Synthesis and Derivatization of Lasso Peptides

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The rise of multiresistant bacteria is a major burden to the health system and leads to increased mortality. Peptide-based antibiotics could provide valuable lead structures with possible new modes of action.[1] Lasso peptides, a subclass of ribosomally-synthesized and posttranslational modified peptides (RiPPs), show excellent stability against heat treatment or enzymatic digestion, and some also display high antimicrobial activity.[2] To evaluate lasso peptides as a scaffold for new antibiotics, it would be advantageous to incorporate non-canonical amino acids.[3] However, their chemical synthesis has proven to be very difficult. Here, we propose to use recently developed automated fast-flow peptide synthesis (AFPS)[4] in combination with enzymatic maturation to produce chemically modified lasso peptides.[5] The first aim of this project is, therefore, the **chemical and enzymatic synthesis of the lasso peptide Microcin J25 (MccJ25), to give rapid access to chemically modified lasso peptides.** We will then synthesize **derivatives of MccJ25 including non-canonical amino acids to compare the activity of all MccJ25 derivatives against various *E. coli* strains**, which are reported to include active transport mechanisms for this lasso peptide.[6]

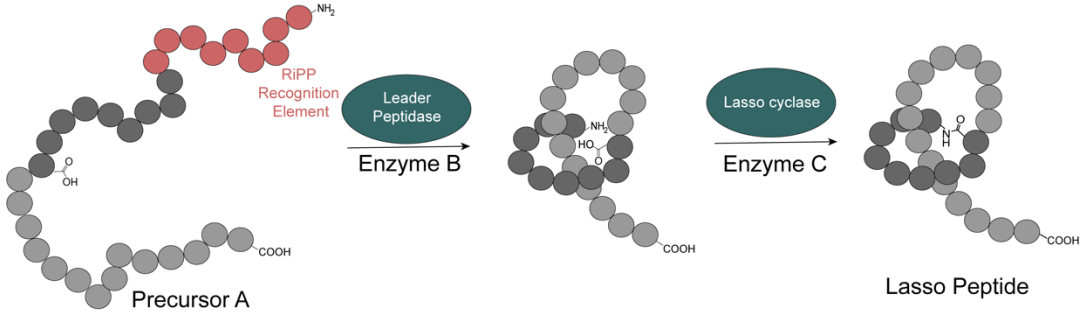

Fig.: Biosynthetic pathways of lasso peptides. The leader sequence (orange) of the precursor peptide A is cleaved by the peptidase B. The lasso cyclase C forms an amide bond between a carboxylic acid sidechain and the amine at the *N*-terminus of the core region (dark grey).

[1] N. Tsomaia, *European journal of medicinal chemistry* **2015,** *94*, 459-470.
[2] J. D. Hegemann, M. A. Marahiel, *Cyclic Peptides*, **2017**; 206-224.
[3] F. J. Piscotta, J. M. Tharp, W. R. Liu, A. J. Link, *Chemical Communications* **2015,** *51* (2), 409-412.
[4] N. Hartrampf, A. Saebi, M. Poskus, Z. P. Gates, A. J. Callahan, A. E. Cowfer, S. Hanna, S. Antilla, C. K. Schissel, A. J. Quartararo, X. Ye, A. J. Mijalis, M. D. Simon, A. Loas, S. Liu, C. Jessen, T. E. Nielsen, B. L. Pentelute *Science* **2020,** *368*.
[5] K. P. Yan, Y. Li, S. Zirah, C. Goulard, T. A. Knappe, M. A. Marahiel, S. Rebuffat, *ChemBioChem* **2012,** *13* (7), 1046-1052.
[6] D. Destoumieux-Garzón, S. Duquesne, J. Peduzzi, C. Goulard, M. Desmadril, L. Letellier, S. Rebuffat, P. Boulanger, *Biochemical Journal* **2005,** *389* (3), 869-876.