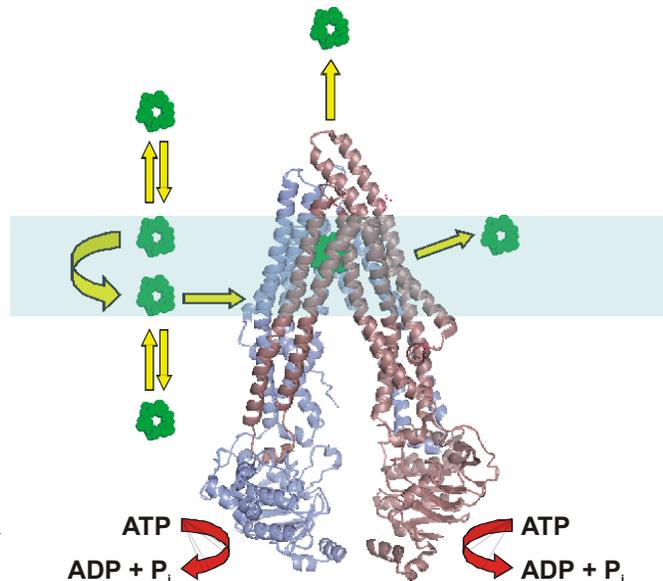


P-Glycoprotein Overview

The P-glycoprotein multidrug transporter (Pgp, ABCB1) is a member of the ABC (ATP-binding cassette) superfamily. This protein can export an astonishing variety of amphipathic drugs, natural products, and peptides from mammalian cells, powered by the energy of ATP hydrolysis. The transporter consists of two homologous halves, each with 6 membrane-spanning helices and a cytosolic nucleotide binding domain. Pgp has been purified and studied extensively for the past 15 years, but its mechanism of action is still not well understood. Recent X-ray crystal structures of Pgp bound to two cyclic peptide substrates showed that the protein has a large flexible drug binding cavity located within the membrane-bound domain. Drugs can bind to several subsites within this pocket, via different sets of interactions, helping to explain the unusual polyspecificity of the transporter. Pgp substrates are generally lipid-soluble, and interact with the protein within the membrane before being either expelled into the extracellular aqueous phase (hydrophobic vacuum cleaner), or moved to the extracellular membrane leaflet (drug flippase). The nucleotide-binding domains likely dimerize during the catalytic cycle to form a “sandwich” with two bound ATP molecules, whose hydrolysis drives transport.

Structure of Pgp shown in side view (pdb 3G60). The N-terminal half of the protein is shown in pink, and the C-terminal half in blue. The transporter is embedded in the membrane, which is indicated in light blue. Molecules of cyclic peptide substrate are shown in green. Substrates partition into the membrane to interact with the large drug-binding cavity, and are then transported to either the extracellular environment or the extracellular leaflet. Transport is powered by ATP hydrolysis at the two cytosolic nucleotide-binding domains.



Pgp substrates include many drugs that are used clinically in the treatment of common human diseases, and the protein plays an important role in drug absorption and disposition in vivo. It is a key determinant in the pharmacokinetic profile of many drugs, and ultimately, the clinical response. The protein is located at the luminal surface of the intestine, and limits absorption of drugs from the gut. Its presence in the luminal membrane of brain capillary endothelial cells also makes a major contribution to the blood brain barrier, and strongly reduces accumulation of many different drugs in the brain. The physiological role of Pgp is thought to involve protection against toxic xenobiotics and endogenous metabolites by efflux or secretion of these compounds. The transporter also plays an important role in the multidrug resistance (MDR) displayed by many human tumors, and it is an important factor in predicting the outcome of chemotherapy treatment.

If a drug interacts strongly with Pgp, the compound will likely have reduced absorption in the gut, very limited entry into the brain, and be unable to enter drug-resistant tumors. Screening drugs for their ability to compete with Pgp-mediated transport of a probe compound can give quantitative information on their affinity for the transporter, and provide an indicator of their behaviour in vivo. The availability of this type of information for a specific drug can be useful in anticipating potential problems with its use in a clinical setting.