Isolated Perfused Lung Models

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NOW... 10 Months Scientific Evidence For Chesterfield

A medical specialist is making regular bi-monthly examinations of a group of people from various walks of life. 45 percent of this group have smoked Chesterfield for an average of over ten years.

After ten months, the medical specialist reports that he observed:

- no adverse effects on the nose, throat and sinuses of the group from smoking Chesterfield.

MUCH MILD

CHESTERFIELD

IS BEST FOR YOU
Overview: IPL & applications

- The isolated perfused lung preparation
- Absorptive transport
- PK modification
- Effect of drug transporters
Table 2. Physiological parameters in mouse, rat, rabbit and human of relevance to the isolated perfused lung preparation (data from Davies et al., 1993). Respiratory tidal volume can be calculated by dividing total ventilation by respiratory rate.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mouse (0.02 kg)</th>
<th>Rat (0.25 kg)</th>
<th>Rabbit (2.5 kg)</th>
<th>Human (70 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung weight (g)</td>
<td>0.12</td>
<td>1.5</td>
<td>18</td>
<td>1000</td>
</tr>
<tr>
<td>Lung volume (ml)</td>
<td>0.1</td>
<td>2.1</td>
<td>17</td>
<td>1170</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>163</td>
<td>85</td>
<td>51</td>
<td>12</td>
</tr>
<tr>
<td>Total ventilation (l/min)</td>
<td>0.025</td>
<td>0.12</td>
<td>0.8</td>
<td>8.0</td>
</tr>
<tr>
<td>Blood volume (ml)</td>
<td>1.7</td>
<td>13.5</td>
<td>165</td>
<td>5200</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>8.0</td>
<td>74</td>
<td>530</td>
<td>5600</td>
</tr>
</tbody>
</table>
IPL: Set up

Complex

Simple
### IPL: Drug administration

<table>
<thead>
<tr>
<th>Aerosol</th>
<th>Instillate/spray</th>
<th>Perfusate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dustgun</td>
<td>Microsprayer</td>
<td>Bolus</td>
</tr>
<tr>
<td>Nebuliser</td>
<td>Solution</td>
<td>Infusion</td>
</tr>
<tr>
<td>PreciseInhale</td>
<td>Propellant-driven</td>
<td></td>
</tr>
</tbody>
</table>
IPL: sampling transfer to perfusate (after drug administration to airways)

Tronde et al 2003
IPL: Sampling accumulation in lungs / washout in perfusate (after vascular administration)

Drug in the lungs

Drug in perfusate

Unpublished data
Investigating effects of lung transporters

- Species (human / KO animals)
- Inhibitors & concentrations
- Drug administration
- Bi-directional transfer of drug
- Lung / perfusate concentration
Model selection

**PRECLINICAL TECHNIQUES**
(Reduced screening capacity, increased expense and ethical issues)

Physico-chemical measures
Subcellular fractions
Lung homogenate
Tissue slices
Cell lines
Primary / organotypic cell culture
Isolated perfused animal lung
Preclinical in vivo studies in animals
Clinical studies in man

* Can be used to study drug absorption / permeability

Tronde et al, 2008
What is the question?
Drug permeability
IPL vs In silico

Tronde et al, 2003
IPL vs intestinal cell line

Tronde et al, 2003
IPL vs airway cell lines

Bosquillon et al (unpublished data)
IPL vs *in vivo*

*Tronde et al, 2003*
Drug delivery
Polymeric drug-ester conjugates

Bayard et al, 2013
Peptide-conjugated macromolecules
Liposomal formulation

Ong et al, 2013
Polymer microparticle formulation

Beck-Broichsitter et al, 2016
Transport mechanisms are complex
Effects of drug transporters
Absorption of ipratropium and L-carnitine into the pulmonary circulation of the ex-vivo rat lung is driven by passive processes rather than active uptake by OCT/OCTN transporters

Ghaith Al-Jayyoussi\textsuperscript{a}, Daniel F. Price\textsuperscript{a}, Katharina Kreitmeyer\textsuperscript{a}, John P. Keogh\textsuperscript{b}, Mathew W. Smith\textsuperscript{a}, Mark Gumbleton\textsuperscript{a}, Christopher J. Morris\textsuperscript{c,*}
OCTN2 transporter?

Gnadt et al, 2012
P-glycoprotein transporter

Manford et al, 2009
P-glycoprotein transporter

Manford et al, 2009
P-glycoprotein transporter

Madlova M, Bosquillon C, Forbes B.

“P-glycoprotein inhibitor, GF120918A, does not affect substrate absorption in the isolated perfused lungs”

“...the efflux transporter losartan was highly transported across the air-blood barrier of the isolated and perfused rat lung, which indicates an insignificant role for efflux transporters such as P-gp.”

Tronde et al. (2003)
P-glycoprotein transporter

Selectivity in the Impact of P-Glycoprotein Upon Pulmonary Absorption of Airway-Dosed Substrates: A Study in Ex Vivo Lung Models Using Chemical Inhibition and Genetic Knockout

GHAITH AL-JAYYOUSSI,1 DANIEL F. PRICE,1 DANIELLE FRANCOMBE,1 GLYN TAYLOR,1 MATHEW W. SMITH,1 CHRIS MORRIS,1
CHRIS D. EDWARDS,2 PETER EDDERSHAW,2 MARK GUMBLETON1

1Cardiff School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Cardiff, Wales CF10 3NB, UK
2Respiratory Translational Sciences, GlaxoSmithKline Stevenage, Hertfordshire SG1 2NY, UK
Fig. 6. Cumulative mass of human IgG (hIgG) transferred from the airways of the IPRL into the perfusate following a 0.1 ml forced solution (pH 6.5) instillation of 0.3 and 2.5 mg/ml of hIgG (nominal doses of 0.03 and 0.25 mg, respectively). When hIgG (0.3-mg/ml solution; dose 0.03 mg) coadministered with a 10-fold excess of rIgG, the transport of hIgG was significantly ($p < 0.05$) suppressed compared to the respective 0.3-mg/ml hIgG instillation in the absence of coadministered rIgG. Data represent mean ± standard deviation from $n = 4$. Dosing solution: (○) 0.3 mg/ml hIgG; (△) 2.5 mg/ml hlgG; (●) 0.3 mg/ml hIgG + 3.0 mg/ml rat IgG (rIgG).

Sakagami et al, 2008
CONCLUSION
Isolated perfused lung model

• Intact organ for study of drug transport without systemic metabolism / non-lung absorbed contribution
• Permits the flexible use of precise and high doses of inhibitors
• A variety of species can be used, including KO models
• Can be combined with approaches such as imaging, receptor occupancy, modelling to provide useful data complimentary to that obtained *in vitro* and *in vivo*