Validation of Organotypic Small Intestine Tissue Model for Drug Permeability, Drug-Drug Interaction, and Metabolism Studies

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Purpose
The goal of this study is to validate a biologically relevant organotypic small intestinal (SMI) tissue model to predict intestinal drug absorption/bioavailability of orally administered drugs. Primary human cell based small intestinal (SMI) 3D tissue models that recapitulate in vivo counterpart phenotypically, structurally and functionally will be a relevant testing model for therapeutic drug screening, drug metabolism, and drug-drug interaction studies. Currently used cell-line based assays are not physiological and do not mimic the in vivo microenvironment.

Methods
Human primary SMI epithelial cells and fibroblasts were used to reconstruct SMI tissues. Outcome measurements include transepithelial electrical resistance (TEER), PCR, and histology. Bioavailability of drugs or efflux transport was analyzed by LC-MS/MS (N = 16 drugs from different Biopharmaceutics Classification System (BCS) classification). The sensitivity and accuracy of the in vitro method compared to historical absorption data was calculated. Test drug with human absorption of >80% and in vitro Papp of >2 \times 10^6 \text{ cm}^{-1} \text{s}^{-1} was considered as high permeable and drugs that showed <80% and in human absorption and an in vitro Papp value of <2 \times 10^6 \text{ cm}^{-1} \text{s}^{-1} was considered as low permeable drug. Expression of intestinal drug metabolizing enzymes was analyzed by qPCR. To assess the metabolic capacity of the in vitro SMI tissue model specific substrates such as Midazolam were used and metabolites were analyzed by LC/MS.

Results
In Concordance with the historical % human absorption data, the apparent permeability coefficient (Papp) values differentiate the test articles as high and low permeability drugs. The SMI tissue model categorizes test drugs as high permeable and low permeable with a sensitivity of 100%, specificity of 89%, and accuracy of 94% compared to the % human absorption data available from the literature. Atenolol (paracellular) transport and propranolol (intercellular) transport with known human absorption of 50% and 90% respectively, were used as markers for ranking the test compounds. The FDA recommended P-glycoprotein substrate (Quinidine) was used as control for efflux transport. Drug-drug interactions were examined using efflux transporter inhibitors and the inhibitors increased drug bioavailability while decreasing the efflux ratio. Efflux ratios of Pgp substrates (talinolol, digoxin, and loperamide) were reduced by 45%, 40%, and 60%, respectively, in the presence of the Pgp inhibitor (verapamil). Efflux ratio of nitrofurantoin (BCRP substrate) was reduced by 63% in the presence of its inhibitor novobiocin. Results from drug metabolism studies also showed Midazolam (CPY3A substrate) was metabolized (6.5% conversion) by the intestinal tissue model.

Conclusion
The newly developed SMI tissue models appear to be promising new tool for evaluation of drug safety, permeability, and metabolism. This novel in vitro intestinal model can serve as a platform for testing bioavailability and effectiveness of drug candidates prior to clinical studies. Availability of primary cell based human 3D intestinal tissue model will also reduce the need for unreliable animal studies.