

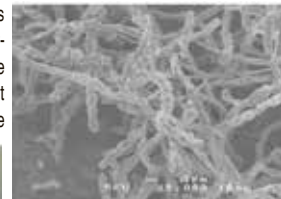


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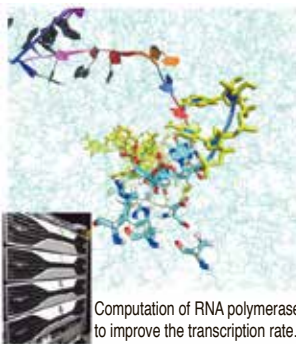
## Frontiers of Nucleoside Antibiotics with Antifungal, Antiviral, and Antitrypanose Activities.

Nucleoside antibiotics comprise a group of microbial products, which has antifungal, antiviral and anti-protozoan activities. These antibiotics, mostly produced by *Streptomyces* species as their secondary metabolites, can inhibit parasite-specific processes such as viral proliferation and protozoan-specific metabolism. Despite the potential utility and yet increasing demands for such powerful antibiotics, there are few successful utilization case of antiviral and anti-parasitic activity of the nucleoside antibiotics, due exclusively to the poor production yield and the difficulty in identifying the biosynthetic genes in the genome of the producer strains. The present research aims to develop an alternative strategy for production improvement by modifying the cellular machineries for transcription and translation to increase and maintain the biosynthetic enzymes without the need of cloning the biosynthetic genes. RNA polymerase genes and ribosomal genes are altered on the genome to increase and maintain the biosynthetic genes.



Nucleoside antibiotic producing strain  
*Streptomyces incarnatus* NRRL8087.

## Engineering RNA polymerase based on Molecular Dynamics Simulation and Density Function Theory Calculation - QM/MM Estimation and Experimental Proof.



Computation of RNA polymerase  
to improve the transcription rate.

RNA polymerase (RNAP) has four conserved residues, which are collectively termed as *rif-1* cluster residues, in the  $\beta$ -subunit. Alteration of the *rif-1* residues by site-directed mutation very often results in production enhancement of the secondary metabolites. The residues are positioned to interact with the newly synthesized mRNA, and they can regulate the polymerization rate. Multiple combination of mutation can alter the interaction between the  $\beta$ -subunit and RNA chain, which is also computed by MD-modeling and Density Function Theory calculation. Computation gives the theoretical consequence of residue change in terms of interaction energy at the electronic levels, and experimental data gives clues on the most appropriate interaction for the highly enhanced production of the secondary metabolite.