

**POSTER 55****REDUCED RIBAVIRIN ANTIVIRAL EFFICACY VIA NUCLEOSIDE TRANSPORTER-MEDIATED DRUG RESISTANCE**

Kristie Ibarra and Julie K. Pfeiffer

Department of Microbiology, University of Texas Southwestern Medical Center, Dallas, TX

Hepatitis C virus is a global health problem affecting approximately 170 million people. Treatment currently consists of pegylated interferon and ribavirin (RBV), a nucleoside analog. Although RBV clearly plays a role in aiding treatment response, its antiviral mechanism is controversial. Regardless of the specific mechanism of RBV, we hypothesize that differences in cellular uptake of RBV may affect antiviral efficacy and treatment success, and that cells may become RBV-resistant (RBV<sup>R</sup>) through reduced uptake. We monitored RBV uptake in various cell lines and determined the effect of uptake level on viral replication. RBV<sup>R</sup> cells had reduced uptake, facilitating increased growth of poliovirus in the presence of RBV compared to ribavirin sensitive (RBV<sup>S</sup>) cells. We found that while both the equilibrative nucleoside transporter 1 (ENT1) and the concentrative nucleoside transporter 3 (CNT3) are capable of transporting RBV into cells, transport is primarily restricted to ENT1 in the human hepatoma cell line Huh 7. By blocking equilibrative transport, using the inhibitor nitrobenzylmercaptapurine riboside (NBMPR), we were able to mimic the resistant phenotype in our RBV<sup>S</sup> cell lines, with a reduction in RBV uptake and increased poliovirus growth. Over-expression of ENT1 increased RBV uptake in RBV<sup>S</sup> cells and restored the uptake defect in most RBV<sup>R</sup> lines tested. It is possible that RBV uptake affects treatment response, either through natural differences in patients or through acquired resistance. If this is the case, diagnostics could be developed to aid in customizing treatment regimens, and/or predicting treatment success.