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# A Pharmacogenomic Study on Regional Dependent gene Expression and Drug Permeability in Rat Intestine

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RNA was isolated from mucosal tissue of the duodenum, jejunum, ileum and colon after perfusion. The gene expression profiles were measured using Affymetrix GeneChip® analysis. Prodrug valacyclovir permeability was 5-fold and 2-fold higher than the parent drug acyclovir in the jejunum and ileum, respectively. Valacyclovir and phenylalanine permeability did not exhibit a significant regional difference between the jejunum and ileum, while propranolol and verapamil showed higher permeability in the ileum than in the jejunum by 1.5-fold and 1.9-fold, respectively. The permeability of propranolol correlated well with the permeability of verapamil in both jejunum and ileum with a correlation coefficient (R2) of 0.791 and 0.909, respectively. This suggests that verapamil and propranolol utilize a similar mechanism for oral absorption. The gene expression profiles showed that 39%-44% of 8739 sequences were expressed in rat intestine. There were dramatic expression differences in the different regions of intestine, in which there were 340-499 sequences that showed more than 5-fold expression differences when comparing small intestine regions to colon. Of 719 sequences of transporters and metabolizing enzymes that determined through GeneChip® analysis, total of 51-76 transporters and metabolizing enzymes showed more than 2-fold expression differences when comparing small intestinal regions to colon. The overall expression levels of expressed transporters and metabolizing enzymes decreased along GI tract from duodenum to colon by at least 2-3-fold with the exception that the expression of some transporters and metabolizing enzymes including mdr1, MLP2, MCT1, brain glucose transporter, and fatty acid transporter increased along the GI tract by 5-25 fold from the duodenum to colon. Cluster analysis of expressed transporters and metabolizing enzymes showed that the duodenum and jejunum exhibited a similar expression pattern, while ileum and colon

showed similar expression pattern. PepT1 mRNA levels detected by GeneChip® analysis was at a similar high level in duodenum, jejunum and ileum, but 64-70-fold lower in colon than in the small intestine regions. Correlation analysis indicated that there is no correlation between valacyclovir permeability and PepT1 mRNA levels detected by GeneChip® analysis in either jejunum or ileum. Interestingly, there were reasonable correlations in both the jejunum and ileum between valacyclovir permeability and expression levels of the sodium/purine transporter (rCNT2), an EST sequence similar to acyl carrier, an ER ATPase, and 7 other non-transporter proteins including alpha-tubulin. This suggests that more than one transporter might be involved in valacyclovir intestinal absorption.

**Keyword** : Pharmacogenomics, Gene expression, Rat intestine, Drugs