Core Data Set – CYP2D6 Metabolism

- Oxidised metabolites seen in pre-clinical species

Inhibitor	Target CYP Isoform	CLint (µL/min/mg protein)	% Inhibition
Control		12.5	-
Furafylline	**1A2**	12.9	**0**
Sulfaphenoxazole	**2C9**	11.9	**4**
Omeprazole	**2C19**	11.7	**6**
Quinidine	**2D6**	6.9	**45**
Ketoconazole	**3A4/5**	10.6	**15**
Trimethoprim	**2C8**	11.5	**8**

Opinion of the group:

- 2D6 metabolism associated with significant clinical experience, particularly with respect to poor metabolizers
- The consensus of the group was to identify 2D6 PMs
    - Prospective genotyping proposed
    - Possible design:
        - Volunteers with increasing dose
        - Exclude PMs initially
        - Include PMs at low dose once higher dose tolerated by EMs

- Conclusion: everyone wants PM information e.g. exclude PMs from initial studies.

Variation 1 – CYP3A4/5 Metabolism

- As per core set, but metabolism is via CYP3A4

Inhibitor	Target CYP Isoform	CLint (µL/min/mg protein)	% Inhibition
Control		12.5	-
Furafylline	**1A2**	12.9	**0**
Sulfaphenoxazole	**2C9**	11.9	**4**
Omeprazole	**2C19**	11.7	**6**
Quinidine	**2D6**	10.6	**15**
Ketoconazole	**3A4/5**	6.9	**45**
Trimethoprim	**2C8**	11.5	**8**

Opinion of the group

- CYP3A4/5 with poorer correlation between genotype and phenotype
- As a result, the consensus of group:
  - Do nothing, collect DNA
- If Blacks: somewhat more important for 3A5 genotyping

Variation 2 – CYP2C8 Metabolism

- As per core set, but metabolism is via 2C8

Inhibitor	Target CYP Isoform	CLint (µL/min/mg protein)	% Inhibition
Control		12.5	-
Furafylline	**1A2**	12.9	**0**
Sulfaphenoxazole	**2C9**	11.9	**4**
Omeprazole	**2C19**	11.7	**6**
Quinidine	**2D6**	10.6	**15**
Ketoconazole	**3A4/5**	10.5	**15**
Trimethoprim	**2C8**	5.6	**55**

Opinion of the group

- CYP2C8 with poor-metabolizer alleles
- However, limited clinical literature on the impact on drug metabolism

Consensus of group:

- DNA collection only, no pro-active genotyping (c.f. CYP2D6)
- Weak penetrance of alleles
- Do CYP2C8 genotyping, when PK or other outliers are identified later during development

Variation 3 – No Oxidised Metabolites

- As per core dataset, but no oxidative metabolites seen in pre-clinical species – compound excreted unchanged in faeces

Inhibitor	Target CYP Isoform	CLint (µL/min/mg protein)	% Inhibition
Control		12.5	-
Furafylline	**1A2**	12.9	**0**
Sulfaphenoxazole	**2C9**	11.9	**4**
Omeprazole	**2C19**	11.7	**6**
Quinidine	**2D6**	6.9	**45**
Ketoconazole	**3A4/5**	10.6	**15**
Trimethoprim	**2C8**	11.5	**8**

Opinion of the group

- Absence of oxidised metabolites suggests that *in vitro* metabolism may not be relevant *in vivo*

Consensus:

- DNA collection only, no pro-active genotyping (c.f. core case)
- Some attention warranted regarding effect in relation to the UM (and PM) phenotypes, in case UMs generate oxidised metabolites in humans

Variation 4 – Reduced CYP2D6 Metabolism

- As per core set, except that CYP2D6 specific metabolism is 22% (as opposed to 40%).

Inhibitor	Target CYP Isoform	CLint (µL/min/mg protein)	% Inhibition
Control		12.5	-
Furafylline	**1A2**	12.9	**0**
Sulfaphenoxazole	**2C9**	11.9	**4**
Omeprazole	**2C19**	11.7	**6**
Quinidine	**2D6**	9.8	**22**
Ketoconazole	**3A4/5**	11.8	**5**
Trimethoprim	**2C8**	11.5	**8**

Opinion of the group

- Weak CYP2D6 metabolism, with uncertain relevance

- Divergence in opinions in group:
  - Determine the non-metabolised clearance
  - 2D6 genotyping for safety issues
  - PMs identified later in development
  - Enriched studies on defined phenotypes

Transporter Studies

- Increasingly, transporters implicated in drug disposition, efficacy and safety
- Compound A (target organ – liver) tested for uptake in cells transfected with human OATP receptors, including known polymorphisms
  - Data for OATP sub-types expressed as rate of uptake into transfected cells
  - Data for OATP1B1 variants expressed as percentage activity of ‘wild-type’ transporter

OATP Transport Data

OATP Sub-type	Rate of Uptake	OATP1B1 Variant	Frequency	Rate of Uptake
Vehicle	0.8	*1a	0.56	12.5
1A2	4.5	*1b	0.26	10.2
1B1	12.5	*5	0.02	1.5
1B3	6.2	*15	0.16	4.5
2B1	3.5			

- The data show significant uptake by OATP1B1, which is greatly reduced in known human variants
- Some uptake is seen with other OATP sub-types

Opinion of the group

- As yet, few examples linking genotype variants to clinical outcome

- Consensus to collect DNA in phase I studies
- A majority recommends prospective genotype studies in phase I
- Agreement that genotyping is necessary during phase IIa efficacy studies

General aspects

- *Ethics committees need to understand the value of prospective DNA collection – still an issue*
- *DMET chips – patients numbers are too small in phase I*
- *DMET chips can be used the whole phase clinical trials*
- *Focus is often on PMs. However, UMs important for metabolite formation (for safety) and during Phase II (for efficacy).*
- *Clinical experience was the critical factor driving pro-active PGx in phase I*