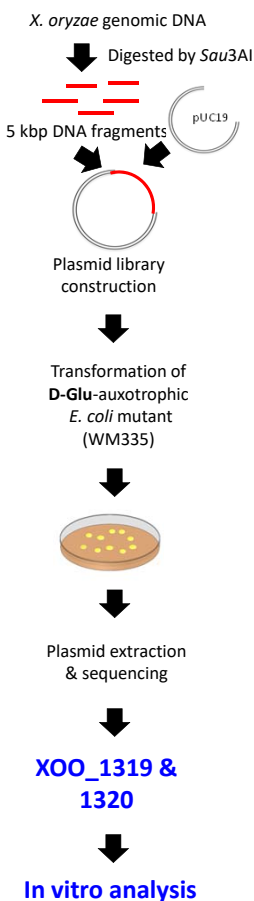


Method

ATP-grasp ligase

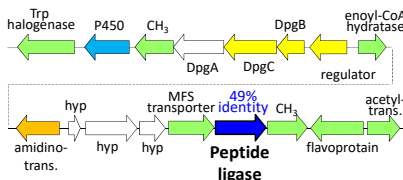


Peptidoglycan

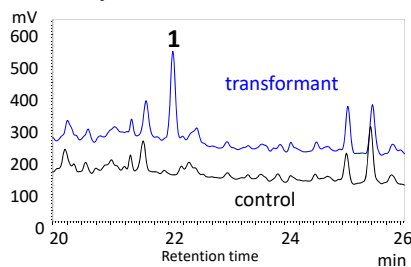


Results

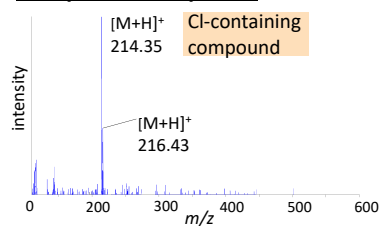
ATP-grasp ligase *Nocardopsis baichengensis*



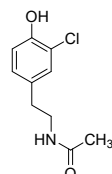
HPLC analysis



MS spectrum of peak 1

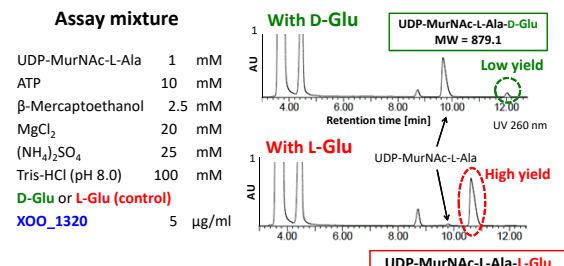


NMR analysis



Peptidoglycan

XOO_1320 Glu ligase assay



XOO_1319 epimerase assay

