

Making peptides the non-ribosomal way: possibilities and limitations

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Several peptides derived from non-ribosomal peptide synthetases (NRPS) are used as clinical drugs to treat infections, cancer or other diseases (see daptomycin, romidepsin or cyclosporin as examples). The architecture of NRPS, often composed of multiple modules for the incorporation and modification of specific building blocks like amino acids (sometimes additionally using carboxylic acids as starting units), makes this enzyme class an ideal example for synthetic biology approaches.

In the past 10 years, we and others developed several NRPS engineering approaches that allow efficient modifications of natural non-ribosomal peptides or even the generation of completely new peptide scaffolds. Recently, we could vary (i) the starting units, responsible for the incorporation of amino acids, fatty acids and amino-, hydroxy- and epoxy-fatty acids, (ii) the ring size of the cyclic (depsi)peptides using different thioesterases and other termination domains, and (iii) the amino acid building blocks itself even allowing the incorporation of non-canonical amino acids, which can be generated in situ from simple aldehydes or carboxylic acids.

Since non-ribosomal peptides can not only be produced in vivo in bacteria but also cell-free, NRPS might offer a complementary approach to chemical peptide synthesis in the future as will be discussed in my talk.