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Identification, activation and engineering production of the antitumor UCS1025A

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UCS1025A is a novel polyketide-non-ribosomal peptide (PK-NRP) hybrid fungal metabolite with a decalin-like structure. UCS1025A isolated from *Acremonium* fungus KY4917 (FERM) and exhibiting antibacterial and antiproliferative activities. Although it is known for a decade, its biosynthesis has not been elucidated. The gene cluster for USC1025A was predicted by bioinformatics analysis and its PKS-NRPS deletion mutation validates its essential role in UCS1025A biosynthesis. Heterogonous engineering of the gene cluster into *Aspergillus nidulans* using yeast recombination-based cloning strategy was successfully performed. Only the gene cluster transformed without transcription factors (AN#2) was able to produce the compound. Activation of the UCS1025A gene cluster in the FERM fungus by over-expressing each transcription factor separately increased the compound production up to 4 times. Similarly activation of the gene cluster in *A. nidulans* transformed with the *UCS1025A* gene cluster containing transcription factors (AN#1) was able to detect affordable amount. Two transcription factors would work as activator and one as repressor. The *UCS1025A* gene cluster (1759) with another gene cluster (1590) comprised a branch of a phylogenetic tree close to lovastatin gene cluster indicating similar compound could be produced by this cluster. This work will help in genetic manipulation and investigation of the UCS1025A biosynthetic pathway.

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