



Superhosts for polyketide drug production

Polyketides are a rich source of therapeutic agents used in human medicine, including antibiotics, antifungals, immunosuppressants and anticancer agents. Sometimes the natural producer of these polyketides can be difficult, or impossible, to cultivate. More often, the titre of the desired polyketide is very low.

Rather than focus on development of many individual polyketide-producing organisms, scientists at Kosan Biosciences have developed three *Streptomyces* spp. as generic hosts for expression of polyketide synthase (PKS) genes that have been cloned from the original producers. The three hosts are, *Streptomyces coelicolor*, *S. fradiae* and *Saccharopolyspora erythraea*.

These three streptomycetes underwent conventional strain improvement and fermentation development to enhance the production of their endogenous polyketides; then the endogenous PKS

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genes were deleted to create 'clean hosts'; finally, genetic methods were developed so that large PKS genes cloned from other sources could be introduced and expressed in these hosts by fermentation.

Heterologous expression of PKS genes in these 'super-hosts' offers several advantages over conventional improvements to separate strains:

- Genes from difficult or unculturable organisms can be expressed.
 - The hosts have already been optimised for polyketide production, and often produce more of the desired polyketide than the original producer of that polyketide.
- Fermentation methods do not have to be developed from scratch.
 - Polyketides that could interfere with purification have been deleted from these hosts.
 - They are genetically tractable, and a robust set of expression vectors have been developed for these strains.

Kosan uses these strains to support its efforts to develop polyketide drugs with new or improved pharmacological properties. For example, genes from different antibiotic-producing organisms were combined in the *S. fradiae* 'Superhost' to produce a hybrid polyketide antibiotic that had not previously been found in nature, as shown in Figure 1. In this case, the original source of each polyketide antibiotic produced less than 0.1g/L of their respective polyketides, whereas the hybrid polyketide was produced at 1.3g/L in the *S. fradiae* host.

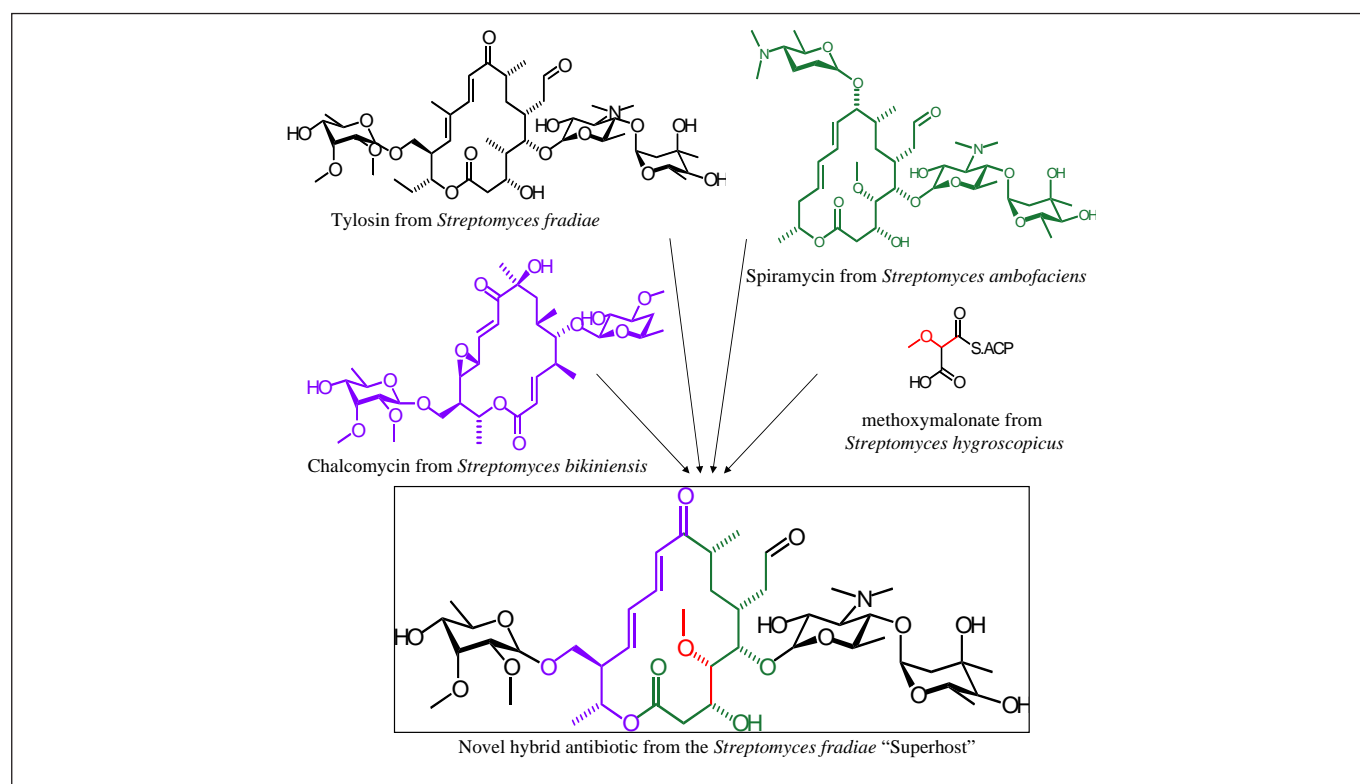


Figure 1. Novel hybrid antibiotic from the *Streptomyces fradiae* 'Superhost'.