A Panel of Translational **Xenoreceptor**, **Cytochrome P450**, **Transporter** and Transplanted **Liver Humanized Mouse Models** for Improved Prediction of Drug Responses in Man

Taconic

Smart Solutions To Improve Human Health

Nico Scheer, 18th April 2013

Objectives



- **To provide a literature overview of genetically ADMET and liver humanized mouse models described to date**

- **To describe a systematic approach of generating genetically humanized ADMET mouse models and combining them into complex, multiple humanized genotypes**

- **To provide selected examples of the utility of these models**

- **To discuss the benefits & limitations of genetically ADMET and liver humanized mouse models**

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Humanized Xenobiotic Receptor Mice



Receptor	Type of genetic modification	Promoter driving human gene expression	Human expression construct	Reference
PXR	KO + RT	Mouse albumin	cDNA	Xie et al., 2000
	RT	Mouse albumin	VP16-PXR cDNA	Xie et al., 2000
	KO + RT	Rat fatty acid-binding protein	cDNA	Zhou et al., 2006
	RT	Rat fatty acid-binding protein	VP16-PXR cDNA	Gong et al., 2006
	KO + RT	Human PXR	genomic	Ma et al., 2007
	KO + RT	Mouse transthyretin enhancer	cDNA	Lichti-Kaiser and Staudinger, 2008
	TR	Mouse Pxr	genomic/cDNA	Scheer et al., 2008
	TR	Mouse Pxr	genomic/cDNA	Scheer et al., 2010
	TR	Mouse PXR	partial cDNA	Igarashi et al., 2012
CAR	KO + RT	Mouse albumin	cDNA	Zhang et al., 2002
	TR	Mouse Car	genomic	Scheer et al., 2008
PPARα	KO + RT	Tetracyclin responsive regulatory element	cDNA	Cheung et al., 2004.
	KO + RT	Human PPARα	genomic	Yang et al., 2008.
AHR	TR	Mouse Ahr	cDNA	Moriguchi et al., 2003
	KO + RT	Mouse transthyretin enhancer	cDNA	Flaveny et al., 2009

KO = knockout, RT = random transgensis, TR = targeted replacement, VP16 = activation domain of herpes simplex.

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Humanized DME & Transporter Mice



Human gene(s)	Features	Reference
CYP1A1 & 1A2	Random transgene of genomic human *CYP1A1/1A2* sequence. Combined with knockout for mouse *Cyp1a1* or *Cyp1a2*.	(Cheung et al., 2005a; Jiang et al., 2005)
	Random transgene of genomic human *CYP1A1/1A2* sequence. Combined with knockout for mouse *Cyp1a1/1a2*.	(Dragin et al., 2007)
CYP2A6	Random transgene of human *CY2A6* cDNA expressed off the mouse transthyretin promoter/enhancer.	(Zhang et al., 2005)
CYP2A13 & 2B6/2F1	Random transgene of genomic human *CYP2A13/2B6/2F1* sequence. Also combined with a mouse *Cyp2f2* knockout.	(Wei et al., 2012)
CYP2C9	Targeted replacement of the mouse *Cyp2c* locus with a genomic/cDNA hybrid of human *CYP2C9*. Human *CYP2C9* is expressed off the mouse albumin promoter.	(Scheer et al., 2012b)
CYP2C18 & 2C19	Random transgene of genomic human *CYP2C18/2C19* sequence.	(Lofgren et al., 2008)
CYP2D6	Random transgene of genomic human *CYP2D6* sequence.	(Corchero et al., 2001)
	Targeted replacement of the mouse *Cyp2d* locus with a genomic human *CYP2D6* sequence.	(Scheer et al., 2012c)
CYP2E1	Random transgene of human *CYP2E1* cDNA expressed off the mouse albumin promoter.	(Morgan et al., 2002)
	Random transgene of genomic human *CYP2E1* sequence. Combined with knockout for mouse *Cyp2e1*.	(Cheung et al., 2005b)
CYP3A4	Random transgene of genomic human *CYP3A4* sequence.	(Granvil et al., 2003; Yu et al., 2005)
	Random transgene of human *CYP3A4* cDNA expressed off the human ApoE promoter.	(van Herwaarden et al., 2005)
	Random transgene of human *CYP3A4* cDNA expressed off the human ApoE promoter. Combined with knockout for mouse *Cyp3a* genes.	(van Herwaarden et al., 2007)
	Random transgene of human *CYP3A4* cDNA expressed off the mouse villin promoter. Combined with knockout for mouse *Cyp3a* genes.	
	Random transgenes of human *CYP3A4* cDNA expressed off the human ApoE and mouse villin promoter. Combined with knockout for mouse *Cyp3a* genes.	
CYP3A4 & 3A7	Random transgene of genomic human *CYP3A4/CYP3A7* sequence.	(Cheung et al., 2006)
	Targeted replacement of the mouse *Cyp3a* locus with a genomic human *CYP3A4/CYP3A7* sequence.	(Hasegawa et al., 2011a)
CYP3A4, 3A5,3A7 & 3A43	Trans-chomosomic mice containing the human *CYP3A* cluster (CYP3A5 inactive). Combined with knockout for mouse *Cyp3a* genes.	(Kazuki et al., 2012)
CYP3A4 & 2D6	Random transgenes of genomic human *CYP3A4* and *CYP2D6* sequences.	(Felmlee et al., 2008)
CYP3A7	Random transgene of human *CYP3A7* cDNA expressed off the mouse metallothionein-1 promoter.	(Li et al., 1996)
NAT2	Random transgene of human *NAT2*4*cDNA expressed off the rat probasin promoter.	(Leff et al., 1999)
	Random transgene of human *NAT2*4* cDNA expressed off the mouse albumin promoter. Combined with knockout for mouse *Nat1/2*.	(Sugamori et al., 2011)
UGT1A	Random transgene of genomic human *UGT1A* sequence.	(Chen et al., 2005)
	Random transgenes of genomic human $UGT1^{A1*1}$ or $UGT1^{A1*28}$ sequences. Combined with knockout for mouse *Ugt1*.	(Fujiwara et al., 2010)
UGT2B7	Random transgene of genomic human *UGT2B7*sequence.	(Yueh et al., 2011)

Human gene(s)	Features	Reference
MRP2	Targeted replacement of mouse *Mrp2* with a cDNA of human *MRP2*. Human *MRP2* is expressed off the mouse *Mrp2* promoter.	(Scheer et al., 2012a)
OATP1B1	Random transgene of human *OATP1B1* cDNA expressed off the human ApoE promoter.	(van de Steeg et al., 2009)
	Random transgene of human *OATP1B1* cDNA expressed off the human ApoE promoter. Combined with knockout of mouse Oatp1a/1b genes.	(van de Steeg et al., 2012)
OATP1B3	Random transgene of human *OATP1B3*cDNA expressed off the human ApoE promoter. Combined with knockout of mouse Oatp1a/1b genes.	(van de Steeg et al., 2012)

Transplanted Humanized Liver Mice



Model	Immune deficiency	Induction of liver failure	Reference
uPA-Scid	SCID	Hepatic expression of urokinase-type plasminogen activator (uPA)	Mercer et al., 2001 Tateno et al., 2004
uPA-NOG	NOD/Shi-scid Il2Rg^{null} (NOG)	Hepatic expression of urokinase-type plasminogen activator (uPA)	Suemizu et al., 2008
TK-NOG	NOD/Shi-scid IL2Rg^{null} (NOG)	Hepatic HSVtk expression combined with Gancyclovir treatment	Hasegawa et al., 2011
FRG	Rag-2^{null}/Il2rg^{null} (/NOD)	Deletion of fumarylacetoacetate hydrolase	Azuma et al., 2007

A Panel of Translational Xenoreceptor, DME, Transporter & Liver Humanized Mouse Models



Xenoreceptor Panel	
Knockouts	**Humanized**
Ahr	AHR
Car	CAR
Pparα	
Pxr	PXR
Pxr/Car	PXR/CAR
Pxr/Car/Ahr	PXR/CAR/AHR
Pxr/Car/Pparα	PXR/CAR/PPARα
Pxr/Car/Ahr/Pparα	PXR/CAR/AHR/PPARα

Cytochrome P450 Panel	
Knockouts	**Humanized**
Cyp1a1/1a2	CYP1A1/1A2
Cyp2c	CYP2C9
Cyp2d	CYP2D6
Cyp3a (BL/6)	CYP3A4/3A7
Cyp3a (FVB)	Liver CYP3A4
	Gut CYP3A4
	Liver/Gut CYP3A4
Cyp2c/Cyp2d/Cyp3a	

Transporter Panel	
Knockouts	**Humanized**
Bcrp	BCRP*
Mdr1a, Mdr1a/1b	MDR1*
Bcrp/Mdr1a/1b	
Mrp1	
Mrp2	MRP2
Oatp1a/1b	OATP1B1
	OATP1B3
	OATP1B1/1B3
Oct1/2	
Oat1/3	OAT1/3

Phase 2 Panel
Humanized
UGT1A1

Composite models
Humanized
PXR/CAR/CYP3A4/3A7
PXR/CAR/CYP3A4/3A7/CYP2D6
PXR/CAR/CYP3A4/3A7/CYP2D6/CYP2C9

Transplanted Liver Humanized Mice
FRG™ (in Collaboration with Yecuris Inc.)

*coming soon

A Panel of Translational Xenoreceptor, DME, Transporter & Liver Humanized Mouse Models

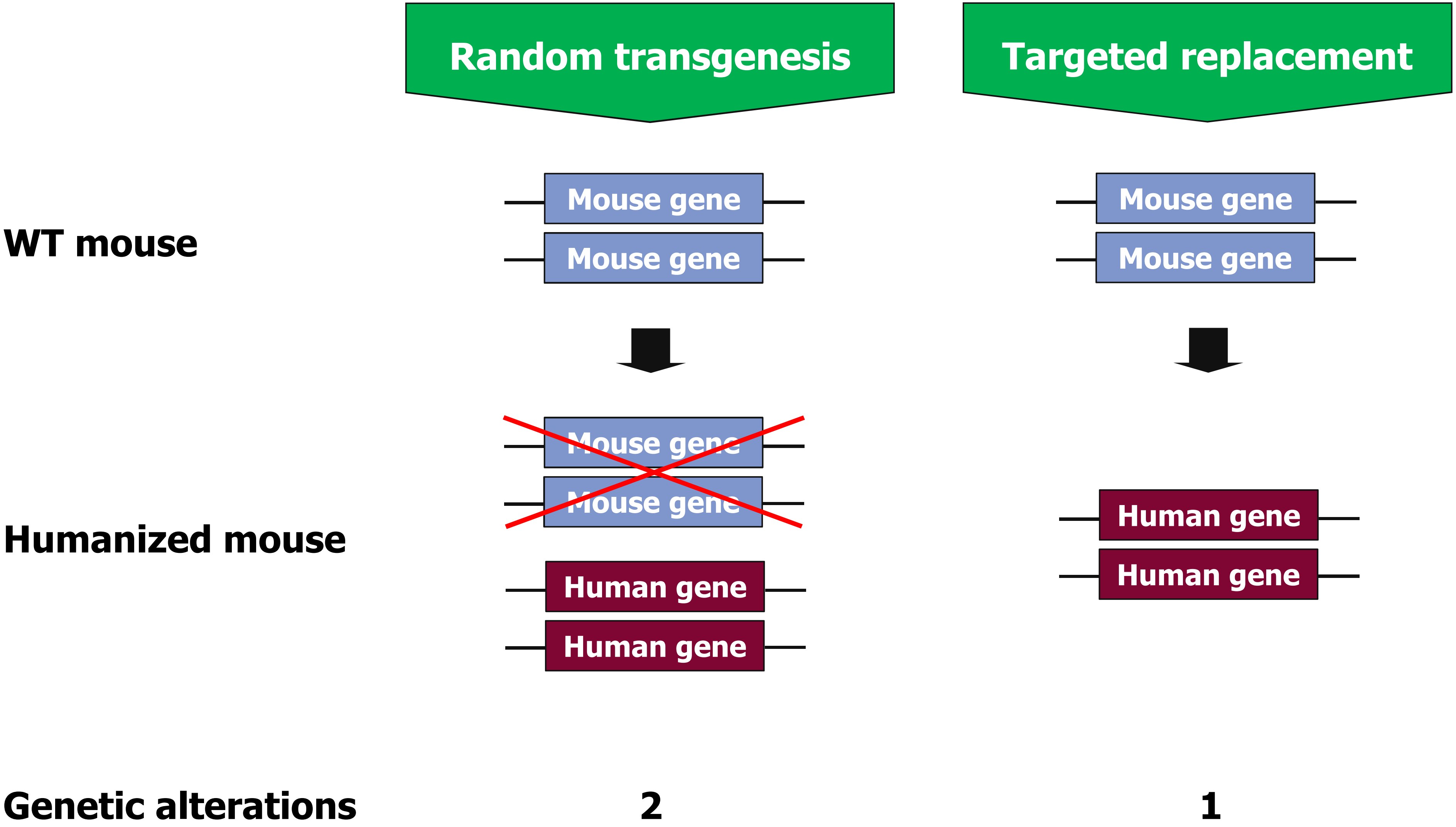


Xenoreceptor Panel		Cytochrome P450 Panel		Transporter Panel	
Knockouts	Humanized	Knockouts	Humanized	Knockouts	Humanized
Ahr	AHR	Cyp1a1/1a2	CYP1A1/1A2	Bcrp	BCRP*
Car	CAR	Cyp2c	CYP2C9	Mdr1a, Mdr1a/1b	MDR1*
Pparα		Cyp2d	CYP2D6	Bcrp/Mdr1a/1b	
Pxr	PXR	Cyp3a (BL/6)	CYP3A4/3A7	Mrp1	
Pxr/Car	PXR/CAR	Cyp3a (FVB)	Liver CYP3A4	Mrp2	MRP2
Pxr/Car/Ahr	PXR/CAR/AHR		Gut CYP3A4	Oatp1a/1b	OATP1B1
Pxr/Car/Pparα	PXR/CAR/PPARα		Liver/Gut CYP3A4		OATP1B3
Pxr/Car/Ahr/Pparα	PXR/CAR/AHR/PPARα	Cyp2c/Cyp2d/Cyp3a			OATP1B1/1B3
				Oct1/2	
				Oat1/3	OAT1/3

Phase 2 Panel	Composite models	Transplanted Liver Humanized Mice
Humanized	Humanized	
UGT1A1	PXR/CAR/CYP3A4/3A7	FRG™ (in Collaboration with Yecuris Inc.)
	PXR/CAR/CYP3A4/3A7/CYP2D6	
	PXR/CAR/CYP3A4/3A7/CYP2D6/CYP2C9	

*coming soon

Approaches of generating genetically humanized mouse models (simplified)



A Panel of Translational Xenoreceptor, DME, Transporter & Liver Humanized Mouse Models

Xenoreceptor Panel	
Knockouts	**Humanized**
Ahr	AHR
Car	CAR
Pparα	
Pxr	PXR
Pxr/Car	PXR/CAR
Pxr/Car/Ahr	PXR/CAR/AHR
Pxr/Car/Pparα	PXR/CAR/PPARα
Pxr/Car/Ahr/Pparα	PXR/CAR/AHR/PPARα

Cytochrome P450 Panel	
Knockouts	**Humanized**
Cyp1a1/1a2	CYP1A1/1A2
Cyp2c	CYP2C9
Cyp2d	CYP2D6
Cyp3a (BL/6)	CYP3A4/3A7
Cyp3a (FVB)	Liver CYP3A4
	Gut CYP3A4
	Liver/Gut CYP3A4
Cyp2c/Cyp2d/Cyp3a	

Transporter Panel	
Knockouts	**Humanized**
Bcrp	BCRP*
Mdr1a, Mdr1a/1b	MDR1*
Bcrp/Mdr1a/1b	
Mrp1	
Mrp2	MRP2
Oatp1a/1b	OATP1B1
	OATP1B3
	OATP1B1/1B3
Oct1/2	
Oat1/3	OAT1/3

Phase 2 Panel
Humanized
UGT1A1

Composite models
Humanized
PXR/CAR/CYP3A4/3A7
PXR/CAR/CYP3A4/3A7/CYP2D6
PXR/CAR/CYP3A4/3A7/CYP2D6/CYP2C9

Transplanted Liver Humanized Mice
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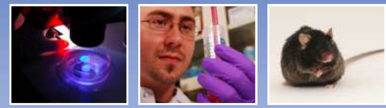
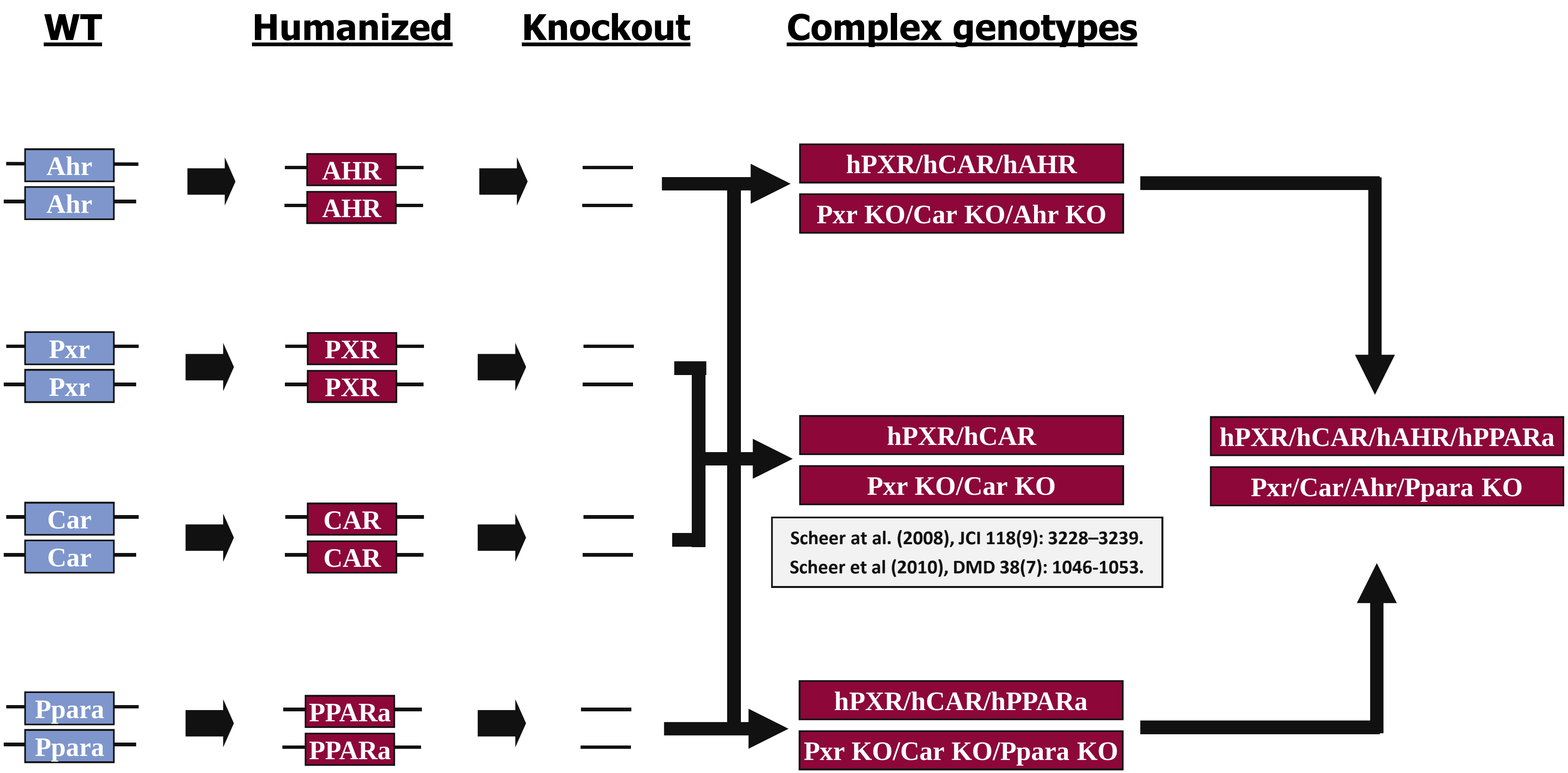
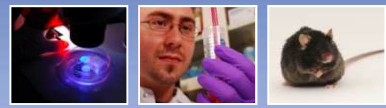
Multiple humanized xenoreceptor mice



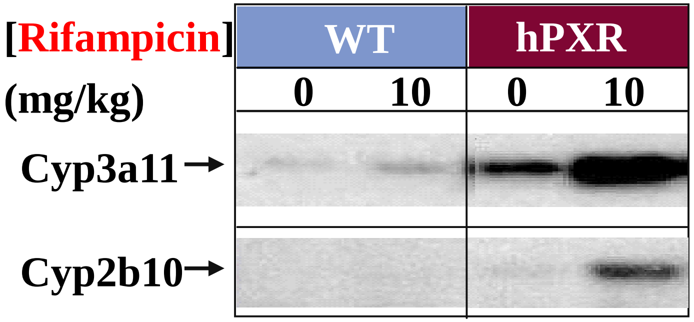


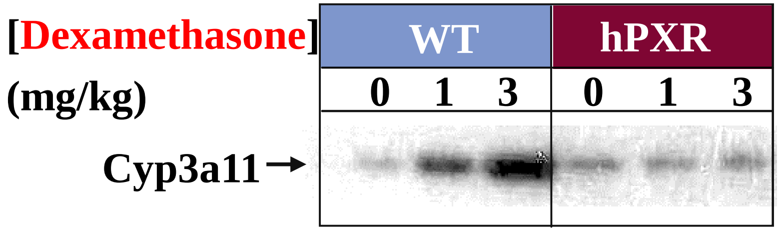
Scheer at al. (2008), JCI 118(9): 3228–3239.
Scheer et al (2010), DMD 38(7): 1046-1053.

Induction studies in xenoreceptor mice

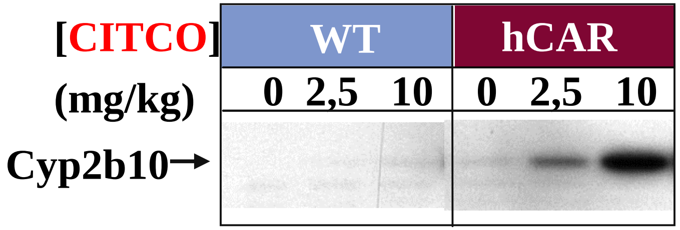


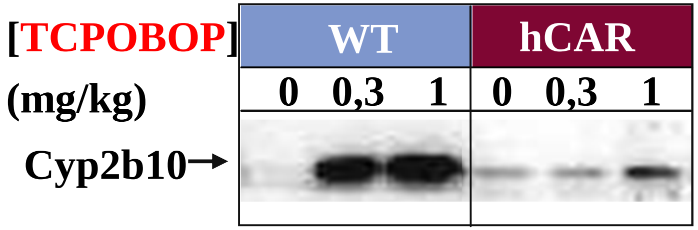
PXR



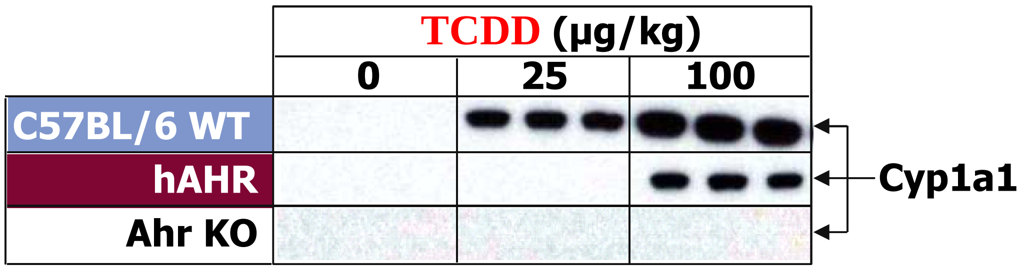


CAR





AHR



A Panel of Translational Xenoreceptor, DME, Transporter & Liver Humanized Mouse Models



Xenoreceptor Panel	
Knockouts	Humanized
Ahr	AHR
Car	CAR
Pparα	
Pxr	PXR
Pxr/Car	PXR/CAR
Pxr/Car/Ahr	PXR/CAR/AHR
Pxr/Car/Pparα	PXR/CAR/PPARα
Pxr/Car/Ahr/Pparα	PXR/CAR/AHR/PPARα

Cytochrome P450 Panel	
Knockouts	Humanized
Cyp1a1/1a2	CYP1A1/1A2
Cyp2c	CYP2C9
Cyp2d	CYP2D6
Cyp3a (BL/6)	CYP3A4/3A7
Cyp3a (FVB)	Liver CYP3A4
	Gut CYP3A4
	Liver/Gut CYP3A4
Cyp2c/Cyp2d/Cyp3a	

Transporter Panel	
Knockouts	Humanized
Bcrp	BCRP*
Mdr1a, Mdr1a/1b	MDR1*
Bcrp/Mdr1a/1b	
Mrp1	
Mrp2	MRP2
Oatp1a/1b	OATP1B1
	OATP1B3
	OATP1B1/1B3
Oct1/2	
Oat1/3	OAT1/3

Phase 2 Panel
Humanized
UGT1A1

Composite models
Humanized
PXR/CAR/CYP3A4/3A7
PXR/CAR/CYP3A4/3A7/CYP2D6
PXR/CAR/CYP3A4/3A7/CYP2D6/CYP2C9

Transplanted Liver Humanized Mice
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*coming soon

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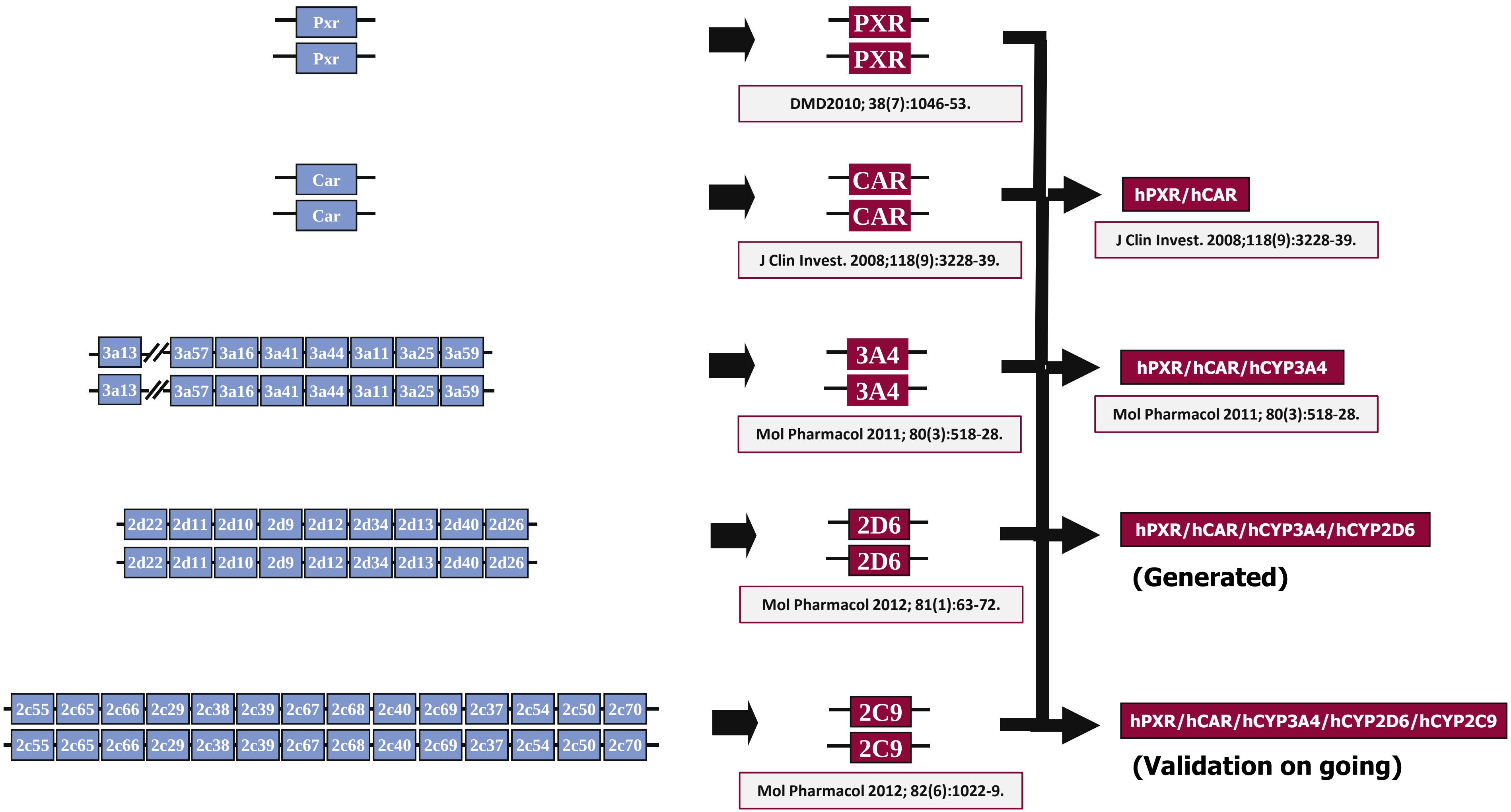
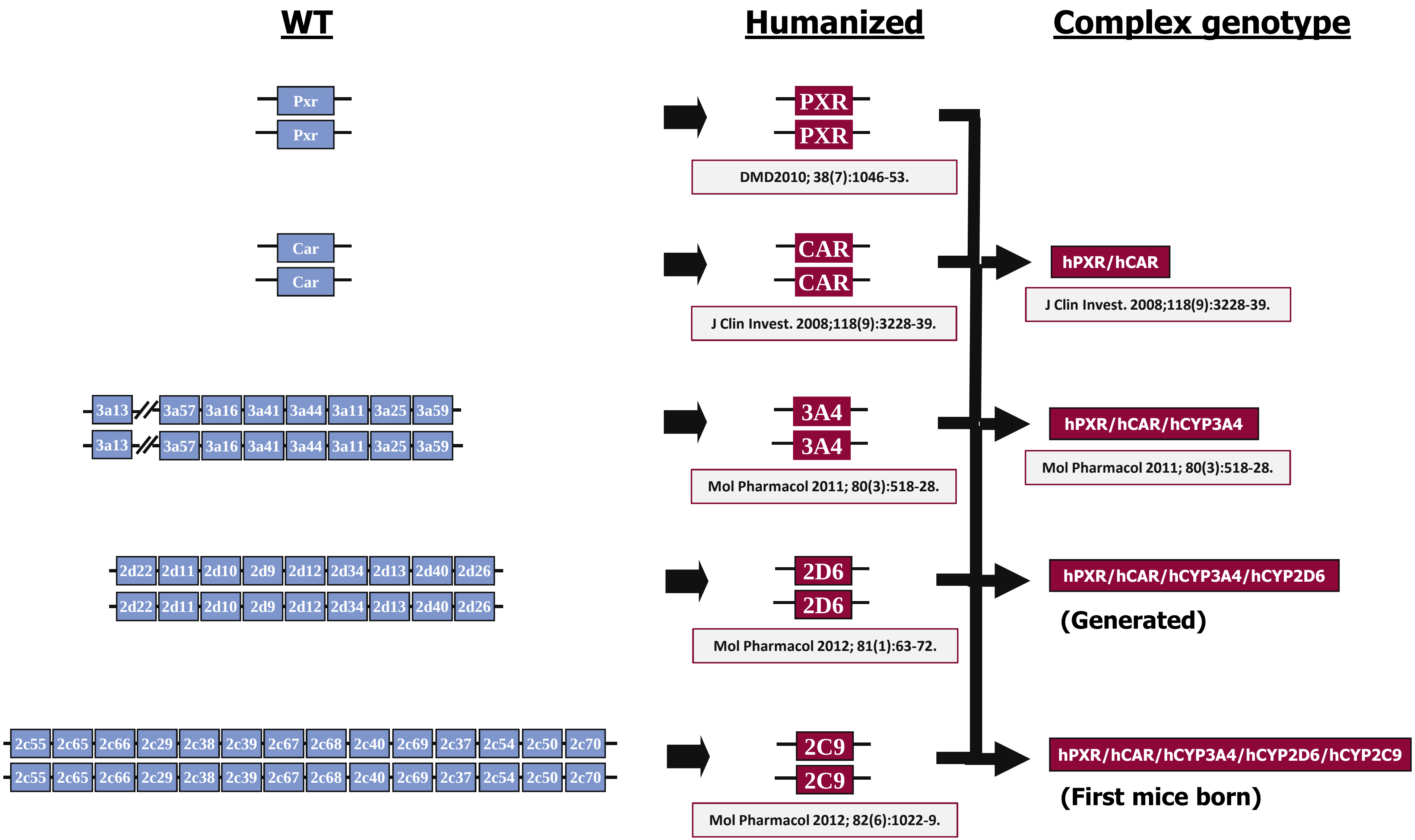
Towards a multiple humanized ADMET mouse model

WT **Humanized** **Complex genotype**



Use of hPXR/hCAR/hCYP3A4 mice for induction studies



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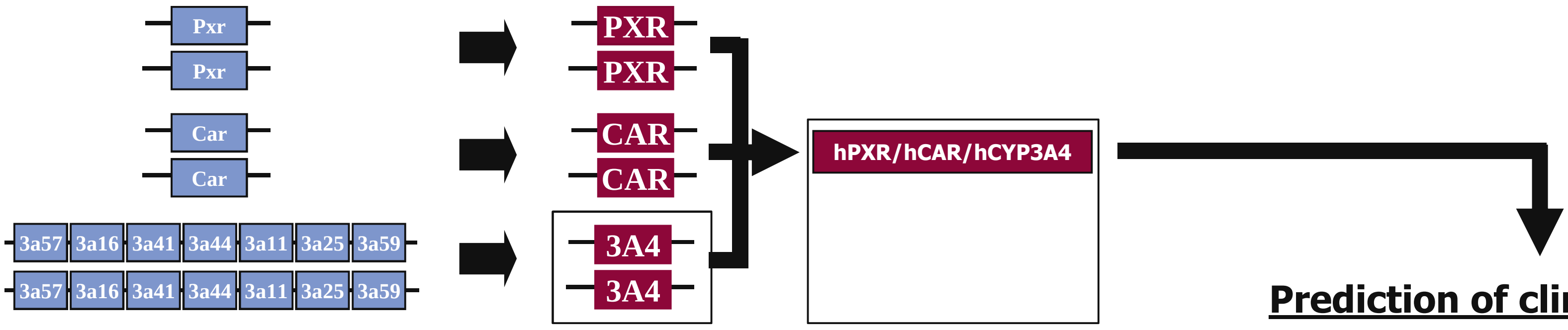
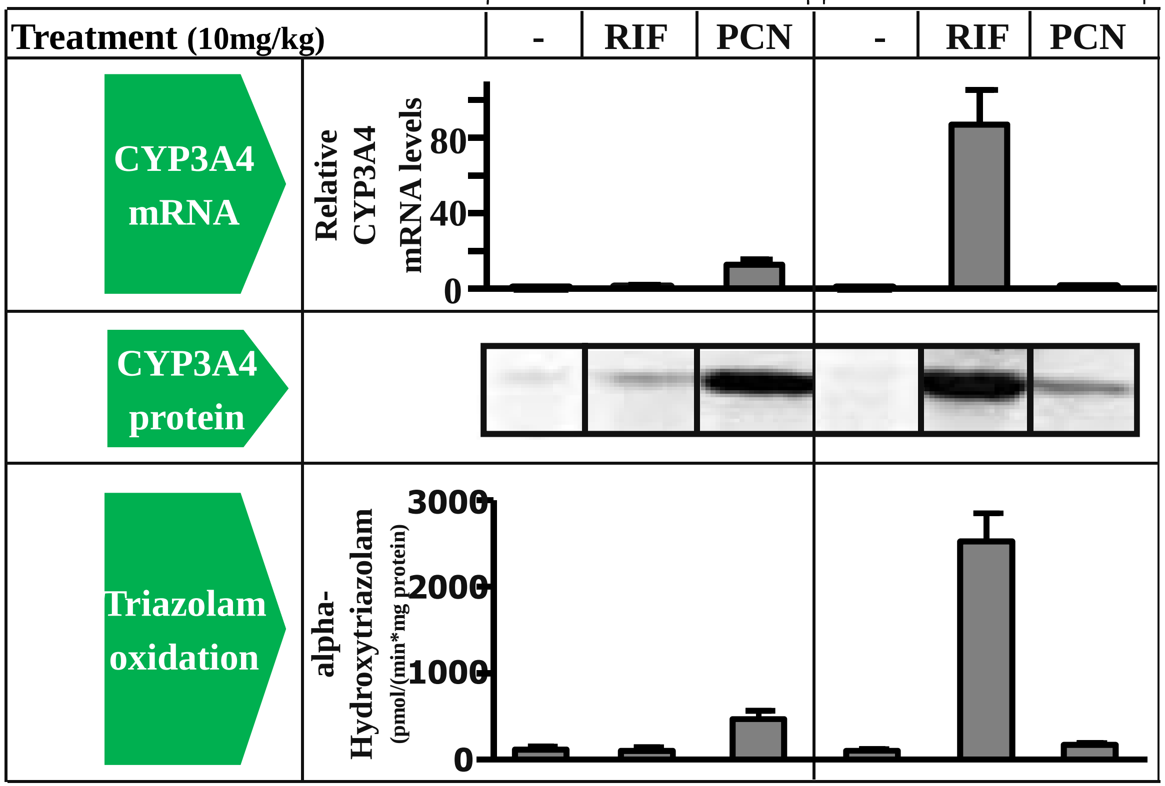
DDI prediction with triple humanized PXR/CAR/CYP3A4 mice

Quantitative prediction of human pregnane X receptor and cytochrome P450 3A4 mediated drug-drug interaction in a novel multiple humanized mouse line.
Hasegawa, Kapelyukh Tahara Seibler , Rode , Krueger, Lee, Wolf , Scheer; Mol Pharmacol. 2011 80(3):518-28.



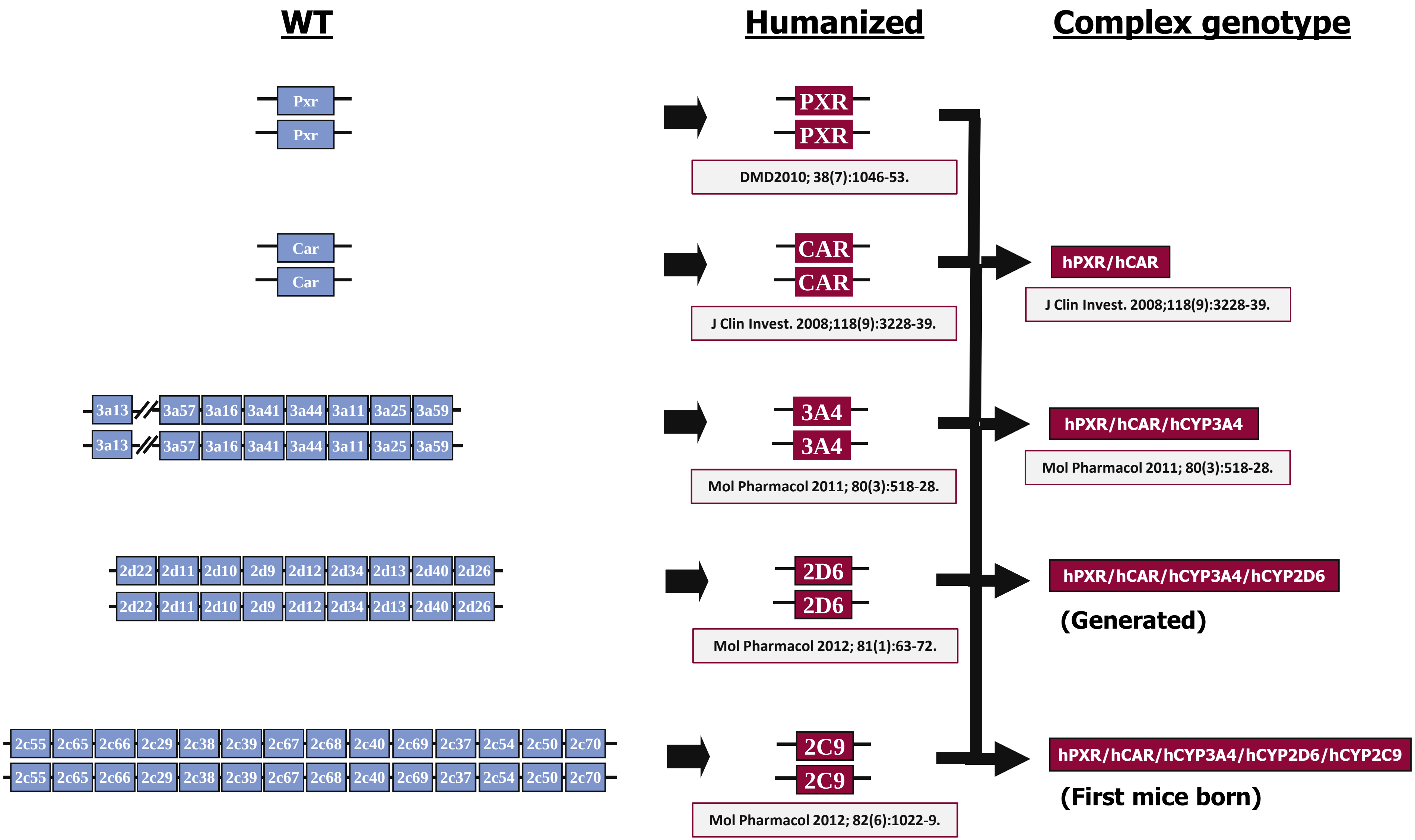
Prediction of clinical DDIs



human / mouse*	Rifampicin	Sulfinpyrazone	Pioglitazone
Hepatic CYP3A4 induction (human)	strong	medium	weak
Hepatic CYP3A4 induction (mouse*)	15-44-fold	4-10-fold	0-4-fold
AUC decrease of a co-administred CYP3A4 substrate (human)	70-95%	38%	0-26%
AUC decrease of a co-administred CYP3A4 substrate (mouse*)	63-90%	15-37%	2%

*All mouse data at clinically relevant doses

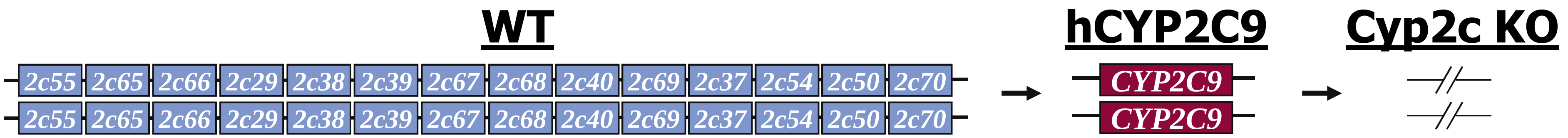
Use of cytochrome P450 humanized mice for inhibition studies



Inhibition studies in CYP2C9 humanized mice

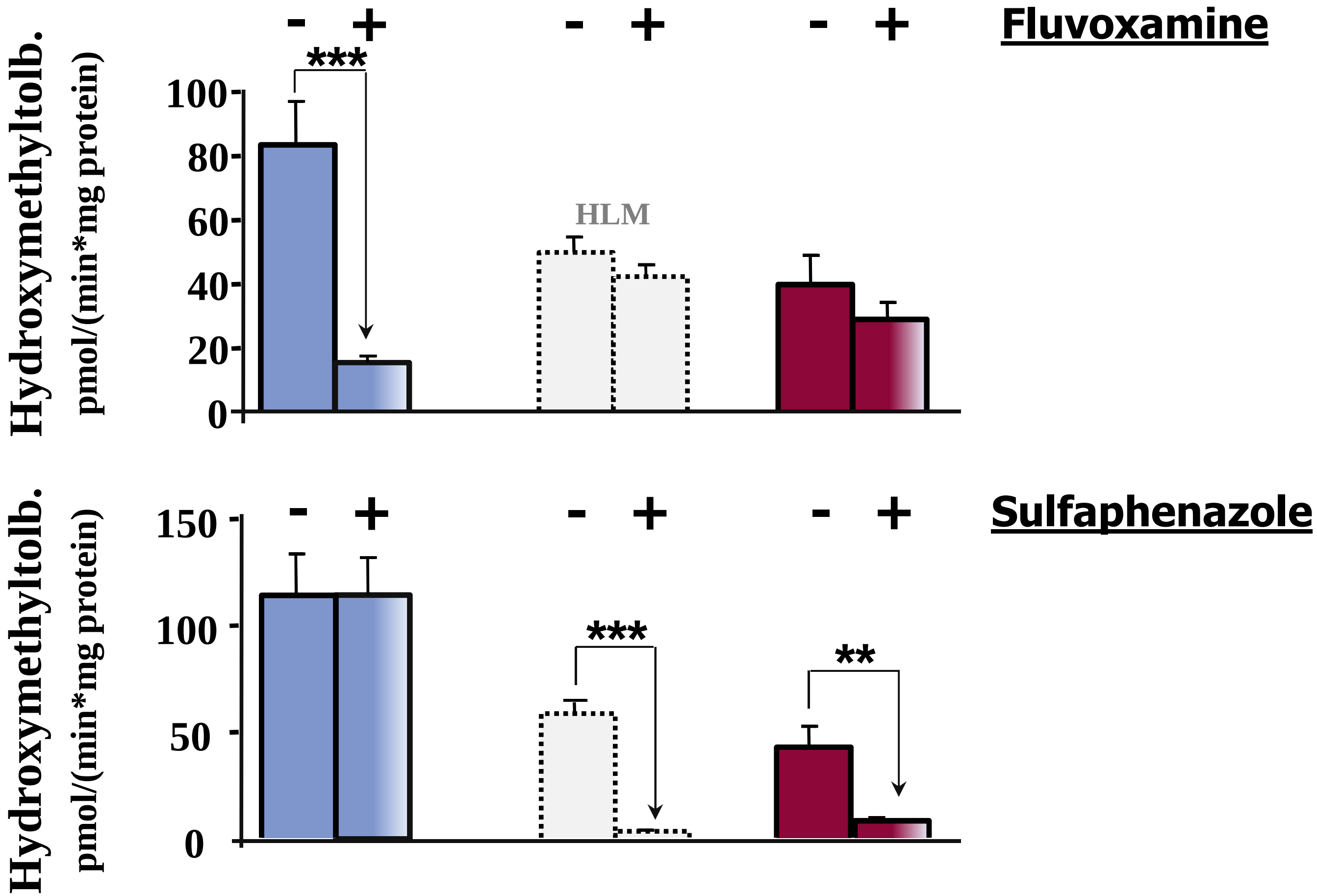
Generation and characterization of novel Cytochrome P450 Cyp2c gene cluster knockout and CYP2C9 humanized mouse lines.

Scheer, Kapelyukh, Chatham, Rode, Buechel, Wolf. Mol Pharmacol 2012; 82(6):1022-9.



Mouse specific inhibition of tolbutamide oxidation in liver microsomes

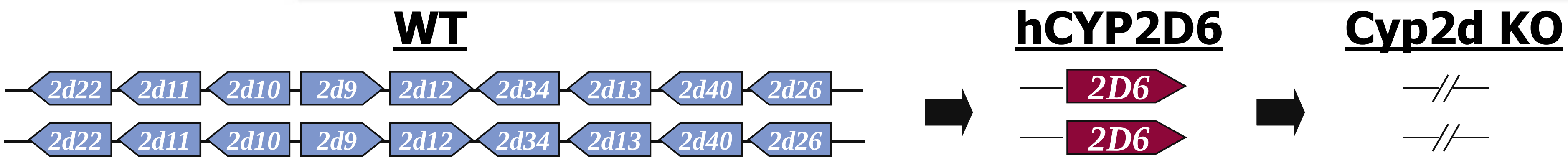
Human specific inhibition of tolbutamide oxidation in liver microsomes



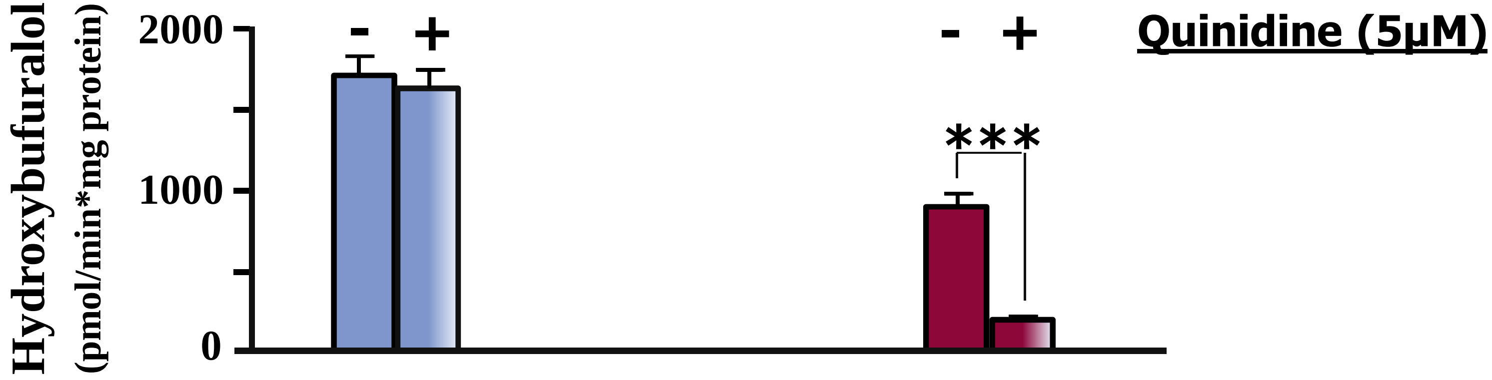
Inhibition studies in CYP2D6 humanized mice

Modeling human cytochrome P450 2D6 metabolism and drug-drug interaction by a novel panel of knockout and humanized mouse lines.

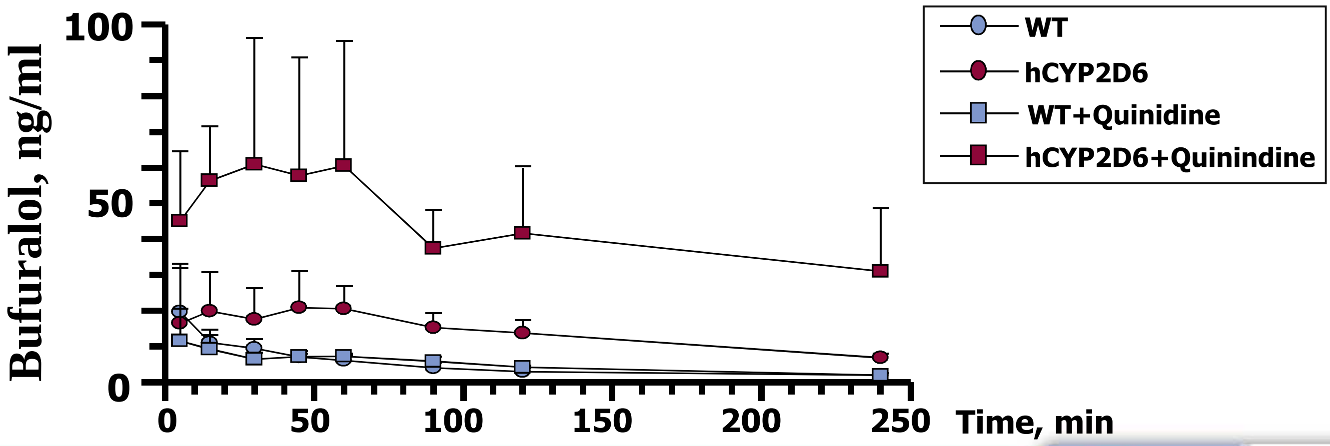
Scheer, Kapelyukh, McEwan, Beuger, Stanley, Rode, Wolf. Mol Pharmacol. 2012;81(1):63-72.



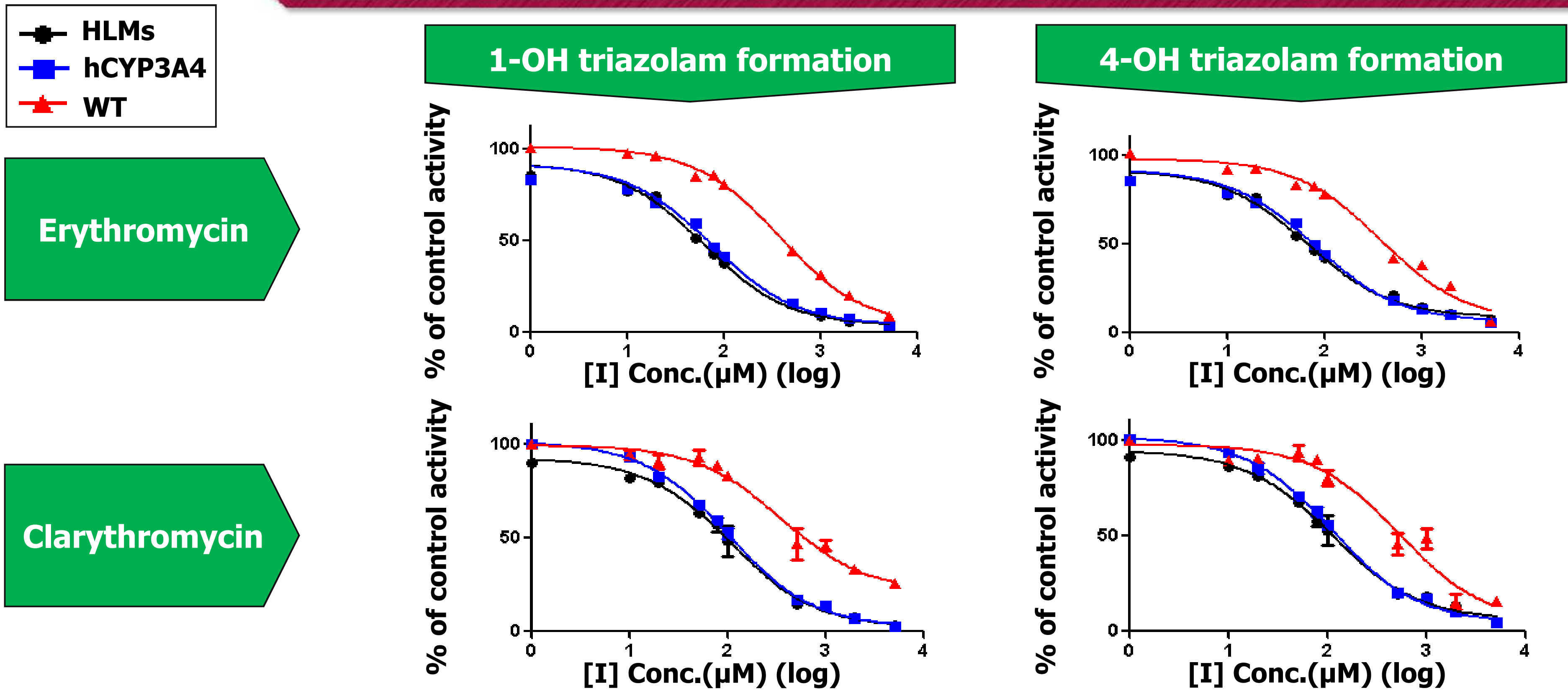
Human specific inhibition of bufuralol oxidation in liver microsomes



Human specific inhibition of bufuralol oxidation in vivo

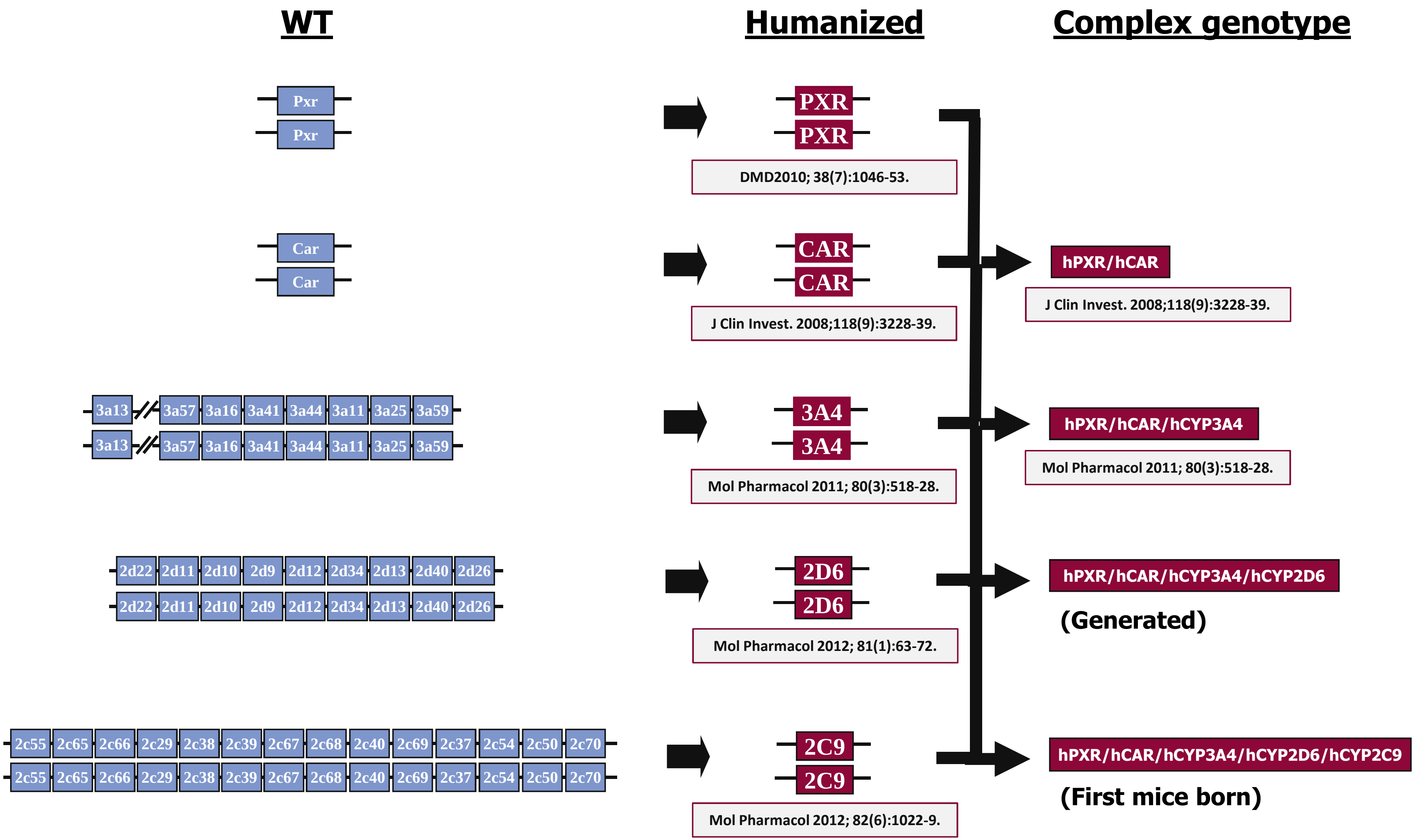


Inhibition of triazolam metabolism in CYP3A4 humanized mice (Liver microsomes)



	1-OH Triazolam			4-OH Triazolam		
	HLM	hCYP3A4	WT	HLM	hCYP3A4	WT
Erythromycin IC_{50}	62.0 µM	74.5 µM	725.4 µM	66.6 µM	80.0 µM	716.0 µM
Clarithromycin IC_{50}	108.0 µM	101.9 µM	349.7 µM	111.5 µM	111.1 µM	527.7 µM

Use of cytochrome P450 humanized mice for human metabolite testing



Identification & safety assessment of metabolites

Metabolites in safety testing: "MIST" for the clinical pharmacologist.
Frederick & Obach.
Clin Pharmacol Ther. 2010 87(3):345-50.

Decision tree

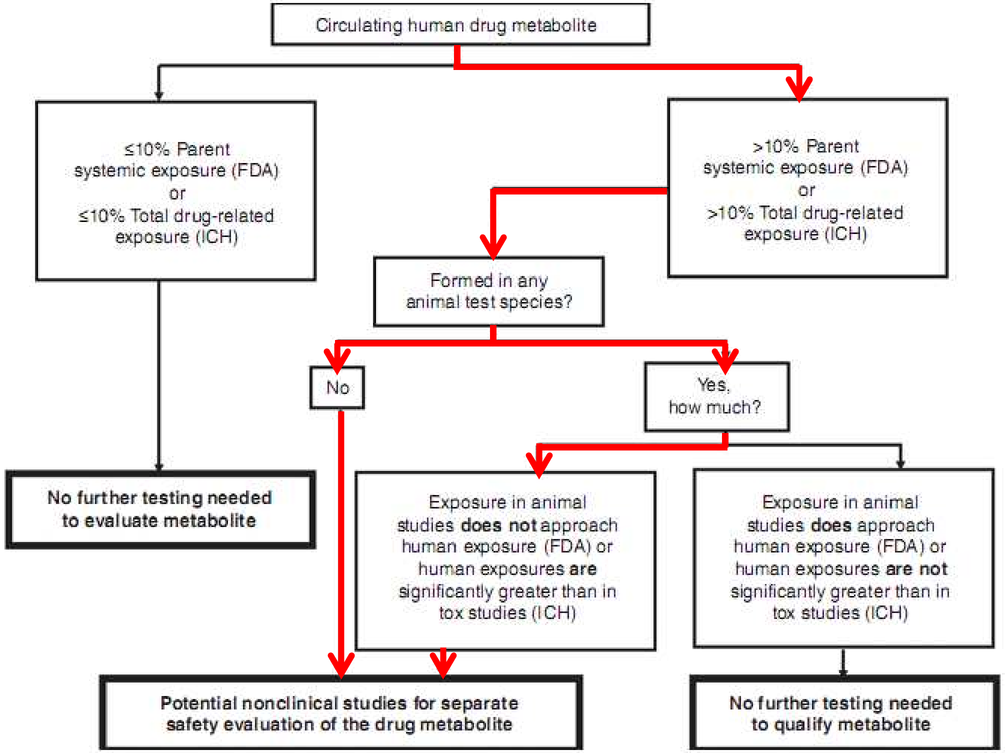
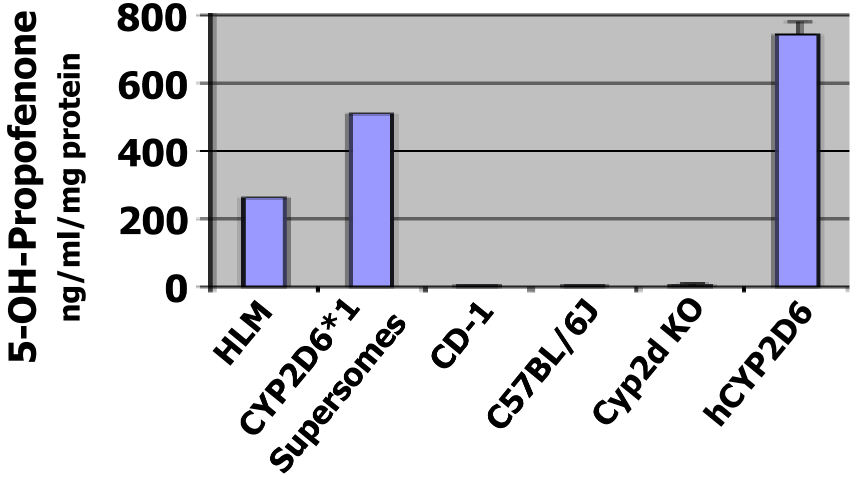


Figure 1 Combined decision tree for the implementation of the 2008 FDA and 2009 ICH guidances on the safety assessment of metabolites of drug candidates. The differences in the regulatory guidances on the decision-making criteria have not been formally resolved, although the criteria provided in the ICH guidance generally take precedence. FDA, US Food and Drug Administration; ICH, International Conference on Harmonisation.

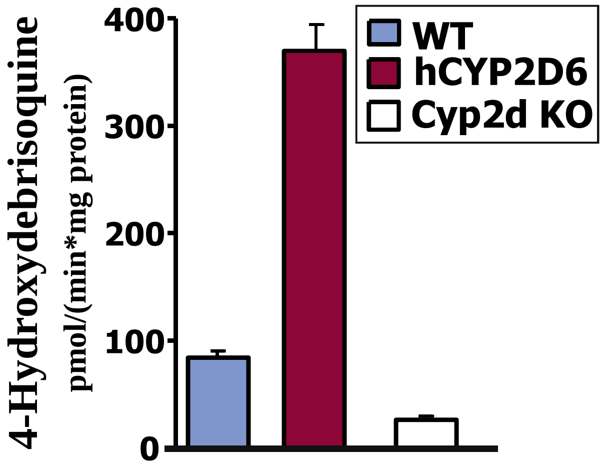
Formation of unique and disproportionate metabolites in humanized CYP2D6 mice

Modeling human cytochrome P450 2D6 metabolism and drug-drug interaction by a novel panel of knockout and humanized mouse lines.
Scheer, Kapelyukh, McEwan, Beuger, Stanley, Rode, Wolf. Mol Pharmacol. 2012;81(1):63-72.

Propofenone oxidation by liver microsomes:

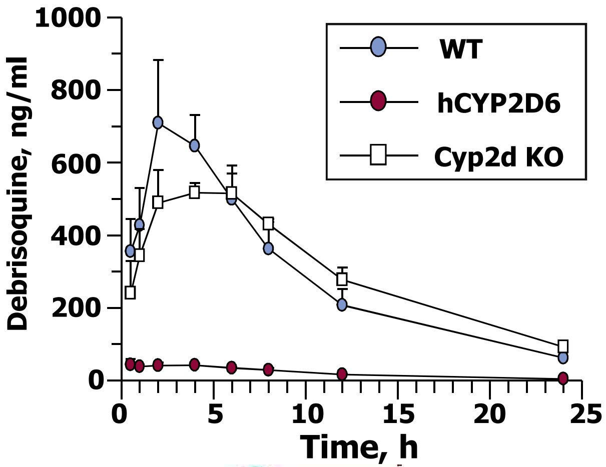


Debrisoquine oxidation by liver microsomes:

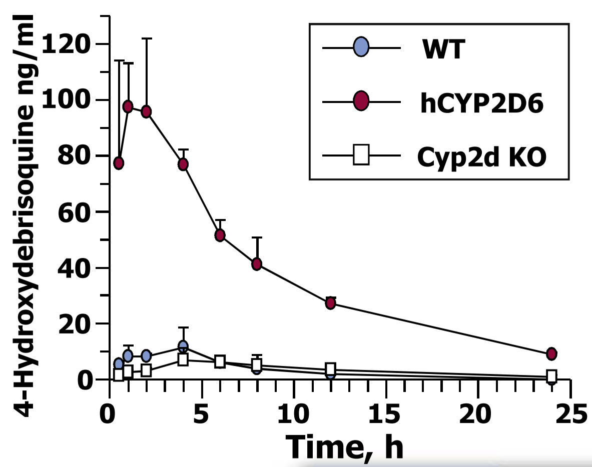


Pharmacokinetic of Debrisoquine & 4-Hydroxydebrisoquine:

Debrisoquine



4-Hydroxydebrisoquine



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A Panel of Translational Xenoreceptor, DME, Transporter & Liver Humanized Mouse Models

Xenoreceptor Panel		Cytochrome P450 Panel		Transporter Panel	
Knockouts	Humanized	Knockouts	Humanized	Knockouts	Humanized
Ahr	AHR	Cyp1a1/1a2	CYP1A1/1A2	Bcrp	BCRP*
Car	CAR	Cyp2c	CYP2C9	Mdr1a, Mdr1a/1b	MDR1*
Pparα		Cyp2d	CYP2D6	Bcrp/Mdr1a/1b	
Pxr	PXR	Cyp3a (BL/6)	CYP3A4/3A7	Mrp1	
Pxr/Car	PXR/CAR	Cyp3a (FVB)	Liver CYP3A4	Mrp2	MRP2
Pxr/Car/Ahr	PXR/CAR/AHR		Gut CYP3A4	Oatp1a/1b	OATP1B1
Pxr/Car/Pparα	PXR/CAR/PPARα		Liver/Gut CYP3A4		OATP1B3
Pxr/Car/Ahr/Pparα	PXR/CAR/AHR/PPARα	Cyp2c/Cyp2d/Cyp3a			OATP1B1/1B3
				Oct1/2	
				Oat1/3	OAT1/3

Phase 2 Panel	Composite models	Transplanted Liver Humanized Mice
Humanized	Humanized	
UGT1A1	PXR/CAR/CYP3A4/3A7	FRG™ (in Collaboration with Yecuris Inc.)
	PXR/CAR/CYP3A4/3A7/CYP2D6	
	PXR/CAR/CYP3A4/3A7/CYP2D6/CYP2C9	

*coming soon

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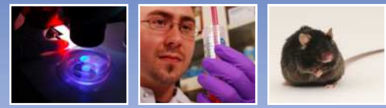
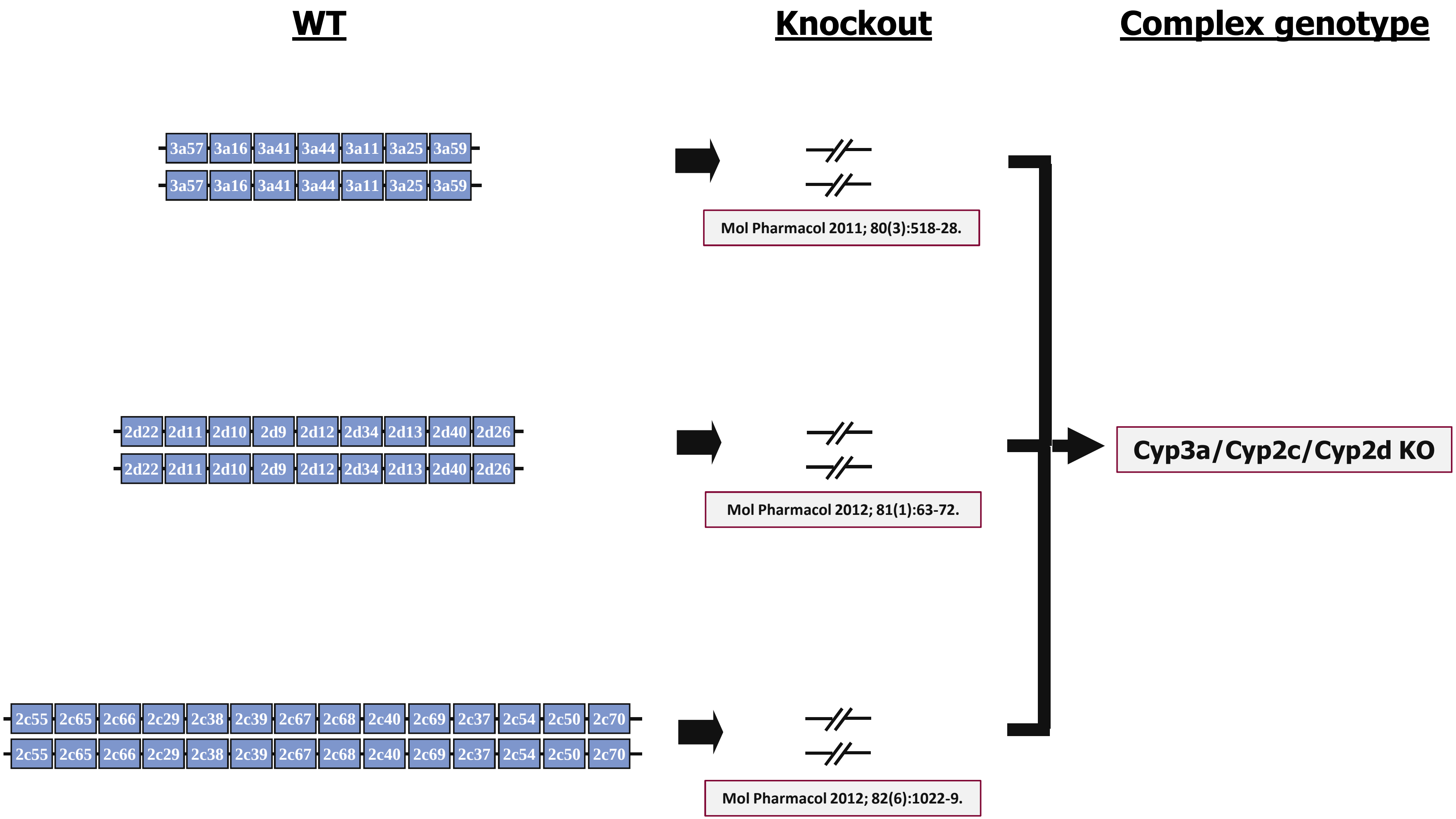
Cyp3a/Cyp2c/Cyp2d KO mice

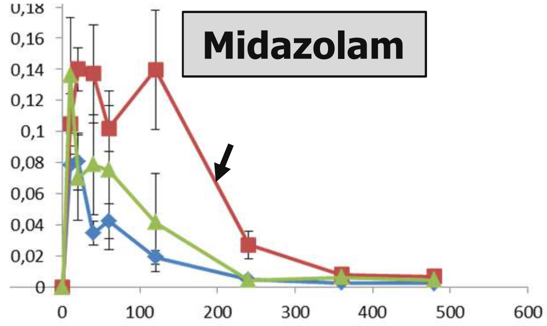


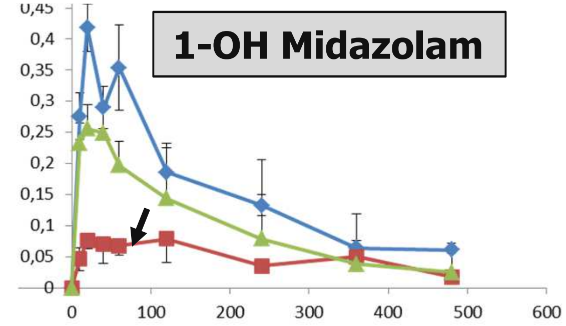


Cyp3a/Cyp2c/Cyp2d KO mice

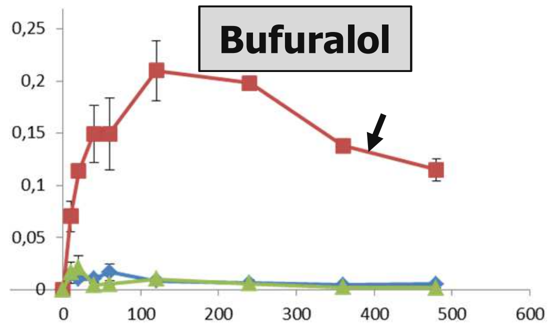
WT
Cyp3a KO
Cyp3a/2c/2d KO

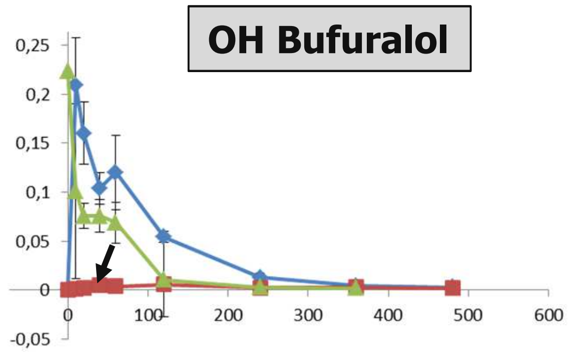
CYP3A substrate



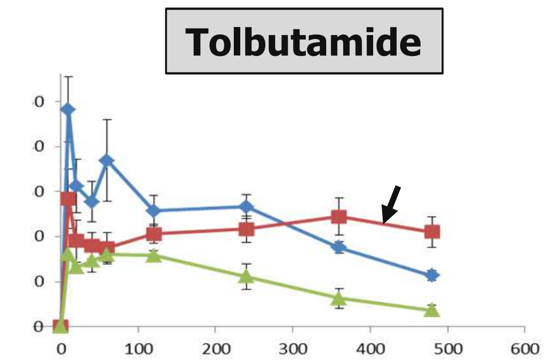


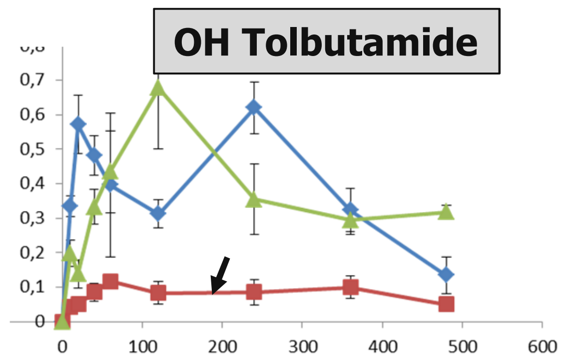
CYP2D substrate





CYP2C substrate





Future vision for genetically humanized mice

Xenoreceptors

- hPXR/hCAR/hAHR/hPPARa

Drug metabolising enzymes

- hPXR/hCAR/hCYP3A4/hCYP2D6/hCYP2C9
- hCYP1A1/1A2
- hCYP2C19
- hUGT1A
- hUGT2B7

→ hPXR/hCAR/hCYP3A4/hCYP2D6/hCYP2C9/2C19/hCYP1A1/1A2/hUGT1A/hUGT2B7

Drug transporters

- hMDR1
- hMRP2
- hBCRP
- hOATP1B1/1B3
- hOAT1/3
- hOCT1/2
- hBSEP

→ hMDR1/hMRP2/hBCRP/hOATP1B1/1B3/hOAT1/3/hOCT1/2/hBSEP

→ hPXR/hCAR/hAHR/hPPARa/hCYP3A4/hCYP2D6/hCYP2C9/2C19/hCYP1A1/1A2/hUGT1A/hUGT2B7/hMDR1/hMRP2/hBCRP/hOATP1B1/1B3/hOAT1/3/hOCT1/2/hBSEP

A Panel of Translational Xenoreceptor, DME, Transporter & Liver Humanized Mouse Models



Xenoreceptor Panel		Cytochrome P450 Panel		Transporter Panel	
Knockouts	Humanized	Knockouts	Humanized	Knockouts	Humanized
Ahr	AHR	Cyp1a1/1a2	CYP1A1/1A2	Bcrp	BCRP*
Car	CAR	Cyp2c	CYP2C9	Mdr1a, Mdr1a/1b	MDR1*
Pparα		Cyp2d	CYP2D6	Bcrp/Mdr1a/1b	
Pxr	PXR	Cyp3a (BL/6)	CYP3A4/3A7	Mrp1	
Pxr/Car	PXR/CAR	Cyp3a (FVB)	Liver CYP3A4	Mrp2	MRP2
Pxr/Car/Ahr	PXR/CAR/AHR		Gut CYP3A4	Oatp1a/1b	OATP1B1
Pxr/Car/Pparα	PXR/CAR/PPARα		Liver/Gut CYP3A4		OATP1B3
Pxr/Car/Ahr/Pparα	PXR/CAR/AHR/PPARα	Cyp2c/Cyp2d/Cyp3a			OATP1B1/1B3
				Oct1/2	
				Oat1/3	OAT1/3

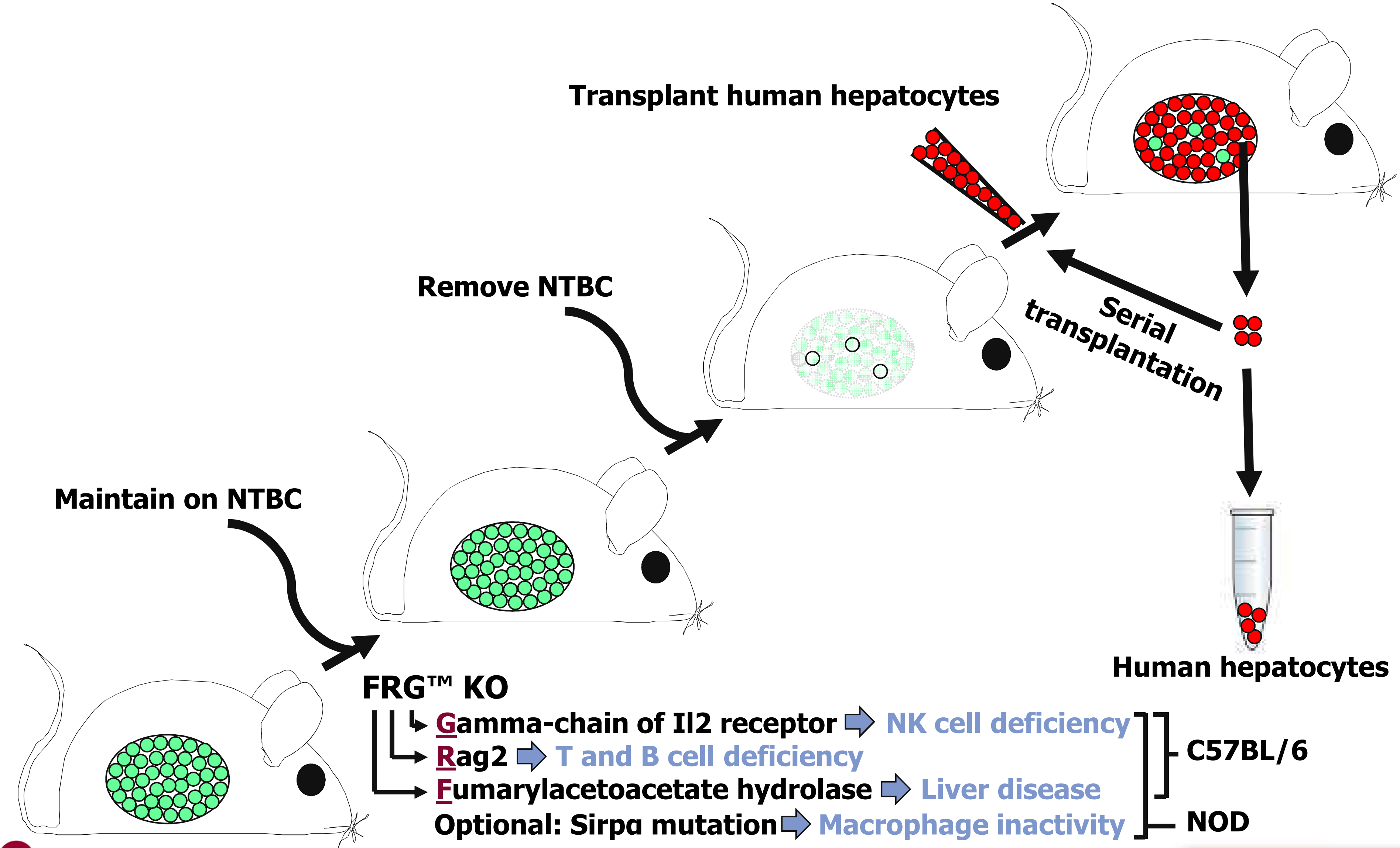
Phase 2 Panel
Humanized
UGT1A1

Composite models
Humanized
PXR/CAR/CYP3A4/3A7
PXR/CAR/CYP3A4/3A7/CYP2D6
PXR/CAR/CYP3A4/3A7/CYP2D6/CYP2C9

Transplanted Liver Humanized Mice
FRG™ (in Collaboration with Yecuris Inc.)

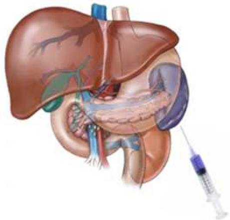
*coming soon

The FRG™ KO Mouse: Basic principle

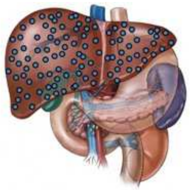


Liver repopulation in FRG™ KO mice

Engraftment (.5-1M Cells)

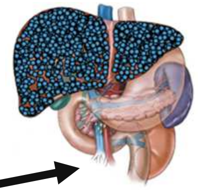


8 weeks (5-10M Cells)

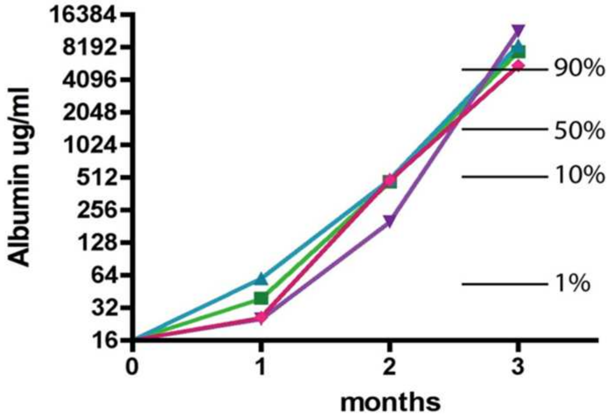


200-500 µg/mL HAS (1-5% repopulation)

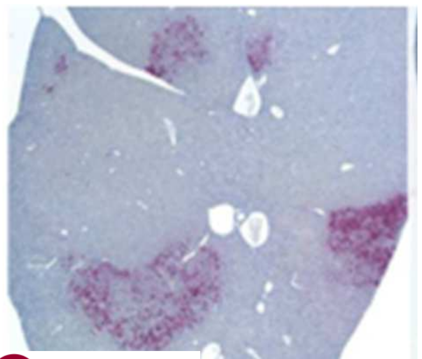
>12 weeks (80-150M Cells)



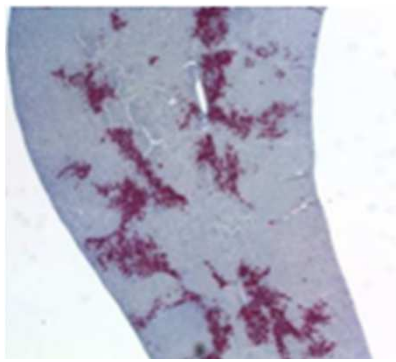
2000-5000 µg/mL HAS (50-98% repopulation)



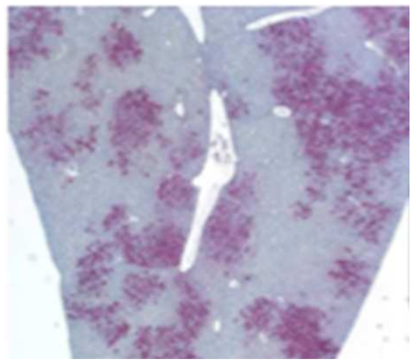
10-20%



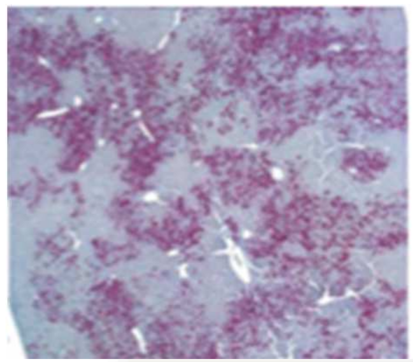
20-30%



30-50%



70-80%



Comparison of genetically and tissue humanized mouse models



Liver transplanted mice

Pros

√ Humanization of all genes in given liver cell

√ Only one mouse line required

√ Ease of generating donor variability

√ Allows for extraction of human hepatocytes

√ Useful to study infectious liver diseases

Cons

x Model has to be recreated continuously

x Varying degree of humanization

x Humanization of liver only

x Presence of residual mouse hepatocytes

x Higher unit price

Transgenic mice

Cons

x Humanization of selected genes only

x Requirement of various mouse lines

x Effort of generating donor variability

x No possibility to extract human tissues

x No infection with human specific pathogens

Pros

√ Permanent models without recreation

√ Invariable quality of mice from each line

√ Expression of human genes in other organs

√ Human genes expressed in all liver cell

√ Lower unit price

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Prospects & limitations



Prospects

The described models may be valuable tools to predict certain aspects of drug responses in man, such as

- **Drug-drug interactions**
- **Effects of human metabolites**
- **Bioavailability & clearance**
- **PKPD relation**
- **Drug-induced toxicity**

Combination of genetically humanized mice into multiple humanized genotypes will further increase their utility.

Limitations

- **Humanization restricted to selected genes (genetically humanized mice) or liver (transplanted models)**
- **General physiological differences between mice and humans**
- **Lower throughput and higher cost compared to in vitro studies**
- **Limited historical data**

These *in vivo* technologies are suited to more detailed investigative studies & to select the most promising drug candidates before first test in man.

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BMS
Kamelia Behnia, Anne Rose
(CYP3A4 inhibition studies)

Yecuris
John Bial, Markus Grompe (FRG™ technology)

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