665 **ALTERED DISPOSITION OF ETOPOSIDE (VP-16) BY TAMOXIFEN (TMX) IN P-GLYCOPROTEIN (P-GP)-CONTAINING TISSUES IN RATS.** *C. Malcon, G.L. Lopes, D. Becker, G. Schwartsmann, D.R.A. Mans* (senior investigator). South-American Office for Anticancer Drug Development (SOAD)/HCPA.

Inhibition of P-gp-mediated enhanced cytotoxic drug efflux in P-gp-overexpressing tumors is an attractive means to overcome multidrug resistance. However, this approach may lead to excessive toxicity to normal P-gp-containing tissues. We investigated, in a rat model, whether the relatively safe P-gp modulator Tmx affects the disposition of VP-16, a well-studied P-gp substrate, in such tissues. Groups of 4-5 rats of about 6 months of age were randomized to receive either: A) VP-16 for 3 days; B) VP-16 plus Tmx for 3 days; C) Tmx at days 1 and 2, and VP-16 for the next 3 days; or D) Tmx at days 1 to 5, and VP-16 at days 3 to 5. Tmx and VP-16 were given i.p. as a bolus of 120 or 100 mg/m^2, respectively. At about 2.5 hours after the last VP-16 injection, the P-gp-containing organs were dissected, homogenized and VP-16 was determined by HPLC, after chloroform extraction. We found an essentially similar disposition of VP-16 among the 4 groups in organs with a low to moderate P-gp content, such as the lungs and the small intestine. By contrast, in the liver, pancreas, and kidney, and possibly also in the brain and the adrenals, VP-16 was 2-3 x higher in group D compared to the other groups. These findings suggest that high-dose Tmx increases VP-16 disposition in constitutively P-gp-overexpressing tissues, when Tmx is given prior to, as well as concomitantly with VP-16. This observation is being confirmed in further studies.