

Preface

The development of resistance is a major obstacle in cancer chemotherapy since decades. Drug resistance may develop during repeated treatment cycles after initially successful therapy (acquired or secondary resistance). Alternatively, tumors may be resistant from the beginning (inherent or primary resistance). The failure of chemotherapy is a major reason for the fatal outcome of tumor diseases in many patients. Even worse, tumors frequently develop resistance not only to single drugs but also to many others at the same time. This phenomenon was termed **multidrug resistance** and decreases the success rates of therapy regimens with combinations of structurally and functionally different drugs.

The pioneering research of Victor Ling, Michael M. Gottesman, and others led to the discovery of the drug efflux transporter **P-glycoprotein** and its encoding gene, *MDR1*. This membrane protein expels a large array of different drugs and xenobiotic compounds out of the tumor cell leading to sublethal intracellular drug concentration and ultimately survival of tumor cells.

The initial cross-resistance profile of P-glycoprotein (P-gp) comprises **anthracyclines** (doxorubicin, daunorubicin), **Vinca-alkaloids** (vincristine, vinblastine), **epipodophyllotoxins** (etoposide, teniposide), **taxanes** (paclitaxel, docetaxel), and others.

P-gp/*MDR1* belongs to the family of ATP-binding cassette (ABC) transporters which are widely distributed in nature from bacteria to humans. The human genome consists of 48 ABC transporter genes, with P-gp/*MDR1* as the best analyzed one. Other drug resistance mediating ABC transporters are the multidrug resistance-related proteins (MRPs), breast cancer resistance protein (BCRP), and others. These ABC transporters are also characterized by specific cross-resistance profiles, which partly differ from the one of P-gp. They can also confer resistance to **camptothecin derivatives** (topotecan, irinotecan), **Mitoxantrone**, **sterols**, **tyrosine kinase inhibitors**, **compounds used in photodynamic therapy** **antimetabolites**, and others.

The uncommonly broad spectrum of anticancer agents that are transported by ABC transporters makes these proteins exquisite targets to search for compounds that inhibit their transport function. The idea is to block ABC transporter-mediated

drug efflux by specific inhibitors and thereby to overcome multidrug resistance. This concept was introduced by Takashi Tsuruo, who described that verapamil is able to inhibit P-gp's transport function. Subsequently, a huge amount of compounds from many pharmacologically established drug classes (e.g., **calcium channel blockers, calmodulin antagonists, cyclosporines, dipyridamole, and other hydrophobic, cationic compounds**) were observed to inhibit P-gp and to reverse multidrug resistance. Interestingly, many natural compounds derived from plants or marine organisms were also found to block ABC transporters' function.

All these fascinating results from basic cancer research were complemented by investigations from clinical oncology. A plethora of analyses have shown that P-gp/*MDR1* is of predictive value for success or failure of chemotherapy and of prognostic value for the survival time of cancer patients. Since certain **radiopharmaceuticals** are also transported by ABC transporters, they can be used for radiological diagnosis of multidrug-resistant tumors.

The importance of ABC transporters for drug resistance in tumors and the thriving development of research in this area can also be documented by the number of papers appearing every year during the past three decades (Fig. 1). ABC transporters have been a hot topic in cancer research for many years and still are. This motivated me to edit a book on this topic to keep scientists and physicians updated with the latest development in this exciting research area. I was fortunate to team up a panel of international experts with renowned expertise in the field of ABC transporters in drug-resistant tumors. The book covers most currently relevant topics in

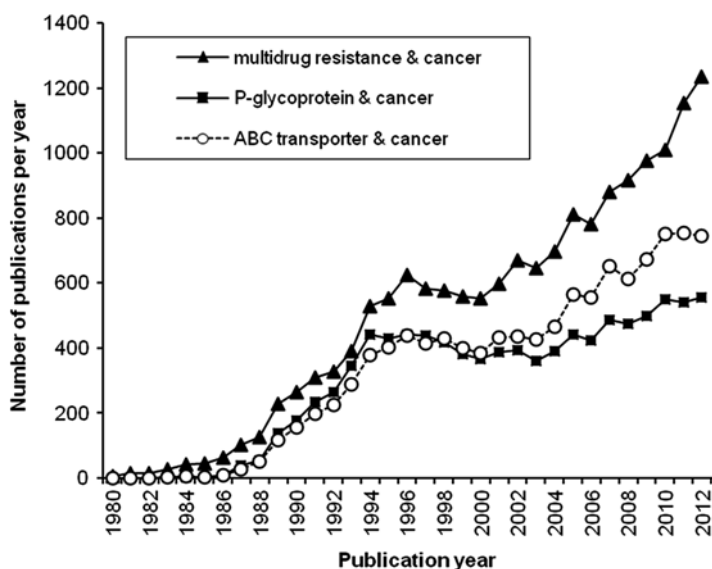


Fig. 1 Survey of the literature deposited in the PubMed database from 1980 to 2012 with the indicated keywords

the field reaching from the clinical relevance of ABC transporters for resistance to novel and established anticancer drugs and prognosis of patients to compounds to modulate multidrug resistance, compounds used in photodynamic therapy, tyrosine kinase inhibitors, and others. Furthermore, the potential of radiopharmaceuticals for diagnosis of multidrug-resistant tumors will be discussed.



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Resistance to Targeted ABC Transporters in Cancer

Efferth, Th. (Ed.)

2015, X, 300 p. 60 illus., 21 illus. in color., Hardcover

ISBN: 978-3-319-09800-5