PHARMACY 150 1876 - 2026

**Medicinal Chemistry**
**STUDENT SEMINAR SERIES**

# Pathway Engineering for Modification of Concanamycin

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11am until 12pm

While combination antiretroviral therapy (cART) has been monumental in the treatment of HIV, HIV remains a lifelong condition with no cure, as HIV tends to persist in latent reservoirs. This latency is partly due to accessory proteins such as Nef, which downmodulates MHC-I and thereby evades cytotoxic T lymphocyte (CTL) clearance. Previous studies identified concanamycin A as a potent inhibitor of Nef-dependent MHC-I downmodulation. Notably, concanamycin A inhibits Nef function at concentrations substantially lower than those required to inhibit V-ATPase, minimizing off-target effects. Its natural analog, concanamycin B—differing only by a methyl substitution for the C-8 ethyl group—displays reduced V-ATPase inhibitory potency. Both compounds are polyketides synthesized in a modular fashion, where an acyltransferase (AT) selects an extender unit for elongation by a ketosynthase (KS). We hypothesize that engineering the 11th acyltransferase (AT11) in the concanamycin biosynthetic pathway could enable structural modification at the C-8 position. To support this goal, we have demonstrated homologous recombination in our highest concanamycin-producing strain, Streptomyces eitanensis. Current work focuses on generating functional AT hybrids capable of incorporating alternative extender units, such as fluoromalonyl-CoA.