# Allocrite Sensing and Binding by the Breast Cancer Resistance Protein (ABCG2) and P-Glycoprotein (ABCB1)

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The ATP binding cassette (ABC) transporters ABCG2 and ABCB1 perform ATP hydrolysis-dependent efflux of structurally highly diverse compounds, collectively called allocrites. Whereas much is known about allocrite-ABCB1 interactions, the chemical nature and strength of ABCG2-allocrite interactions have not yet been assessed. We quantified and characterized interactions of allocrite with ABCG2 and ABCB1 using a set of 39 diverse compounds. We also investigated potential allocrite binding sites based on available transporter structures and structural models. We demonstrate that ABCG2 binds its allocrites from the lipid membrane, despite their hydrophilicity. Hence, binding of allocrite to both transporters is a two-step process, starting with a lipid-water partitioning step, driven mainly by hydrophobic interactions, followed by a transporter binding step in the lipid membrane. We show that binding of allocrite to both transporters increases with the number of hydrogen bond acceptors in allocrites. Scrutinizing the transporter translocation pathways revealed ample hydrogen bond donors for allocrite binding. Importantly, the hydrogen bond donor strength is, on average, higher in ABCG2 than in ABCB1, which explains the higher measured affinity of allocrite for ABCG2. $\pi$-$\pi$ stacking and $\pi$-cation interactions play additional roles in binding of allocrite to ABCG2 and ABCB1. With this analysis, we demonstrate that these membrane-mediated weak electrostatic interactions between transporters and allocrites allow for transporter promiscuity toward allocrites. The different sensitivities of the transporters to allocrites' charge and amphiphilicity provide transporter specificity. In addition, we show that the different hydrogen bond donor strengths in the two transporters allow for affinity tuning.

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