

## WAM5-6

### **Cancer stem cells in murine breast cancer are resistant to PDT with photosensitizer substrates of the multiple drug resistance transporter ABCG2**

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Many porphyrins are substrates of the ATP-dependent transporter and multiple drug resistance (MDR) pump ABCG2. ABCG2 present in the plasma membrane can pump out substrate photosensitizers such as the pyropheophorbide analogue HPPH leaving intracellular concentrations which may be insufficient for a phototoxic effect. Many cancer cells appear to be negative for ABCG2 in the bulk of the tumor. However, a small proportion of cells, often < 1% of the tumor, expresses ABCG2 and effluxes fluorescent dyes such as Hoechst, producing a (blue/red) double negative side population (SP) in flow cytometry. The SP compared to the Non-SP phenotype is enriched for stem cell-like properties and can recapitulate the original tumor if transplanted. If the SP can evade phototoxicity, then the tumor is likely to regrow from the survivors. To determine the susceptibility of 4T1 SP cells to phototoxicity, tumors *in vivo* and *in vitro* were treated with PDT with the ABCG2 substrate HPPH and the non-substrate HPPH-Gal (a galactose conjugate of HPPH). 24-72 h after PDT cells were harvested and analysed for the presence of a SP. The relative proportion of surviving cells in the SP was greater when cells were treated with HPPH- compared to HPPH-Gal-PDT. Sensitivity to HPPH-PDT could be restored with tyrosine kinase inhibitors (TKI) of ABCG2 activity, which prevent efflux of HPPH. The relative resistance of SPs in tumors to PDT with ABCG2 substrates may be responsible for recurrences observed both pre-clinically and clinically. Resistance may be abrogated by inhibiting ABCG2 activity for example with specific TKIs or by using non-substrate photosensitizers.