Developing novel antimicrobials by synthetic biology and biosensor-based screening.

Oscar P. Kuipers, Auke van Heel, Dongdong Mu, Liang Zhou, Andrius Buyvidas, Manuel Montalbán-López
Department of Molecular Genetics, University of Groningen; o.p.kuipers@rug.nl

Antibiotic resistance in human pathogens is on the rise and this rise is not met with new approved antibiotics to combat these resistant bacteria. To solve this growing problem of resistance, alternative sources of antibiotics should be explored. One of these sources could be the class of ribosomally synthesized, post-translationally modified peptides called lantibiotics. We'll describe four different approaches to develop novel antimicrobials and the concommittant high troughput screening procedures:

1. Developing a synthetic biology approach to efficiently use the large amount of sequenced genomes (>10,000) as a resource for novel lantibiotics.
2. Use of heterologously expressed post-translational modification enzymes to hypermodify lantibiotics. Various documented posttranslational modifications have been introduced into lantibiotic peptides broadening the antimicrobial spectrum
3. Design and production of novel lantibiotics by ring module- and hinge-variation. Specific lantibiotic modules have been randomly fitted in a defined architecture, and the nisin induction and modification machinery are exploited for the required modifications. The screening of more than 10,000 chimeric molecules for biological activity has already rendered several more active antimicrobials.
4. Biomodules for introducing various types of circular and heterocyclic modifications in lantibiotics. Purpose is to design three unique biomodules that introduce heterocyclic, cyclic and circular (head-to-tail) modifications in lantibiotics (already containing lanthionine rings).