Why do we know so little about absorption pathways in the lung?
The potential role of transporters in pulmonary drug disposition

Carsten Ehhardt
Trinity College Dublin

Although there is a modest body of literature on the absorption of inhaled pharmaceuticals, there is still a surprising lack of knowledge about the details of the process. Where are molecules absorbed, how well are different lung compartments penetrated and what mechanisms are involved?

Effect of drug transporters
In drug development, particular attention has been paid to transporters expressed in epithelia of the intestine, liver and kidney and in the endothelium of the blood-brain barrier. Nevertheless, drug transporter effects on pulmonary drug disposition have also been hypothesized for several years. Initially, in vitro studies presented data consistent with the idea that drug absorption from the lungs is not exclusively mediated by passive diffusion. Instead, it was suggested that airway residence times of drugs may be altered by facilitative diffusion via channels or transporters and pathways requiring primary or secondary cellular energy such as symporters, antiporters or efflux pumps. (See definitions.) These pioneering studies showed the expression of drug transporters in lung tissues in situ or demonstrated transporter-related effects in cultured cells, but the translation of these data into the clinical reality was still missing. Are transporters facilitating the absorption of locally- or systemically-acting drugs? Can efflux pumps extend the residence time in the airspace? How will inhaled drugs interfere with physiological transporter substrates? How will genetic variations impact bioavailability (and potentially toxic systemic side effects) in patient populations? These questions are difficult to answer in a test tube.

Recent advances
Recently, however, studies conducted in experimental animal models and human volunteers reported findings that support the hypothesis that drug transporters have the ability to modulate access of drugs to intracellular targets and submucosal lung tissues, and potentially influence drug absorption profiles into and from the systemic circulation. In this context, both uptake transporters and efflux pumps are of interest. Nakashima and colleagues demonstrated the contribution of organic cation transporters to tracheobronchial absorption of ipratropium bromide, by showing that the accumulation of the drug in mouse tracheal tissue was time- and concentration-dependent and could be attenuated by known inhibitors of organic cation transporters. In an intact isolated rat lung model, alongside two isolated mouse lung models, using either specific chemical P-glycoprotein (P-gp) inhibitors or knockout animals, Al-Jayyoussi, et al., showed that P-gp can indeed affect drug absorption from the lung and, therefore, the lung residence time of certain inhaled drugs. The first clinical evidence for transporter effects after inhalation came from a study by Mehta and colleagues, who investigated the impact of the orally administered P-gp inhibitor, verapamil (240 mg SR tablet, one hour prior to inhalation), a moderate P-gp and weak breast cancer resistance protein (BCRP) inhibitor, on the pharmacokinetics of inhaled umecinium and vilanterol in healthy volunteers. The areas under the curve (AUC) of both drugs were increased with co-administered verapamil at early time points and these differences eventually became significant at later time points (i.e., 2 hours post inhalation). Whether these enhanced AUC values were caused by efflux pump inhibition in the lung (and thus, enhanced absorption) or decreased clearance in the kidneys, however, remains to be confirmed.

Implications
Orally administered drugs are routinely screened for drug-transporter interactions during preclinical development. Should similar standards be applied to inhaled drugs? In this context, it is important to establish relevant organotypic in vitro systems. These models need valid in vitro parameter values in order to accurately predict pharmacokinetics (PK) under a variety of conditions. A better understanding of the determinants of pulmonary drug absorption and disposition will enable safer and more effective inhaled medicines in the future.
References


Definitions

A transport protein in the cell membrane allows for selective passage of specific molecules to and from the external environment. Each transport protein is specific to a certain substrate molecule.

A symporter is a transport protein that simultaneously transports two substances across a membrane in the same direction.

An antiporter is a transport protein that simultaneously transports two or more substances across a membrane in opposite directions.

An efflux pump is a transport protein involved in the extrusion of substrates (including many classes of clinically-relevant drugs) from within cells into the external environment. This process generally requires cellular energy.

Carsten Ehrhardt is an Associate Professor in Pharmaceutics and Pharmaceutical Technology, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Panoz Institute, Dublin 2 Ireland, Tel: +353 1 896 2441, EHRHARDC@tcd.ie.