# Peptide extension after chain reversal by Ureido-Forming Condensation Domains

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A subset of nonribosomal peptide synthetases (NRPSs) and polyketide synthases (PKSs) are encoded in their biosynthetic gene clusters (BGCs) with enzymes annotated as lantibiotic dehydratases. The functions of these putative lantibiotic dehydratases remain unknown. We characterized an NRPS-PKS BGC with a putative lantibiotic dehydratase from the bacterium Stackebrandtia nassauensis (sna). Heterologous expression revealed several metabolites produced by the BGC, and the omission of selected biosynthetic enzymes revealed the biosynthetic pathway towards these compounds. The final product is a bisarginyl ureidopeptide with an enone electrophile. The putative lantibiotic dehydratase catalyzes peptide bond formation that extends the peptide scaffold opposite to the NRPS and PKS biosynthetic direction. The condensation domain of the NRPS SnaA catalyzes the formation of a ureido group, and bioinformatics analysis revealed a distinct active site signature EHHXXHDG of ureido-generating condensation ($C_{urea}$) domains. This work demonstrates that the annotated lantibiotic dehydratase serves as a separate amide bond-forming machinery in addition to the NRPS, and that the lantibiotic dehydratase enzyme family possesses diverse catalytic activities in the biosynthesis of both ribosomal and non-ribosomal natural products.