

SFB 35 Colloquia in Membrane Transport

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna,

"Leseraum"

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Monday 12.6.2017 14:00 s.t.

Host: Karl Kuchler

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"Mechanism and Inhibition of ABC Transporters that Mediate Multidrug Resistances in Cancer"

John G. Wise

Abstract.

Cancers recurring after chemotherapeutic treatment often present resistances to most of the currently available anti-cancer drugs. Similar resistances also occur in the chronic treatment of diseases like HIV-AIDS, epilepsy, and other important disorders. Such insensitivities to therapies pose immense problems to the treatment of the affected patients. One cause of such drug resistances is the overproduction of members of the ABC transporter membrane proteins, P-glycoprotein (P-gp, ABCB1), breast cancer resistance protein (BCRP, ABCG2), and/or the Multidrug Resistance-associated Protein 1 (MRP1, ABCC1). These ABC-transporters pump therapeutics out of cells, thereby lowering effective intracellular concentrations of the drugs to sub-therapeutic levels. In this study, we have investigated the mechanism of transport by P-glycoprotein using molecular simulation methods and have identified a number of inhibitors of P-glycoprotein and BCRP using massively parallel computational methods. Initial validation of the in silico identified inhibitors in biochemical, biophysical, and cell culture assays as well as novel optimization of hits will be reported.

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