

## Analysis of the angucycline biosynthetic gene cluster in Streptomyces sp. QL37 and implications for lugdunomycin production

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#### Stellingen

#### Propositions accompanying the thesis

# Analysis of the angucycline biosynthetic gene cluster in *Streptomyces* sp. QL37 and implications for lugdunomycin production

- 1. The capacity of a strain to produce lugdunomycin does not correlate to the phylogeny of the producer (Chapter 3).
- 2. The observation that multiple biosynthetic gene clusters (BGCs) may specify a single compound has major implications for synthetic biology approaches (Chapter 4).
- 3. Screening for the presence of orthologues of *lugOIII* and *lugOV* in angucycline BGCs can lead to the discovery of novel rearranged angucyclines (Chapter 5).
- 4. Transcriptional activation of the *lug* gene cluster by the SARP regulator LugRV can be employed to increase angucycline production (Chapter 6).
- 5. To obtain insight into the regulatory network and biosynthesis of a natural product, transcriptomics data should be the foundation of follow-up research questions (Amos *et al.*, 2017, PNAS 114: E11121-E11130).
- 6. Blocking the production of a single natural product can have unexpected consequences for other pathways for specialized metabolism and for growth (Singh *et al.*, 2009, *J Ind Microbiol Biotechnol* 36:1257-1265, Culp *et al.*, 2019, *Nat Biotechnol* 37: 1149-1154).
- 7. Mass spectral molecular networking is ideally suited for the discovery of novel metabolic intermediates, providing insight into the biosynthesis pathway of a natural product (Zhu *et al.*, 2020, *Chem Commun* 56: 10171-10174; Iorio *et al.*, 2021, *Sci Rep*:5827).
- 8. The rich chemical diversity of angucyclines offers a huge enzymatic toolbox for combinatorial (bio)synthesis (Fewer and Metsä-Ketelä, 2020, *FEBS*, *J.* 287: 1257-1259, Kharel *et al.*, 2012 *Nat Prod Rep* 29 :264).
- 9. Aristotle said that the whole is often more interesting than the sum of its parts. This thesis shows that this applies well to collaborations between biologists and chemists.
- 10. Do not compare your yoga poses to those of other yogis, especially when a pose is difficult. The same rule applies to a PhD trajectory.

Helga U. van der Heul Leiden, 21 december 2022