halogen atoms, but this aim would require that neither of the other ABC transporters be involved in chemoresistance. Only a few examples of this approach have been published.[68]

2.3 INDIRECT INHIBITORS OF MDR

The Pgp expression and function is influenced by several enzymes like cyclooxygenase 2[69] or glucosylceramide synthase,[70] which can be indirect targets in MDR inhibition. Certain compounds, such as the anticancer drug ecteinascidin-743, can prevent *mdr1* gene expression,[71] which can also be achieved by RNA interference through small RNA constructs (siRNA).[72] However, inhibition of the biosynthesis of the transport proteins by use of antisense oligonucleotides related to MRP or Pgp mRNAs seems to be of low clinical relevance despite previous good *in vitro* results.[73] Inhibitors of the Pgp ATPase activity with compounds such as the vanadate ion have also been proposed as adjuvants in the chemotherapy of solid tumors.[74] Other alternative approaches that can be used to kill cells expressing the MDR phenotype[75] are based on optimization of drug delivery by use of nanoparticles or liposomes,[76] which may be combined with hyperthermia.[77]

2.4 IMPORTANCE OF THE PGP INHIBITION DATA IN NEW DRUG APPLICATIONS

All efforts to achieve clinically relevant efflux pump inhibitors have revealed that a new molecular entity should be examined as a substrate or inhibitor of these transporters in drug development and regulatory reviews. Recommendations on methodologies and strategies for studying key transporters including Pgp[78] advise that the timing of transporter investigations should be driven by efficacy, safety, and clinical trial enrollment questions.[79]

3 GLUTATHIONE AND GLUTATHIONE *S*-TRANSFERASE IN ANTICANCER DRUG RESISTANCE

Glutathione (L-γ-glutamyl-L-cysteinyl-glycine, GSH) is an antioxidant intracellular tripeptide that plays an important role in the maintenance of cellular redox potential, although it also functions in many other biological processes. GSH is a radical scavenger through its transformation to the disulfide derivative, but it is also a nucleophile that reacts with electrophiles to form deactivated conjugates readily excreted by a glutathione synthase (GS)-conjugated export pump, in a reaction that may occur spontaneously or with the help of the enzyme glutathione *S*-transferase (GST).[80] In addition, GSH may directly or indirectly participate in DNA repair because it modulates the expression of transcription factors such as *c-fos* and *c-jun* that potentially affect DNA repair and apoptosis.[81] Also, through the preservation of protein mercapto groups in a reduced state due to its antioxidant function, it protects tumor cells against apoptotic cell death.[82]

Due to its reactivity and high intracellular concentrations, glutathione has been implicated in resistance of several chemotherapeutic agents, such as platinum-containing agents,[83] alkylating agents,[84] and anthracyclines.[85] For instance, Bcl-2-mediated cisplatin resistance in MCF-7 breast cancer cells is dependent on upregulation of glutathione production, which contributes to cell survival by mechanisms independent of cisplatin inactivation or inhibition of DNA adduct formation.[86]