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Unraveling the human multidrug resistance p-glycoprotein poly-specificity

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Abstract

One main mechanism of drug resistance involves multi-drug efflux pumps which expel drugs out of the cells. How these proteins pump out hundreds of toxins, and among them anticancer drugs, while displaying marked specificities is mysterious. We bring here a molecular basis of this mechanism of poly-specificity, having localized the H- and R-sites of the human P-gp, two main sites by which drugs efflux occurs, here exemplified with Hoechst 33342 and daunorubicin**.** We achieved this by characterizing *in cellulo* the inhibition mechanisms of the selenohexapeptide inhibitor QZ59 enantiomers, the first compounds ever co-crystallized with the mouse P-gp, combining these data with the structural analysis of the conformations recently reported.

Results show that the SSS QZ59 enantiomer competitively inhibits Hoechst 33342 and Daunorubicin transports, with $K_{I,app}$ of 0.15 and 0.3 µM respectively, 13 and 2 times lower than corresponding $K_{m,app}$. QZ59-RRR in contrast non-competitively inhibited drugs transport, with a moderate efficacy ($K_{I,app}$ ≥1.6 µM) but became competitive towards Hoechst 33342 at high concentrations ($K_{I,app}$ ~5 µM). This suggests a positional QZ59 groove – drugs-transport sites overlap, full for the H-site and partial for the R-site. The latter may share the most embedded QZ59-SSS location as supported by docking analyses.

These results will guide the design of compounds acting at the molecular level to block P-gp-mediated drug efflux with the highest efficiency.

Biography

Pierre Falson got his PhD at the LYON University. He is a CNRS Research Director, enzymologist and membrane proteins biochemist, co-leading the *Drug resistance mechanism and modulation* team in the BMSSI CNRS-UCBL1 Research Unit. PF has published 54 publications, patented 6 inventions and licensed2 to CALIXAR, a startup which he co-founded. He was awarded in 1991 by the Maurice Nicloux prize from the French Society of Biochemistry and Molecular Biology, in 2010 and 2011 by the “National competition of innovative start-ups” and by the Innovation and Transfer Technology prize from the CNRS.