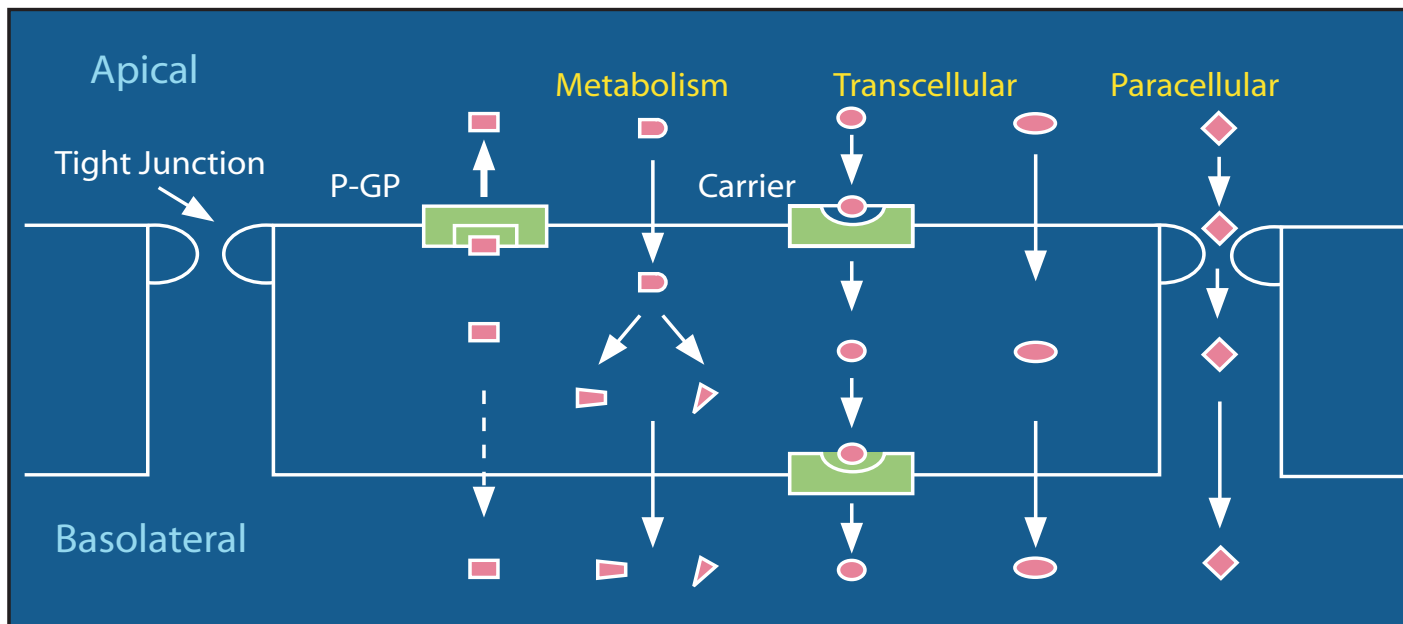




In Vitro Permeability Models



Cellular transport pathways

In vitro permeability studies can assess the oral absorption potential and characteristics of drug candidates. Typically Caco-2 and/or Madin-Darby canine kidney (MDCK) cells grown as monolayers in Transwells are used for these types of studies. The Caco-2 system is preferred over other systems, such as everted gut segments or intestinal rings, for the study of oral absorption because (1) it uses human-derived cells, (2) both disappearance of the compound from the apical (luminal) side and appearance of the compound on the basolateral (serosal) side can be monitored, (3) good correlation can be obtained between permeability across Caco-2 cell monolayers and absorption in humans for a large variety of chemical series, and (4) the system is amenable for elucidating factors (e.g., efflux transporters, metabolism, paracellular transport) associated with poor transport of drug molecules.

Advantages of Caco-2 (Human Carcinoma of the Colon) Cells

- Derived from human colon carcinoma cells
- Easy to use and analytically clean, with good viability and reproducibility
- Differentiate into polarized cells that mimic the small intestine
- Provide absorption/transport information at cellular level
- Easily manipulated to obtain information on transport mechanism(s)

(continued)



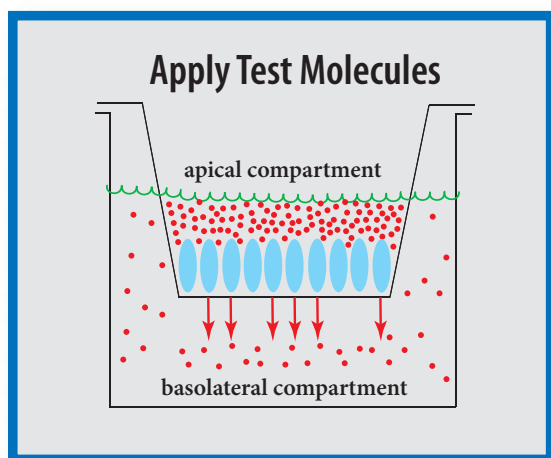
In Vitro Permeability Models *(continued)*

Applications of Caco-2 Permeation Screens

- Transport mechanisms—passive diffusion
- Transport mechanisms—carrier-mediated
- Assessment of prodrugs
- pH effects on transport
- Cytotoxicity vs absorption enhancement
- Chemotherapeutics
- Rapid absorption screen

Features of Caco-2 Cell Monolayers

- Form tight junctions between cells
- Express many of the transporters found in the small intestine (bile acid, amino acid, dipeptide, tri-peptide, etc.)
- Express the p-glycoprotein efflux pump
- Exhibit metabolizing enzymes on the brush border membrane and in the cytosol



Permeability assay assessment

MDCK cells are a well-established polarized epithelial cell line that, like Caco-2 cells, have been shown to differentiate and form tight junctions when cultured on semipermeable membranes. As a result of their more rapid growth rate, MDCK cells offer the advantage of higher throughput than Caco-2 cells, which are limited by both a 3-week growth period and regular maintenance feeding requirements. MDCK cells provide information about the passive permeability of a chemical class and therefore are a more simplistic system. Also, specific cell lines have been generated that possessed single expressed transporters, such as the MDR1 construct, for use in a more defined experiment.

Advantages of MDCK (Madin-Darby Canine Kidney) Cells

- Easy to use and analytically clean, with good viability and reproducibility
- Passive diffusional transport information at the cellular level
- Lack of substantial levels of metabolizing systems or p-glycoprotein pumps
- Three-day growth period

RTI currently has Caco-2 cells, MDCK cells, and MDCK-MDR1 (multi-drug resistance 1) cells available for use in its study designs.

For more information about RTI's drug metabolism and pharmacokinetics services, contact

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