Prediction of Antiretroviral Drug Penetration into the Female Genital Tract Using a Novel QSAR Model

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Abstract O_03
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Antiretroviral (ARV) Genital Tract Penetration

- Critical for pre-exposure prophylaxis (PrEP)
  - Adequate concentrations in the female genital tract (FGT) determine PrEP success
- May also have implications for HIV eradication
- Highly unpredictable
  - 108% inter- and 21-215% intra-class variability
- Determined by clinical testing
  - Costly
  - May not occur until late-stage development

Mechanisms to identify highly penetrative compounds which can be reserved for PrEP are greatly needed

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Quantitative Structure Activity Relationship (QSAR) Modeling

• A predictive model created from known characteristics
  – Chemical descriptors (e.g. chemical structure, functional groups)
  – Pharmacokinetic properties (e.g. volume of distribution, plasma protein binding)

• Relevant previous uses
  – Prediction of antiviral activity of integrase inhibitors\(^1\)
  – Prediction of BBB penetration\(^2\)

• No QSAR has been developed to predict FGT penetration

\(^1\) Kaushik et al. *Med Chem* 2011
\(^2\) Zhang et al. *Pharm Res* 2008
Aim

• Develop a predictive QSAR model for FGT penetration
  – Use chemical descriptors for model development, and rilpivirine (RPV) and dolutegravir (DTG) for prospective evaluation
  – Identify concordant trends within chemical clusters
  – Create a pharmacophore for highly penetrative compounds

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Methods

• Data Identification
  – PubMed, EMBASE, and Web of Science from 1950-2012 for lower FGT PK
    • Vaginal tissue (VT), cervical tissue (CT), or cervicovaginal fluid (CVF)
    • “tissue penetration ratio” (TPR) used as a measure of drug penetration
      – ratio of VT, CT or CVF to blood plasma; created when not explicitly reported

• Database Compilation
  – TPR, PK parameters (protein binding, volume of distribution), and chemical structure for each compound
    • MDR1, MRP2, MRP4 substrate probability determined by previously validated QSAR model¹
    • TPRs stratified into the following 3 groups:

0.00  0.50  1.00  1.50  2.00
Poor  Good  Excellent

¹Sedykh et al Pharm Res 2013
Methods

Model Building

• Used PK parameters and computed chemical descriptors
  – # hydrogen bonds, # chlorine atoms, etc
• Machine learning techniques included:
  – k nearest neighbor (kNN)
  – Random Forest (RF)
  – Multiple regression
• 5-fold cross-validation
  – Build with 80%, test on 20%
Results

58 Compounds Identified

Antiretrovirals

- NRTI (n=7)
- PI (n=7)
- NNRTI (n=4)
- Integrase inhibitor (n=2)
- CCR5 antagonist (n=1)
- NNRTI (n=4)

Antibiotics

- Fluoroquinolone (n=7)
- Cephalosporin (n=10)
- Macrolide (n=6)
- Carbapenem (n=3)
- Nitroimidazole (n=1)
- Sulfonamide (n=1)
- Antifolate (n=1)
- Lincosamide (n=1)

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# Results

**Dichotomous Versus Continuous**

<table>
<thead>
<tr>
<th>DESCRIPTOR</th>
<th>POOR (&lt;0.50) VS REST</th>
<th>EXCELLENT (&gt;1.50) VS REST</th>
<th>CONTINUOUS ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRAINING SET</td>
<td>ENTIRE SET</td>
<td>TRAINING SET</td>
</tr>
<tr>
<td>PROTEIN BINDING CONSTANT</td>
<td>1.5</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>PLASMA PROTEIN BINDING (%)</td>
<td>1.6</td>
<td>1.8</td>
<td>0.7</td>
</tr>
<tr>
<td>MRP2 SUBSTRATE STATUS</td>
<td>0.7</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>MDR1 SUBSTRATE STATUS</td>
<td>0.4</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>MRP4 SUBSTRATE STATUS</td>
<td>0.6</td>
<td>0.3</td>
<td>2.7</td>
</tr>
<tr>
<td>H-BOND ACCEPTORS</td>
<td>0.9</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>H-BOND DONORS</td>
<td>0.1</td>
<td>0.4</td>
<td>0.9</td>
</tr>
<tr>
<td>CHLORINE ATOMS</td>
<td>2.2</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>FLUORINE ATOMS</td>
<td>0.3</td>
<td>0.1</td>
<td>1.3</td>
</tr>
<tr>
<td>NITROGEN ATOMS</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>OXYGEN ATOMS</td>
<td>1.0</td>
<td>1.1</td>
<td>1.0</td>
</tr>
<tr>
<td>SULFUR ATOMS</td>
<td>0.7</td>
<td>0.5</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Z score ≥2 = \( p \leq 0.05 \)

PPB and MRP4 substrate status are predictive variables

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Results

Individual properties are not predictive

- MRP4 (probability to be substrate): $R^2 = 0.0085$, $p=0.49$
- Plasma Protein Binding (%): $R^2 = 0.0608$, $p=0.06$

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Results

Best performing model explains 47% of TPR variability

Residual Plot of Test Set

Experimental log_{10} Tissue to Plasma Ratio vs Predicted log_{10} Tissue to Plasma Ratio

<table>
<thead>
<tr>
<th>Drug</th>
<th>Predicted TPR</th>
<th>Measured TPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPV</td>
<td>1.17</td>
<td>0.67-1.2</td>
</tr>
<tr>
<td>DTG</td>
<td>0.67</td>
<td>0.05-0.1</td>
</tr>
</tbody>
</table>

Model overestimates RPV by up to 1.7 fold and DTG by up to 9.5 fold

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Results

Hierarchy of Chemical Clusters

• Chemical clusters were identified without regard to TPR

Adapted from Fourches et al 2013, unpublished
Results

Example Cluster

Emtricitabine
logTPR=0.59
Excellent

Lamivudine
logTPR=0.61
Excellent

Zidovudine
logTPR=0.37
Excellent

Stavudine
logTPR=-1.30
Poor

Aztreonam
logTPR=-0.11
Good

Adapted from Fourches et al 2013, unpublished Thompson C et al. 14th IWCPHT
Results

**Best Pharmacophore ~50% Predictive**

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Conclusion

• Literature data for lower FGT PK are unstandardized & highly variable
• Using available data, QSAR model predictive, but unstable
  – Best model explains 47% of variability
• MRP4 substrate status and plasma protein binding contribute to FGT penetration
  – MRP4 expression in FGT confirmed \textit{ex vivo} \textsuperscript{1}
• Model overestimated RPV by only 1.7 fold, but overestimated DTG by 9.5 fold
  – useful for only certain drug classes?
• Data from additional compounds are required to enrich the dataset and allow further external validation

\textsuperscript{1}Nicol et al. 20\textsuperscript{th} CROI, Atlanta 2013

\textbf{MRP4 Expression}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{MRP4Expression.png}
\caption{Expression Relative to Beta Actin}
\end{figure}
Acknowledgments

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