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Biosynthesis and diversification of lipoglycopeptide antibiotics

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The emergence of bacterial resistance to clinically used antibiotics threatens life. New generations of drugs with better efficacy thus are urgently demanded. While countless efforts have been made in searching for new drugable chemical entities, the thirsty for them is much more than it was. For this concern, diversity-oriented biosynthesis for privileged natural products as a new means for new drugs may ease the high demand.

The privileged compounds here are clinically important lipoglycopeptide antibiotics teicoplanin and A40926. A lipo-sugar moiety in these compounds has been known playing a pivotal role to enable the compounds the better bactericidal activity. The biosynthetic pathway for this lipo-sugar moiety has been elucidated. In this study, the activity of deacylase (Orf2) in this pathway was expanded on the basis of ligand-bound deacylase crystal structures. With new facets of Orf2 and other enzymes, we are in a position to redirect the synthetic pathway for new compounds (e.g. reposition of N-acyl Glm from one residue to another).

In addition, crystal structures of Dbv29 in the pathway free and in complex with a intermediate were also solved. Of the structural information that the aldehyde group of the intermediate is exposed and susceptible to derivatization, a one-pot chemo-enzymatic synthesis was developed to generate new analogs of teicoplanin/A40926, some of which showed marked potency and efficacy against multi-drug resistant pathogens.