Utility of NHP in characterizing transporter-mediated disposition and DDIs

This document provides an outline of a presentation and is incomplete without the accompanying oral commentary and discussion. Conclusions and/or potential strategies contained herein are NOT necessarily endorsed by Pfizer management. Any implied strategy herein would be subject to management, regulatory and legal review and approval before implementation.
SSS

OATP DDIs IVIVE

IVIVC Hepatic uptake

Cocktail probe for t-DDIs

2014
Collaboration with Univ. Manchester (CAPKER)

2015-17
Internal effort

2015-17
Collaboration with Univ. Manchester (CAPKER)

2017
Internal effort
**Problem statement**
Lack on direct IVIVC in human, and so need for SFs.

**Goals**
Evaluate IVIVC in higher species?
Can monkey IVIVC be employed to scale human CL from heps?

**Plans**
In vivo IV PK studies in Cyno (9 - cassette of 3) - Pfizer
In vitro uptake studies in monkey and human heps - UoM

Tom De Bruyn, Ayşe Ufuk, Carina Cantrill, Aleksandra Galetin and J Brian Houston

Rachel E. Kosa, Yi-an Bi, Jian Lin, Sweta Modi, David Rodrigues, Larry Tremaine, Manthena Varma
In vitro data

1. pravastatin, 2. fexofenadine, 3. rosuvastatin, 4. valsartan, 5. repaglinide, 6. pitavastatin, 7. cerivastatin, 8. telmisartan, 9. bosentan
**IVIV scaling of hepatic uptake CL**

1. pravastatin, 2. fexofenadine, 3. rosuvastatin, 4. valsartan, 5. repaglinide, 6. pitavastatin, 7. cerivastatin, 8. telmisartan, 9. bosentan

### Methods

<table>
<thead>
<tr>
<th>gmfe</th>
<th>Direct</th>
<th>ESF_{av}</th>
<th>ESF_{sd}</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.8</td>
<td>2.5</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>rmse</td>
<td>2964</td>
<td>2433</td>
<td>3141</td>
</tr>
<tr>
<td>% within 2-fold</td>
<td>33</td>
<td>33</td>
<td>67</td>
</tr>
</tbody>
</table>

**Individual SF from Cyno IVIVC**

**Avg. SF from Cyno IVIVC**

**Human in vitro CL_{int,uptake}**
Summary:
- Cyno monkey based IVIVC may be helpful in PK predictions.
**Problem statement**

i. Substrate-dependent, time-dependent, experimental variability in Ki reported.

ii. Limited knowledge on IVIVE of Ki.

iii. Some cases indicate potent Ki value needed to recover AUC ratios.

iv. Clinical data is sparse to address above.

**Goals**

- Evaluate the predictability of OATP1B-mediated DDIs from in vitro inhibition data.
- Understand the in vivo relevance of the effect of pre-incubation and substrate-dependency in rifampicin inhibition potential measured in vitro.

**Plans**

- Study PK of 2 statins following simultaneous IV (stable-labelled) and oral (cold) dose to cyno (n=4 animals) and over a wide rifampicin dose range (1-30 mg/kg).
- Extrapolate rifampicin in vitro IC$_{50}$ data obtained using monkey hepatocytes to the in vivo changes in systemic clearance and plasma (i.v./oral) exposure of statins.
Pitavastatin:
Rif dose-dependent change in Pitava PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_{iv}</td>
<td>↓</td>
</tr>
<tr>
<td>Vdss</td>
<td>↓</td>
</tr>
<tr>
<td>T1/2</td>
<td>↓</td>
</tr>
<tr>
<td>Fa.Fg</td>
<td>↔</td>
</tr>
<tr>
<td>Fh</td>
<td>↑</td>
</tr>
<tr>
<td>F</td>
<td>↑</td>
</tr>
<tr>
<td>Fe</td>
<td>↔</td>
</tr>
</tbody>
</table>
Rosuvastatin:
Rif dose-dependent change in Rosuva PK parameters

<table>
<thead>
<tr>
<th></th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLiv</td>
<td>↓</td>
</tr>
<tr>
<td>Vdss</td>
<td>↔</td>
</tr>
<tr>
<td>T1/2</td>
<td>↔↑</td>
</tr>
<tr>
<td>Fa.Fg</td>
<td>↑</td>
</tr>
<tr>
<td>Fh</td>
<td>↑</td>
</tr>
<tr>
<td>F</td>
<td>↑</td>
</tr>
<tr>
<td>Fe</td>
<td>↔</td>
</tr>
<tr>
<td>CLrenal</td>
<td>↔</td>
</tr>
<tr>
<td>Substrate</td>
<td>In vitro IC₅₀ (µM)</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>1.14 ± 0.34**</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>3.80 ± 1.82</td>
</tr>
</tbody>
</table>

**Summary:**
- Substrate-dependency in IC₅₀ measurement was seen.
- Effect of pre-incubation was noted with one probe substrate.
- Potent in vitro IC₅₀ was close to in vivo IC₅₀; and also predicted AUCR of both statins using mechanistic static model.
Simultaneous t-DDIs assessment in Cyno

Problem statement:
Limited knowledge on IVIVE of Ki. Some cases indicate SFs need for Ki. Substrate-dependent, time-dependent, experimental variability in Ki reported. Delineate intestine-liver role.

Goals
• Establish an in vivo model to enable simultaneous assessment of inhibition potential of an investigational drug on OATP1B1/1B3, P-gp, BCRP and OAT3.

Plans
• Pharmacokinetics of substrate cocktail consisting of pitavastatin (OATP1B substrate), rosuvastatin (OATP1B/BCRP/OAT3), sulfasalazine (BCRP) and talinolol (P-gp) were obtained in cynomolgus monkey– alone or in combination with transporter inhibitors.
• Validate it against rifampicin, probenecid and elacridar as probe inhibitors.
Simultaneous t-DDIs assessment in Cyno

Pitavastatin

(A)

Talinolol

(C)

P-gp

Rosuvastatin

(B)

Sulfasalazine

(D)

OATP1B

OATP1B/BCRP/OAT3

Pfizer

WORLDWIDE RESEARCH & DEVELOPMENT

BCRP
Simultaneous t-DDIs assessment in Cyno

**In vitro data: Uptake by Heps**

- **Cyno plated Heps**
  - Graph showing uptake activity (% of control) for various drugs.
  - Drugs include Pravastatin, Rosuvastatin, Telmisartan, and Sulfasalazine.

- **Human plated Heps**
  - Graph showing uptake activity (% of control) for various drugs.
  - Drugs include Pravastatin, Rosuvastatin, Telmisartan, and Sulfasalazine.

**In vitro data: BCRP/Pgp inhibition in Cyno MVs**

- Graphs showing BCRP activity (% of control) for various inhibitors.

**In vitro and in vivo potency on Efflux transporters**

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Cyno Pgp IC_{50} (µM)</th>
<th>Cyno BCRP IC_{50} (µM)</th>
<th>Human Pgp IC_{50} (µM)</th>
<th>Human BCRP IC_{50} (µM)</th>
<th>Cyno Gut congestion (µM)</th>
<th>Human Gut congestion (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>14.3</td>
<td>79</td>
<td>23</td>
<td>14</td>
<td>3645</td>
<td>2916</td>
</tr>
<tr>
<td>Eclacitdar</td>
<td>0.6</td>
<td>0.16</td>
<td>0.09</td>
<td>0.5</td>
<td>5319</td>
<td>2387</td>
</tr>
<tr>
<td>Probencid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PS9835 (Pgp control)</td>
<td>0.24</td>
<td>-</td>
<td>0.03</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ko143 (BCRP control)</td>
<td>0.19</td>
<td>-</td>
<td>0.19</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note: Monkey Pgp IC_{50} and BCRP IC_{50} were calculated based on rifampicin/eclacitdar dose of 30 mg/kg and assuming luminal volume of 10 ml/kg. Human Pgp IC_{50} was calculated based on rifampicin/eclacitdar dose of 600 mg/400 mg and assuming luminal volume of 250 ml (Amidon et al., 1995; Karari, 1995).*
Considerations in applying this approach

**Perpetrator DDIs**

- In vitro → I/IC\(_{50}\) fail Regulatory cutoffs, but we believe risk is low.
- or, Clinical DDI is not tolerable

**Yes**

- At CAN → May employ Probe drug cocktail in Cyno to compliment in vitro findings.
- Considerations to dose/exposure, tox, etc.

**Yes**

- At FIH → Employ biomarkers (OATP1B, OCT2/MATEs)
- For P-gp, BCRP and OAT1/3, clinical DDI studies may be needed eventually

**Victim DDIs**

- Class 1B/3B – Anticipate hepatic uptake victim DDIs

**Yes**

- Class 3/4 - Anticipate Efflux liability and renal DDIs

- At CAN → May employ Probe inhibitor in Cyno to investigate CL mech. and project DDI liability
- Use probe inhibitors validated

**Yes**

- At FIH → Efflux liability may be elucidated from dose-linearity.
- For hepatic/renal transporters, clinical DDI studies may be needed eventually

**Yes**
CL predictions

Understanding OATPs role

“What Monkeys Can Teach Us About Human” Transporter-Mediated Disposition!!!

Mechanistic IVIV characterization

Valuable in DDI predictions

Others:
- Biliary CL
- Kpuu
- Biomarkers

- Cocktail probe for t-DDIs
- IVIVC
- Hepatic uptake
- SSS
- OATP DDIs IVIVE

Pfizer
WORLDWIDE RESEARCH & DEVELOPMENT


Acknowledgments

Transporter Sciences Group
- Yi-an Bi
- Emi Kimoto
- Sumathy M
- Sarah Lazzaro
- Mark West
- Chester Costales
- Bo Feng
- Manthena Varma
- Larry Tremaine
- David Rodrigues

University of Manchester (CAPKR)
- Ayse Ufuk
- Tom De Bruyn
- Aleksandra Galetin
- J. Brian Houston

Solvo Biotechnology for providing monkey BCRP and P-gp membrane vesicles and tech support.
- Marko Andric, Emese Kis, Beáta Tóth

Project leads & ADME CoE
- Dennis Scott
- James Gosset
- Li Di
- Anthony Carlo
- Jian Lin
- Theunis Goosen
- John Litchfield
- Amit Kalgutkar
- Matt Troutman
- Mark Niosi

Systems Modeling & Simulations group
- David Tess
- Rui Li
- Tristan Maurer