Rapamycin is a secondary metabolite produced by the actinomycete Streptomyces rapamycinicus (=S. hygroscopicus ATCC 29253) isolated from a soil sample collected from Rapa Nui (Easter Island) during a screening in the early 1970s for novel antifungal compounds. Rapamycin is a polyketide macrocyclic triene compound with a characteristic UV spectrum (three \( \lambda_{\text{max}} \) at 267, 277, 288 nm) [1].

In 1995, the agent was assigned the name Sirolimus and the trademark Rapamune© by Pfizer. In September 1999 Food and Drug Administration (FDA) approved it as an immunosuppressant in renal transplant.

Further experiments to optimize medium B composition were carried out by the following approaches:
- Increasing glucose concentrations were tested
- Different carbon and nitrogen sources were evaluated
- L-lysine was added to the medium as precursor of piperolic acid, which is incorporated into Rapamycin [2].

A fed-batch process with glucose feeding and pH control in a range of 4.3-0.2 was scaled up to avoid Azalomycin B biosynthesis and prolong Rapamycin production phase. A six-fold improvement was achieved (160 mg/L).

**RIBOSOME ENGINEERING**

Ochi et al. described an innovative method to increase antibiotic production in bacteria by modulating ribosomal components and RNA-polymerase activity by the introduction of mutations conferring drug resistance to streptomycin, gentamicin and rifampicin [4].

Till now we selected resistants to streptomycin and rifampicin. Among them we found an Azalomycin B 6-fold higher producing strain.

**CONCLUSIONS**

This work shows preliminary trials to improve Rapamycin production from a strain available in a public collection. 1.5-fold improve was achieved by medium optimization at flask level. Scaling up at 2L pH controlled fed batch fermentation gave 6-fold higher productivity. Strain improvement is ongoing.