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Using Fluorescent Spectroscopy to Study P-glycoprotein

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Using Fluorescent Spectroscopy to Study P-glycoprotein

P-glycoprotein (P-gp), a member of the ATP Binding Cassette (ABC) superfamily, is a drug transporter that effluxes a broad spectrum of therapeutic agents. P-gp is expressed in many tissues important in drug disposition including the intestine, liver, kidneys, and blood-brain-barrier, [where it](#) acts to decrease drug absorption following oral administration, facilitate elimination from the body, and decrease drug exposure in tissues such as the brain. This 170 kDa protein consists of two similar halves, each composed of 6 helical transmembrane regions and an ATP-binding domain. Genetic variations in the *ABCB1* gene that encodes P-gp lead to alterations in P-gp expression and activity, which can affect [interindividual variation in the development of](#) multidrug resistance and drug disposition [of P-gp substrates like chemotherapeutic agents, immunosuppressive agents and calcium channel blockers](#). [We hypothesize, however, that current methods are lacking in their ability to determine the functional consequence of ABCB1 genetic variation on P-gp activity. The goals of our research are](#) to biochemically and biophysically characterize P-gp [binding and activity](#) to understand how *ABCB1* genetic [variations](#) alter activity. One biophysical technique we are using to study [variation in](#) P-glycoprotein [activity](#) is fluorescent spectroscopy. [In our experiments, a](#) fluorescent [substrate](#) is excited using polarized light and emitted photons are measured in both the horizontal and vertical directions. [The data collected](#) [Changes in the polarization of the light](#) can be used to characterize binding interactions, changes in a [fluorescent probe's](#) environment, and the degree [of interaction between molecules under investigation](#). [Using a wild-type P-gp our results have shown that.....](#) [We are interested in how](#) fluorescent spectroscopy [can be](#) used to understand the way in which *ABCB1* genetic [variation](#) can lead to differences in [binding affinity with substrates being effluxed](#), transport activity, and structural [motions of the protein](#). [We will show how](#) binding of two [P-gp fluorescent probe substrates](#), Rhodamine-123 and BODIPY-FL-Verapamil, [can be used to measure P-gp function](#) in [nanodiscs](#), a [lipid bilayer](#) model system. Understanding the differences [in P-gp activity as a function of genetic variation in the ABCB1 gene will enhance our understanding of interindividual variability in the disposition of P-gp substrates and the development of](#) multidrug resistance.