

Novel PXR/CAR Humanised Mouse Models to Predict Human Drug Disposition and Toxicity

CXR Biosciences Ltd, Dundee, Scotland and Artemis Pharmaceuticals GmbH, Köln, Germany.



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Target Genes for Humanisation

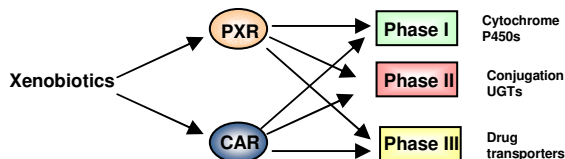
Phase I (e.g. **Cytochrome P450s**) & Phase II (e.g. **UGT's**) drug metabolising enzymes and Phase III drug transporters (e.g. **MDRs**), all play pivotal roles in determining the efficacy, bioavailability and/or side effects (including toxicity) of drugs.

Undesirable interactions of drugs with these systems or the transcription factors regulating them can be a major reason for drug failure.

These enzymes vary markedly between species in their multiplicity, their substrate specificity, and their regulation.

To address these issues, the aim of this work was to create mouse models that are 'humanised' for genes which regulate drug metabolism and disposition.

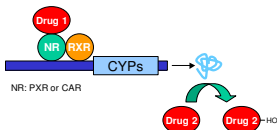
Nuclear Receptors control the expression of drug metabolising enzymes



PXR & CAR function in drug metabolism

Interaction with PXR & CAR is a critical factor in drug candidate selection. The PXR & CAR xenosensors:

- are key regulators of genes which play major roles in drug disposition in man (e.g. CYP3A, CYP2B and MDR1)
- mediate drug-drug interactions.
- exhibit species differences in their interaction with drugs.



A novel humanised mouse model

PXR & CAR targeting vectors **replace** mouse PXR & CAR with human counterparts, retaining physiological and appropriate tissue expression patterns and levels by endogenous regulatory elements.

Partial conversion of exon/intron-structure of human PXR & CAR ensures splice variants potentially coding for proteins with distinct physiological function.

Replacement of murine PXR and CAR by human genes

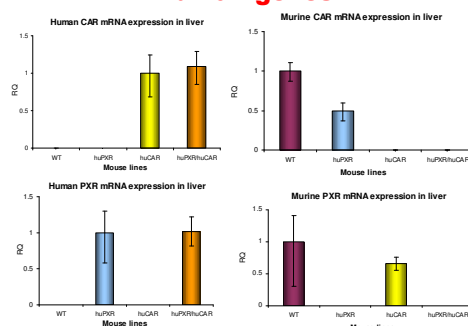


Fig. 1: TaqMan[®] analysis of PXR and CAR in liver

Humanised PXR and CAR mice reflect known human differences in the responses to drugs

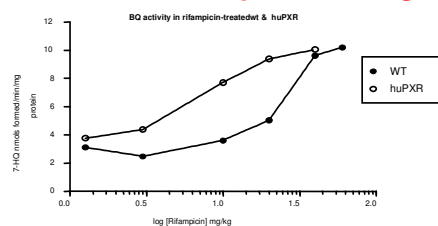


Fig. 2: huPXR mice are much more sensitive to Rifampicin

PROD activity in CITCO-treated huCAR and WT mice

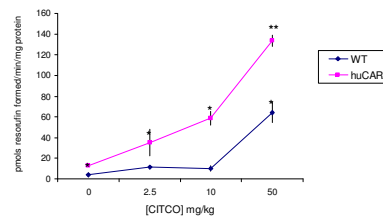


Fig. 3: huCAR mice are much more sensitive to CITCO

Humanised PXR mice provide key insights into clinical drug disposition and toxicity

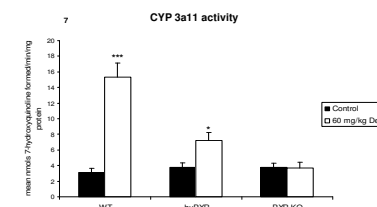


Fig. 4: Influence of dexamethasone on CYP activity

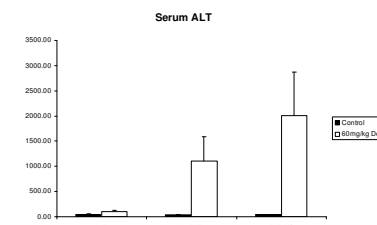


Fig. 5: Influence of dexamethasone on toxicity

Conclusions

- The human, but not the mouse PXR & CAR mRNA was expressed in huPXR/huCAR humanised mice.
- PXR & CAR mRNA levels and tissue distribution in the transgenic model were comparable to those in the WT mouse and in human (ie liver and small intestine).
- Functional human PXR & CAR proteins were expressed.
- Marked species differences in their interaction with rifampicin, CITCO, and dexamethasone (and others not shown) were demonstrated.
- These models provide a much more accurate indication of how compounds may affect human drug disposition and toxicity.