DRUG Metabolism Holds its Destiny in its own Hands

Dennis A. Smith, 2010
In future drug metabolism will have evolved into a set of separate sections and disciplines capable of being outsourced and multiplexed into partner lines thus providing the science with a robust future.
Wrong !
How permeable is the molecule? I don’t know, I do the PK / PD, you better ask the screening group in China...
Is permeability central to small molecule drug metabolism?
Glomerular filtration

Plasma

- Mrp3 Abcc3
- Organic acid and cation transporters

UDPG; ST

- Mrp2 Abcc2
- Bcrp Abcg2

Bile

Liver

Urine

Kidney

Lipoidal diffusion
# Permeability: pivotal to ADME fate

<table>
<thead>
<tr>
<th>Permeability</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA/LogP</td>
<td>High</td>
<td>Medium</td>
<td>Low</td>
</tr>
<tr>
<td>Absorption</td>
<td>Low <em>(aliskeran)</em> unless MWt less than 250 daltons and absorbed by paracellular route <em>(atenolol)</em></td>
<td>Variable. Influenced by permeability and transporters <em>(nelfinavir)</em></td>
<td>High via transcellular route <em>(propranolol)</em></td>
</tr>
<tr>
<td>Bioavailability</td>
<td>As for absorption</td>
<td>As for absorption and metabolism</td>
<td>Variable. Influenced by metabolism</td>
</tr>
<tr>
<td>Clearance</td>
<td>Renal or Biliary (possible transporter involvement)</td>
<td>Transporters and metabolism</td>
<td>Metabolism</td>
</tr>
</tbody>
</table>
Transport v. passive diffusion
Low permeability: large impact of transporter
Transport v. passive diffusion
High permeability: small impact of transporter
P-gp influenced flux rates—how do we measure permeability: deconvolution or convoluted guess?

<table>
<thead>
<tr>
<th></th>
<th>Log P</th>
<th>PSA</th>
<th>A –B Nm.s⁻¹</th>
<th>`B-A Nm.s⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propanolol</td>
<td>3.0</td>
<td>42</td>
<td>450</td>
<td>700</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>4.4</td>
<td>167</td>
<td>2</td>
<td>395</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>5.3</td>
<td>202</td>
<td>16</td>
<td>852</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>7.0</td>
<td>127</td>
<td>35</td>
<td>786</td>
</tr>
</tbody>
</table>
BCS and Oral Dosing Transporter Effects

<table>
<thead>
<tr>
<th>High Solubility</th>
<th>Low Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class 1</strong></td>
<td><strong>Class 2</strong></td>
</tr>
<tr>
<td>Transporter effects</td>
<td>Efflux transporter</td>
</tr>
<tr>
<td>minimal in gut and</td>
<td>effects predominate</td>
</tr>
<tr>
<td>liver</td>
<td>in gut, but both</td>
</tr>
<tr>
<td></td>
<td>uptake &amp; efflux</td>
</tr>
<tr>
<td></td>
<td>transporters can</td>
</tr>
<tr>
<td></td>
<td>affect liver</td>
</tr>
</tbody>
</table>

| Low Permeability/    | **Class 3**        |
| Metabolism          | Absorptive transporter effects predominate (but can be modulated by efflux transporters) |

| Low Permeability/    | **Class 4**        |
| Metabolism          | Absorptive and efllux transporter effects could be important |

Slide provided by Les Benet
SAR- Phenomena or target based

- Attempts to change the influence of transporters, particularly Pgp and brain or tumour entry are now being published.
2,4-diaryl-2,5-dihydropyrrole kinesin spindle protein inhibitors

<table>
<thead>
<tr>
<th>R</th>
<th>MDR ratio</th>
<th>pKa</th>
<th>Log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1200</td>
<td>10.3</td>
<td>1.2</td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>135</td>
<td>10.7</td>
<td>1.6</td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;F</td>
<td>32</td>
<td>8.8</td>
<td>2.6</td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CHF&lt;sub&gt;2&lt;/sub&gt;</td>
<td>2</td>
<td>7.0</td>
<td>3.4</td>
</tr>
<tr>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>1</td>
<td>5.2</td>
<td>&gt;3.2</td>
</tr>
</tbody>
</table>
SAR- Phenomena or target based

- Attempts to change the influence of transporters, particularly Pgp and brain or tumour entry are now being published.

- In almost all cases it is impossible to separate increased intrinsic permeability from decreased transporter affinity or rate.

- Quoted from the publication
  1. Penetration to the target was increased by modulation of the basicity of the side chain by b-fluorination.
  2. With these improvements (there are some reductions in potency) in access to the target it is not possible to separate if this is due to decreased Pgp activity or on intrinsic permeability.
Access to Pgp is from the cytosol not the membrane (propafenone analogues)

CCRF-CEM cells
Membrane association
Rapid steady state across membrane

CCRF-CEM cells
No membrane association
No transfer across membrane
Inside out CCRF-ADR5000 cells
Accumulation in presence of ATP
No accumulation in absence of ATP

Substrate binding site open to cytosol with lipophilic residues exposed

Lipophilic regions of substrate bind to protein

ATP consumption triggers protein conformational change due to hydrophobic collapse

Hydrophilic residues now prominent

In binding cavity open to exterior aqueous environment of cell
Log P = Mwt - PSA

Mwt space

ADME

PSA

Lipophilicity

500

5

140
Properties of typical antagonists

- PSA (x10)
- MW (x100)

- Free diffusion
- Limited diffusion

- Aminergic 7 Tm's
- Tyrosine Kinases
- Proton Pump
- CETP
- Ca Channel
- Non aminergic Tm's
- HMG CoA
- Thrombin
- HIV Protease

MW (x100)
Is this drug going to be an oral drug? What we miss with TPSA calculations

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Log D</td>
<td>0.5</td>
</tr>
<tr>
<td>Log P</td>
<td>4.4</td>
</tr>
<tr>
<td>pKa</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>PSA</strong></td>
<td><strong>182</strong></td>
</tr>
<tr>
<td>MW</td>
<td>444</td>
</tr>
<tr>
<td>H bond</td>
<td>17</td>
</tr>
<tr>
<td>Freely rotatable bonds</td>
<td>7</td>
</tr>
</tbody>
</table>

Not an Oral Drug
Doxycycline

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log D</td>
<td>0.5</td>
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</tr>
</tbody>
</table>

98% bioavailability
Doxycycline

Log D 0.5
Log P 4.4
pKa 10.8
PSA 182
MW 444
H bond 17
Freely rotatable bonds 7

<table>
<thead>
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<td>7</td>
</tr>
</tbody>
</table>
Cyclosporine A

- Mwt 1200
- Log P oct 2.9 Log P hep 1.4
- CaCo flux 2.3
- Backbone N-H groups involved in intramolecular H bonds in aprotic solvent
- In aqueous solution all N-H groups point towards solvent
- Low energy cost of N-H desolvation
Doxurubicin (PSA 206 A2, cLog P 3.1) analogue with low Pgp flux

Atazanavir-H bonding networks in modern drugs
How do we put permeability into its rightful central role?
Is the metabolism of drugs PK / PD?
The hunt for oxidised october

- Rule 1 All unexpected pharmacodynamic events of any molecule or any project are due to a previously undetected or uncharacteried metabolite.
- Rule 2 Drug metabolism will set off gleefully to do as its name suggests and return empty handed
The hunt for oxidised october

• Meanwhile we will convey plasma concentration data as
  • C max ng / ml
  • AUC ng.h/ml

What information does this impart instantaneously to scientists?
Phenytoin

- Phenytoin used as an anticonvulsant
- Therapeutic action due to sodium channel blockade
- Phenytoin is a teratogen

Rodent teratology has consistent findings:

- Decreased foetal weights
- Cleft lip
- Distal digital effects
- Cardiovascular abnormalities
Phenytoin
Must be metabolites
Phenytoin activity due to Na\(^+\) channel block. Activity against binding site 2 of the sodium channel receptor IC\(_{50}\) is 47 \(\mu\)M.

Phenytoin is also an I\(_{Kr}\) channel blocker (HERG ED\(_{50}\) around 50 \(\mu\)M).

Salvati et al., *JPET.*, 288, 1151, 1999
Kallen et al.. *Reprod. Toxicol.*, 20, 209, 2005
I_{Kr} \text{ present in fetal but not adult rat hearts}

I_{Kr} \text{ blockers at concentrations not affecting the adult cause bradycardia, arrhythmia and cardiac arrest in the fetus leading to:}

– Hypoxia (embryonic death and growth retardation)

– Reoxygenation and reactive oxygen species generation (orofacial clefts and distal digital reduction)

– Alterations in embryonic blood flow (cardiovascular defects)
Unbound drug concentrations of phenytoin in pregnant rats and resultant effects Data converted to $C_{max}$ and $C_{av}$ values. Decrease in in vitro foetal heart rate first observed at $12\mu M$

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose level (mg/kg)</th>
<th>$C_{max}$ (μM)</th>
<th>$C_{av(0-24,h)}$ (μM)</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>150</td>
<td>7</td>
<td>5</td>
<td>No effects</td>
</tr>
<tr>
<td>IP</td>
<td>100</td>
<td>18</td>
<td>12</td>
<td>Small decrease in foetal weights</td>
</tr>
<tr>
<td>IP</td>
<td>150</td>
<td>33</td>
<td>29</td>
<td>Embryonic death, decreased foetal weight, teratogenicity</td>
</tr>
</tbody>
</table>
Instantaneous PK/PD

• Insist on molar units throughout drug discovery, development and drug research
• Supplement AUC values with Cav

D.A. Smith et al., The use of Cav rather than AUC in safety assessment. Reg Tox and Pharmacol., 57, 70-73, 2010
Metabolites-why are we interested, has anyone crisply articulated it

• “Circulating metabolites are of interest primarily because they can directly and probably reversibly interact with macromolecules, particularly proteins and cause a change in conformation and function of the protein to elicit a biological effect (beneficial or hazardous).

• These effects can be similar and additional to the parent molecule or may in some rare cases be different (usually as a result of elevated concentrations). Identifying and analysing these metabolites in the same matrix as the parent allows concentrations to be measured and thereby assessment of PK / PD.”
Circulating (stable) metabolites-whats important

- Circulating concentrations
- Structure (relationship to parent and known structure activity relationships)
- Physicochemistry (In particular lipophilicity, polar surface area and charge)

Smith, D.A. and Obach R.S. (2005) Seeing through the MIST. Commentary on Metabolites in safety testing. Drug Metab. Dispos. 33, 1409-141


Smith D.A., Obach, R.S., Williams, D.P. and Park, B.K. (2009) Clearing the MIST (Metabolites in Safety Testing) of time: the impact of duration of administration on drug metabolite toxicity. Accepted for publication Chem Biol. 179, 60-67

The facts (mine) are

• Most metabolites are inactive
• SAR accounts for the few times metabolites are more potent
• Metabolites with similar structures to the parent may have similar receptor binding properties against known targets (selectivity); this can reasonably be extended to the whole proteome.
• Inactive metabolites including those with different structure to the parent; many secondary metabolites, N-dealkylation of central nitrogens, loss of a key functional group (e.g. deamination of a GPCR ligand) will probably be devoid of pharmacological or toxicological effects; unless they are present at reasonably high concentrations (above $1\mu$M unbound).
Tramadol and o-desmethyl metabolite

Morphine
\(\mu\)-receptor partial agonist
Tramadol and o-desmethyl metabolite
## The circulating metabolite facts for kinase inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active metabolite</th>
<th>Potency and selectivity of metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imatinib</strong></td>
<td><img src="image" alt="Imatinib Structure" /></td>
<td>CGP74588</td>
</tr>
<tr>
<td><strong>Erlotinib</strong></td>
<td><img src="image" alt="Erlotinib Structure" /></td>
<td>M523595</td>
</tr>
<tr>
<td><strong>Gefitinib</strong></td>
<td><img src="image" alt="Gefitinib Structure" /></td>
<td>Desmethyl-gefitinib</td>
</tr>
<tr>
<td><strong>Sunitinib</strong></td>
<td><img src="image" alt="Sunitinib Structure" /></td>
<td>SU12662</td>
</tr>
<tr>
<td><strong>Lapatinib</strong></td>
<td><img src="image" alt="Lapatinib Structure" /></td>
<td>GW690006</td>
</tr>
</tbody>
</table>
The SAR case for change in selectivity

PSA 127 A2
cLog P 2.8

PSA 115 A2
cLog P 5.1

CAQ
EGFr inhibition

4557 W
EGFr / C-erbB-2 inhibition
Circulating (stable) metabolites-whats important

- Circulating concentrations
- Structure (relationship to parent and known structure activity relationships)
- Physicochemistry (In particular lipophilicity, polar surface area and charge)

Smith, D.A. and Obach R.S. (2005) Seeing through the MIST. Commentary on Metabolites in safety testing. Drug Metab. Dispos. 33, 1409-141


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**Observed odds for *in vitro* promiscuity and toxicity**
(Defined as multiple receptor interactions at 10 μM for 108 compounds and *in vivo* toxicity defined as effects above 1μM free drug)

<table>
<thead>
<tr>
<th><em>in vitro</em> Promicuity*</th>
<th>TPSA&gt;75 A²</th>
<th>TPSA&lt;75 A²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clog P &lt; 3</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Clog P &gt; 3</td>
<td>0.4</td>
<td>6.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><em>in vivo</em> Toxicity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clog P &lt; 3</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Clog P &gt; 3</td>
<td>0.8</td>
<td>2.6</td>
</tr>
</tbody>
</table>


Comparison of terfenadine and its carboxylic acid metabolite fexofenadine.

IKr blockade is estimated to be $100\mu M$ for the metabolite.

<table>
<thead>
<tr>
<th></th>
<th>PSA $A^2$</th>
<th>Log P</th>
<th>Log D$_{7.4}$</th>
<th>Activities $&lt;100$ nM</th>
<th>Activities $&lt;1\mu M$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Terfenadine</strong></td>
<td>44</td>
<td>6.5</td>
<td>4.2</td>
<td>H1 (5nM) IKr (50nM)</td>
<td>Ca++ channel Na+ channel (site 2) DA transporter 5HT2A 5HT2B</td>
</tr>
<tr>
<td><img src="image1" alt="Terfenadine structure" /></td>
<td><img src="image2" alt="Terfenadine structure" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fexofendine</strong></td>
<td>81</td>
<td>4.8</td>
<td>2.3</td>
<td>H1 (12nM)</td>
<td></td>
</tr>
<tr>
<td><img src="image3" alt="Fexofendine structure" /></td>
<td><img src="image4" alt="Fexofendine structure" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Physicochemical changes associated with metabolism

<table>
<thead>
<tr>
<th>Metabolic Step</th>
<th>Increase in TPSA</th>
<th>Reduction in cLog P</th>
<th>Ionisation, log D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliphatic hydroxylation</td>
<td>20.23 A²</td>
<td>-1.99</td>
<td></td>
</tr>
<tr>
<td>Aromatic hydroxylation</td>
<td>20.23 A²</td>
<td>-0.67</td>
<td></td>
</tr>
<tr>
<td>Dealkylation of tertiary amine</td>
<td>8.8 A²</td>
<td>-0.6 for a methyl group: increases with fragmental value of leaving function</td>
<td>Increase in basicity of approximately +1pKa. Decrease in Log D₇.₄ of 1 unit</td>
</tr>
<tr>
<td>Dealkylation of secondary amine</td>
<td>14 A²</td>
<td>-0.6 for a methyl group: increases with fragmental value of leaving function</td>
<td></td>
</tr>
<tr>
<td>Oxidation of hydroxyl to carboxylic acid</td>
<td>17 A²</td>
<td>Little change in cLog P</td>
<td>Introduction of acidic charge and pKa 3-5. Reduction in log D₇.₄ of 3-5 units. Formation of a zwitterions for basic parent molecules.</td>
</tr>
</tbody>
</table>

Manner C N, Payling D W, Smith, D A, Distribution coefficient, a convenient term for the relation of predictable physico-chemical properties to metabolic processes, Xenobiotica. 18 (3), 331-350, 1988
• Do we carefully analyse our metabolism data in terms of concentration, structure against target SAR, and physicochemistry?
Excreted Metabolites

- Excreted metabolites are of interest primarily, in human, because they allow the proportion of the parent converted to a particular metabolite to be determined and thereby support the \textit{in vitro} enzymological evaluations for population variations and drug-drug interactions.

- In addition they allow the detection of the downstream products of reactive metabolites and, moreover, allow an estimation of the amount (mass) formed. Recommendation is the total of these products in human needs to be $>10mg$ to be considered for further study.
Observations

• That despite an earlier belief, to the contrary, all toxicity caused by reactive metabolites shows a **dose response relationship**. The earlier confusion was prompted by the relative rarity of immunoallergenic events and the difficulty in obtaining any useful dose relationship over very sparse data and a limited dose range.

• **Structural alerts.** These are chemical groups which have historically been associated with reactive metabolites and leading to toxicity. Incorporation of such grouping into a molecule increases the risk of the formation of reactive metabolites.
## Reasons for withdrawal

<table>
<thead>
<tr>
<th>Primary Pharmacology</th>
<th>Secondary Pharmacology</th>
<th>Idiosyncratic Toxicity-reactive metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic name</td>
<td>Daily dose mg</td>
<td>Generic name</td>
</tr>
<tr>
<td>Alosetron</td>
<td>1</td>
<td>Astemizole</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>0.3</td>
<td>Cisapride</td>
</tr>
<tr>
<td>Encainide</td>
<td>150</td>
<td>Dextenfluramine</td>
</tr>
<tr>
<td>Flosequinan</td>
<td>100</td>
<td>Fenfluramine</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>25</td>
<td>Grepafloxacine</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Rapacuronium</td>
<td>100</td>
<td>Ticrynafen</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>120</td>
<td>Troglitazone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trovafloxacin</td>
</tr>
</tbody>
</table>
Are reactive metabolites selective. Is it the nature of the reactive species or the overall shape of the molecule.

Reactivity dictates distance.

Selectivity-reactivity / structure.
Pharmacological targets and selectivity

- Clopidogrel reactive metabolite is an irreversible inhibitor of platelet purinergic P2Y12 receptor formed in the liver (CYP3A4 and CYP2C19). Only one isomer of the eight isomers exhibits in vitro anti-aggregating activity

Can we categorise reactive metabolites systematically-have I MIST it?

- Reactivity-stability
- Structural descriptors of molecule
- Physicochemistry
- Amount formed
• Drug Metabolism.....leading personalised medicine from the back of the field?
Back to clopidogrel-Personalised medicine?

• Separating fact from fiction...once you rely on others then
  • Establishing facts=1/number of papers²
Pharmacological targets and selectivity

- Clopidogrel reactive metabolite is an irreversible inhibitor of platelet purinergic P2Y12 receptor formed in the liver (CYP3A4 and CYP2C19). Only one isomer of the eight isomers exhibits in vitro antiaggregating activity.

More questions than answers

• 2-oxo clopidogrel formed mainly be CYP3A4
• Formation of active thiol by hydrolysis or further oxidation?
• Further oxidation by multiple CYPs or is CYP2C19 selective for the active isomer of thye metabolite?
• Is the lack of response in CYP2C19*2 due to metabolism or a link to polymorphism in the P2Y12 receptor?
• All the above have had positive and negative views in the plethora of papers
Black Box Warning of Clopidogrel

• WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

• Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.

• Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.

• Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.

• Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.
Too late now (maybe), but easy to do earlier in China (14% 2C19 PMs)

• CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel.

• Although a higher dose regimen (600 mg loading dose followed by 150 mg once daily) in poor metabolizers increases antiplatelet response an appropriate dose regimen for this patient population has not been established in clinical outcome trials
P2Y12 receptor gene variation is major factor in direct antagonist variation

Bourman et al. Thrombosis and Haemostasis 103, 379-386, 2010
Would drug metabolism lead this from the front now?
Because once the bandwagon gets rolling it starts to go only downhill
Is this CYP2C19 inhibition or something else?

- 72 healthy subjects were administered Plavix (300 mg loading dose followed by 75 mg per day) alone and with omeprazole (80 mg at the same time as Plavix) for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 46% (Day 1) and 42% (Day 5) when Plavix and omeprazole were administered together. Mean inhibition of platelet aggregation was diminished by 47% (24 hours) and 30% (Day 5).

- 72 healthy subjects were given the same doses of Plavix and omeprazole but the drugs were administered 12 hours apart; the results were similar, indicating that administering Plavix and omeprazole at different times does not prevent their interaction.
Is this CYP2C19 inhibition?

• Suggestions of accumulative mechanism based inhibition by esomeprazole (s-enantiomer of omeprazole) on its own clearance. No effect of R-enantiomer

• Esomeprazole showed less inhibitory potency compared with omeprazole and its R-enantiomer as reversible inhibitors.
  Xue-Qing et al. Drug Met Disposit., 32, 821-827, 2004

• Omeprazole is a time-dependent inhibitor of CYP2C19 in human hepatocytes

• Omeprazole classified as a moderate reversible inhibitor of CYP2C19

• Multi-factorial interaction proposed including the PPI and clopidogrel inhibition of CYP2C19
Classification of drugs with PGx in product label

- Maraviroc
- Clopidogrel
- Irinotecan
- Warfarin
- Celecoxib
- Atomoxetine

- Trastuzumab
- Rasburicase
- Abacavir
- Carbamazepine
- Cetuximab
- Azathioprine

Diagnostic is a guide:
Clinical signs still regarded as most important:
*TPMT testing cannot substitute for complete blood count monitoring
Conclusions

• Drug Metabolism must be integrated and not seen as separate functions
• Only this way will it lead (and survive)
• Future directions must include a closer relationship with clinical outcomes in terms of safety and efficacy
• Probably can be the biggest influence on personalised medicine if we start early enough in the drug discovery / development cycle