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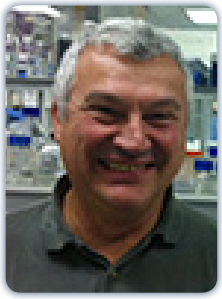

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Multidrug resistance ABC pumps as targets for reducing efflux and improving bioavailability of drugs

ABC transporters constitute a key family in the field of public health, being responsible in humans for the cellular multidrug resistance phenotype encountered during chemotherapeutic treatments against cancer and viral diseases. The same type of proteins is found in bacteria, parasites, yeasts and plants. In humans, the P-glycoprotein, P-gp/ABCB1, the multidrug resistance protein, MRP1/ABCC1 and the breast cancer resistance protein, BCRP/ABCG2 are manly involved in this phenotype; MRP2/ABCC2 is also involved in cisplatin resistance. The same transporters are also enriched at physiological barriers such as the brain-blood barrierwhich hampers any anticancer chemotherapy.Since 2006, several 3D structures have been released, in 2 main conformations, in which the drug-binding region is accessible to the cytosol or to the extracellular space. Such conformations suggest thatABC transporters may pump substrates through an alternating-access mechanism, as described for lactose/proton symporterLacY and the glycerol-3-phosphate/Pi antiporterGlpT, which supposes two distinct states of the pump with different accessibilities and affinities. Some ABC pumps display an allosteric behavior which strengthens this hypothesis. But ABC transporters have the capacity to pump out of cells hundreds of cytotoxics by a mechanism of poly-specificity which is far to be understood.A ligand-based drug approach led to the development of specific and potent inhibitors, which, together with chemical modifications, allowedto obtain insights in the mechanism of drug efflux.The co-crystallization of 2 enantiomers of QZ59, a seleno-tricylcopeptide, allowed to locate the drug binding region. The elucidation of their inhibition mechanism towards drugs binding to the H- and R-sites of the P-gp, was useful to map these sites through which drugs are translocated, and to bring a molecular basis of the poly-specificity which characterize these fascinating class of membrane proteins. Structural information opens the way to a structure-based development of inhibitors, a route that may be more difficult than expected when considering the plasticity of these pumps.

Biography

Pierre Falson got his PhD at the LYON University. He is a CNRS (National Centre for Scientific Research) Research Director, enzymologist and membrane proteins biochemist, co-leading the Drug resistance mechanism and modulation team in the BMSSI CNRS-UCBL1 Research Unit. PFhas 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 theCNRS.

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