Impromptu Seminar

Venue: Medical University Vienna, Center for Physiology and Pharmacology,
Institute of Pharmacology, Waehringerstrasse 13a, 1090 Vienna, "**Leseraum**".
(Harald Sitte, Tel.: (01) 40160 31323, *harald.sitte@meduniwien.ac.at*)

Friday 21.06.2013 14:00 s.t. **Gergely Szakacz** (host: M. Sibilia)

Institute of Enzymology
Research Centre for Natural Sciences
Hungarian Academy of Sciences
Budapest

"Defeating drug resistant cancer"

Gergely Szakacz (szakacs@biomembrane.hu)

Abstract:
Progress in the prevention, early diagnosis, and treatment of cancer has led to a steady decline in cancer death rates. Most who succumb to cancer die because their disseminated cancer doesn't respond to available chemotherapies. We have learned much about drug action, and efforts to elucidate the molecular basis for resistance have revealed a variety of mechanisms that either prevent a drug from reaching its target, deploy compensatory mechanisms promoting survival, or lull cancer cells into a dormant state. In case of targeted therapies, mechanisms of resistance may be limited to the specific drugs whose action is dependent on a given cancer-specific target. Combination treatments may lose efficacy due to cellular mechanisms that induce resistance to multiple cytotoxic agents. Of these mechanisms, the one that is most commonly encountered in the laboratory is the increased efflux of a broad class of hydrophobic cytotoxic drugs that is mediated by ATP-binding cassette (ABC) transporters such as P-glycoprotein (Pgp).
Conceivably, by circumventing resistance mechanisms, the efficacy of first line drugs could be restored. Strategies to circumvent the reduced drug accumulation conferred by ABC ("ATP-binding cassette") transporters have relied on attempts to develop drugs that bypass extrusion (often with a sacrifice in activity); or the exploration of clinical inhibitors that, although showing promise *in vitro*, have not translated to the clinic. Our proposed approach is to target the Achilles' heel of cancer cells by exploiting the paradoxical hypersensitivity of otherwise multidrug resistant (MDR) cells. Collateral sensitivity (CS) of MDR cells has been described as a curious anomaly, brought about by a diverse array of compounds including local anesthetics, steroid hormones and non-ionic detergents. Using a systematic approach we show that the activity of most of the reported CS compounds is cell-line specific, and is not influenced by P-glycoprotein. In contrast, MDR-selective compounds that we identify in the National Cancer Institute's DTP drug repository retain a P-glycoprotein –dependent toxic activity across diverse cell lines. Significant progress in reducing death and suffering from cancer will only come after means have been found to reduce the impact of drug resistance on current treatment protocols. The discovery of the MDR-selective compound set shows the robustness of the developing field of MDR-targeting therapy as a new strategy for resolving Pgp-mediated MDR.