S17-6 Cellular phototoxicity evoked through the inhibition of human ABC transporter ABCG2 by cyclin-dependent kinase inhibitors in vitro

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The physiological importance of the human ABC (ATP-binding cassette) transporter ABCG2 has been recognized with regard to porphyrin-mediated photosensitivity. Functional impairment owing to inhibition of ABCG2 by drugs or its genetic polymorphisms may lead to the disruption of porphyrin homeostasis, which in turn causes cellular toxicity. In the present study, we evaluated the impact on photosensitivity of the inhibition of ABCG2 function. For this purpose, we established new methods for photosensitivity assays by using Flp-In-293 cells and plasma membrane vesicles prepared from Sf9 insect cells. With the new methods, we subsequently tested CDK (cyclin dependent kinase) inhibitors, i.e., purvalanol A, WHIP180, bohemine, roscovitine, and olomoucine. Among them, purvalanol A was found to be the most potent inhibitor (IC_{50}=3.5 μM) for ABCG2-mediated hematoporphyrin transport. At a concentration of 2.5 μM, it evoked the photosensitivity of ABCG2-expressing Flp-In-293 cells treated with pheophorbide a. WHI-P180 moderately inhibited ABCG2 function, exhibiting weak phototoxicity. In contrast, the phototoxicity of bohemine, roscovitine, and olomoucine were minimal in our assay system. It is suggested that the planar structure is an important factor for interactions with the active site of ABCG2. The present study provides a new approach to studying drug-induced phototoxicity *in vitro*.