# *COLLOQUIA IN MEMBRANE TRANSPORT*

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
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Monday 07.04.2014 14:30 s.t. **Armin Buschauer** (host: G. Ecker)

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## *"Modulation of the efflux transporters ABCB1 and ABCG2: An approach to overcome the blood brain barrier and cancer chemoresistance"*

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Abstract: P-glycoprotein (P-gp, ABCB1) and breast cancer resistance protein (BCRP, ABCG2) are physiologically relevant efflux pumps, strongly affecting absorption, distribution and excretion of various drugs. The chemotherapy of malignant brain tumors is considerably compromised by the activity of the efflux transporters P-gp and BCRP, located at the blood-brain barrier. Furthermore, over-expression of ABC transporters by tumor cells is one of the major mechanisms of anticancer drug resistance. Hence, at least in theory, modulation of ABCB1 and/or ABCG2 is an attractive strategy to improve the therapy of both, tumors in the CNS and malignancies in the periphery.
Previously, in a proof-of-concept study, we demonstrated that co-administration of the ABCB1 modulator valspodar resulted in a considerable increase in paclitaxel levels in the brains of nude mice [1]. The treatment of nude mice, bearing orthotopically growing human glioblastoma xenografts, led to a decrease in tumor volume by 90 % [1]. Increased peripheral toxicity due to elevated plasma levels of the cytostatic, characteristic of combination treatment with valspodar, was not observed with the 3rd generation ABCB1 modulators tariquidar or elacridar [2]. Nevertheless, preclinical in vivo studies suggested that the physicochemical properties of the latter are not optimal. Aiming at more selective modulators with improved physicochemical properties, we synthesized, in an initial approach, compounds chemically derived from tariquidar and performed in vitro studies to explore their potential value in cancer chemotherapy. Surprisingly, in addition to ABCB1 inhibitors, we identified potent and highly selective inhibitors of the ABCG2 transporter [3-6]. Whereas first compounds were prone to rapid enzymatic cleavage and showed very poor solubility, bioisosteric approaches led to next generations ABCG2 modulators with improved properties. This lecture will give an overview of our approach, based on tumor pharmacology and medicinal chemistry concepts. Examples of ABCB1 and ABCG2 modulators will be presented in the context with in vitro and in vivo investigations.

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