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Activation and Inhibition of the Multidrug ABC Transporter MsbA. Christopher L. Reyes, Geoffrey Chang, Dept. of Molecular Biology, The Scripps Research Institute, 10550 N. Torrey Pines Rd. CB105, La Jolla, CA, 92137, clreyes@scripps.edu.

ATP binding cassette transporters transport a wide variety of substrate molecules across the cell membrane. MsbA, LmrA, and human MDR1 P-glycoprotein are members of the ABC transporter family that have been implicated in multidrug transport by coupling ATP binding and hydrolysis to drug efflux that results in resistance to antibiotics and chemotherapeutic drugs in the treatment of infections and cancers. We report two X-ray structures of MsbA: *i*) in complex with transition state mimic ADP·Vi and the human immunomodulatory substrate Ra lipopolysaccharide, and *ii*) in complex with a clinical multidrug resistant MDR) modulator. MsbA undergoes a rigid-body torque of its two transmembrane domains coupled to ATP hydrolysis. Lipid “flip-flop” from the inner to the outer membrane leaflet is driven on the membrane exposed surface of MsbA suggesting two possible transport pathways. The structure of MsbA with the MDR inhibitor reveals an unexpected binding site that decouples ATP hydrolysis from substrate binding and closes the transmembrane translocation pathways. Taken together, these structures help to elucidate the molecular basis for transport and transport inhibition for this class of ABC transporters.