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TRANSMEMBRANE DRUG TRANSPORT IN MICROGRAVITY

Abstract

Introduction: Several reports suggest enzimes and trans-membrane channels function differently in microgravity (Graebe, *et al.* 2004; Goldemann *et al.* 2001; Maccarrone *et al.* 2001; Giachetti *et al.* 2001; Tash *et al.* 1999). Water-lipid interactions, especially when affecting cell membrane, have been hioptetized to explain some of these observations. ABC (ATP Binding Cassette) transporter family is an active trans-membrane transport systems in human cells involved in pharmacokinetics, drug-to-drug interactions and drug resistance (Galvinas *et al.* 2004; Beringer *et al.* 2005; Choudhuri 2006). This project aims to determine whether microgravity can modify ABC transporter mediated trans-membrane drug transport in human model cells. Additionally this research wills to enhance knowledge on ABC transporters and provide new information for improving Earth treatments.

Methods: Developed by students under the auspices of the "Fly your thesis" project and flying on 51st ESA Parabolic Flight Campaign, a tailored electro-mechanical prototype was designed following ESA / Novespace specifications. Such system enabled combination of reactives at controlled temperatures and timeframes. MRP2 (Multi-drug Resistance Protein 2) vesicles (SolvoBiotechnology TM) were chosen to study the effect of microgravity on vesicular transport of estradiol-17-β-glucuronide when activated by adenosine-tri-phosphate (ATP). Other susceptible processes such as simple diffusion or spontaneous transport activity were also evaluated in

three additional conditions (defective vesicles, addition of benzobromarone (BZM) a well-known transport-inhibitor, and no-ATP mix). Estradiol detection was performed by a standardized steroidal drug protocol using high sensitivity Gas Chromatography coupled with Mass Spectrometry (GC-MS) technique. Results were compared to those obtained with on-ground reference samples. T-Student test assuming different variance of samples, with $p<0.025$ (double tailed), was used to compare results.

Results: In 0g MRP2 fully activated controls showed expected behaviour presenting higher transport speed than no-ATP, MRP2-defective and BZM controls ($p<0.001$), therefore demonstrating feasibility of the proposed assay, accuracy of the prototype and validity of methods used. When results are compared to 1g reference samples, a trend to an enhanced active transport, reduced simple diffusion and facilitated MRP2 inhibition in microgravity is observed, however definitive statistical evaluation is pending upon completion of remaining sample analysis before next October.