**Metabolic Engineering of new Streptomyces sp. From Extreme Environments for Novel Antibiotics and Anticancer Drugs**

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**Highlights**

* Streptomycetes from the Atacama Desert are a good source of bioactive compounds.
* A genome-scale model for *Streptomyces* C34 was developed to study its metabolism.
* This genome-scale model is also used to optimize production.
* Microorganisms from the Atacama Desert inhibit important fungal pathogens.

**1. Introduction**

Today there is a tremendous need for new antibiotics and novel cytotoxic compounds against cancer cells to develop efficient alternative treatment to chemotherapy. We have searched for highly active Streptomyces strains in the driest desert in the world, the Atacama Desert in northern Chile. We have identified several new strains and found many novel antibiotics and anticancer agents (“Chaxamycins”, “Chaxalactins” and “Atacamycins”) from *Streptomyces* C34 and C38 [1-3]. With the high-quality genome sequence of *Streptomyces* C34 we identified the biosynthetic gene cluster of Chaxamycins and Chaxalactins showing the genomic potential of this strain to produce bioactive compounds [4,5]. Our aim is to improve the production of these novel compounds through metabolic engineering and to find new interesting bioactive specialised metabolites.

**2. Methodology**

To find metabolic engineering targets for increasing the production of Chaxamycins and Chaxalactins, we developed a genome-scale model of *Streptomyces leeuwenhoekii* C34 following standard methodology and we performed flux balance analyses. The selected overexpression targets were cloned under a constitutive strong promoter in an integrative plasmid.

The culture collection from the Atacama Desert was subjected to standard bioassays to find bioactive compounds against important fungal pathogens. The selected strains were subjected to chemical fractionation and HPLC-MS/MS analysis.

**3. Results and discussion**

The genome-scale model, *i*VR1007, has 1726 reactions including 239 for transport, reactions for secondary metabolite biosynthesis, 1463 metabolites and 1007 genes. The model was validated with experimental data of growth on 89, 54 and 23 sole carbon, nitrogen and phosphorous sources, respectively, and showed a high level of accuracy (82.5 %). We have included reactions for desferrioxamines, ectoine, Chaxamycins, Chaxalactins and for the hybrid polyketides/non-ribosomal peptide synthesized by the halogenase cluster. A detailed Metabolic Flux Balance Analysis was carried out in order to study the metabolic pathways of Chaxalactins, Chaxamycins and the product of the halogenase cluster, by recognizing overexpression targets and useful knock-out sites to increase production of these secondary metabolites [6]. Among the metabolic engineering targets found we have successfully overexpressed some of them and found that they indeed improve the production of the antibiotic compounds.

In parallel, we identified several strains belonging to the *Streptomyces* genera, that have antibiotic activity against *Botrytis cinerea, Fusarium oxysporum,* among other fungus of agroindustry importance. The strains that showed higher bioactivities were subjected to HPLC-MS/MS analysis. We are identifying novel compounds that could be responsible for the observed bioactivity.

Our recent results concerning these two topics showing the genomic potential for producing bioactive compounds of the microorganisms of the Atacama Desert and how to improve their compound production will be presented and discussed in this presentation.

**4. Conclusions**

The development of a genome-scale model for *S. leeuwenhoekii* C34 was useful for the identification of metabolic engineering targets that enhance the production of Chaxamycins and Chaxalactins.

The *Streptomyces* strains isolated from the Atacama Desert have antibiotic activity against important fungal pathogens.

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