# The effect of environment on the recognition and binding of vancomycin to native and resistance forms of lipid II

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A combination of molecular dynamics (MD) simulation and free energy calculations has been used to examine the of binding of the antibiotic vancomycin to its cellular target, membrane bound lipid II. Dimeric vancomycin was observed to bind spontaneously to two lipid II molecules. The initial recognition of lipid II by vancomycin was *via* the N-terminal amine group of vancomycin and the C-terminal carboxyl group of lipid II. The average root mean square deviation (RMSD) of the finial structure of the membrane bound complex with respect to the crystal structure of Ac-D-Ala-D-Ala and vancomycin complex was within 0.11 nm, suggesting vancomycin binds lipid II in a similar mode based on lipid II analogues in solution. Free Energy (FE) calculations of the relative binding affinities of native, resistant and synthetic forms of lipid II in solution reproduced experimental binding affinities to within of 6 kJ/mol. The relative binding energy on the mutations of lipid II in the membrane were found to be the same as those in solution, suggesting currently used analogues were able to give a reasonable prediction of the relative affinity of vancomycin to different forms of lipid II in the membrane.