MICROBIAL ENGINEERING OF NEW STREPTOMYCES SP. FROM EXTREME ENVIRONMENTS FOR NOVEL ANTIBIOTICS AND ANTICANCER DRUGS

J.A. Asenjo, Centre for Biotechnology and Bioengineering, CeBiB, University of Chile
juasenjo@ing.uchile.cl
V. Razmilic, CeBiB, University of Chile
J.F. Castro, CeBiB, University of Chile
J.P. Gomez, John Innes Centre, Norwich, U.K.
A. T. Bull, University of Kent, Canterbury, U.K.
M. Goodfellow, Newcastle University, U.K.
M. Jaspars, University of Aberdeen, U.K.
M. Bibb, John Innes Centre, Norwich, U.K.
B.A. Andrews, CeBiB, University of Chile

Keywords : streptomyces, antibiotics, anticancer drugs

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.

A genome scale model of the metabolism of *Streptomyces leeuwenhoekii* C34 has been developed from its genome sequence. The model, iVR1007, 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 in 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.

Alternatively we have identified the gene cluster in *S. leeuwenhoekii* C34 responsible for the biosynthesis of the Chaxamycins and Chaxalactins and have cloned the whole gene cluster in a much more efficient strain of Streptomyces, namely *S. coelicolor A3* whose heterologous expression of gene clusters from other Streptomyces strains has been successfully tested. Our recent results concerning these two alternative strategies for identification and overproduction of these important secondary metabolites will be presented and discussed in this presentation.