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Laboratory of **Comparative Genomics**

CHARACTERIZATION OF PORCINE REGULATORS OF DRUG METABOLISM

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Introduction

- Drug metabolizing enzymes (DMEs) play a central role in the metabolism, elimination and detoxification of xenobiotics and drugs.
- Analysis of the pig genome has revealed high homology between porcine and human genes, including genes associated with drug metabolism.
- Orphan nuclear receptors including constitutive androstane receptor (CAR), liver X receptor (LXR) and peroxisome proliferator activated receptor (PPAR) are critical regulators of DMEs and drug detoxification transporter molecules
- Recent pharmacodynamic studies have shown that the mouse is not an ideal model for predicting human clinical drug study outcomes.
- The characterization of porcine drug metabolism genes and the genes involved in regulating drug metabolism can provide insights into human drug metabolic diseases and individual variability of responses towards a drug.

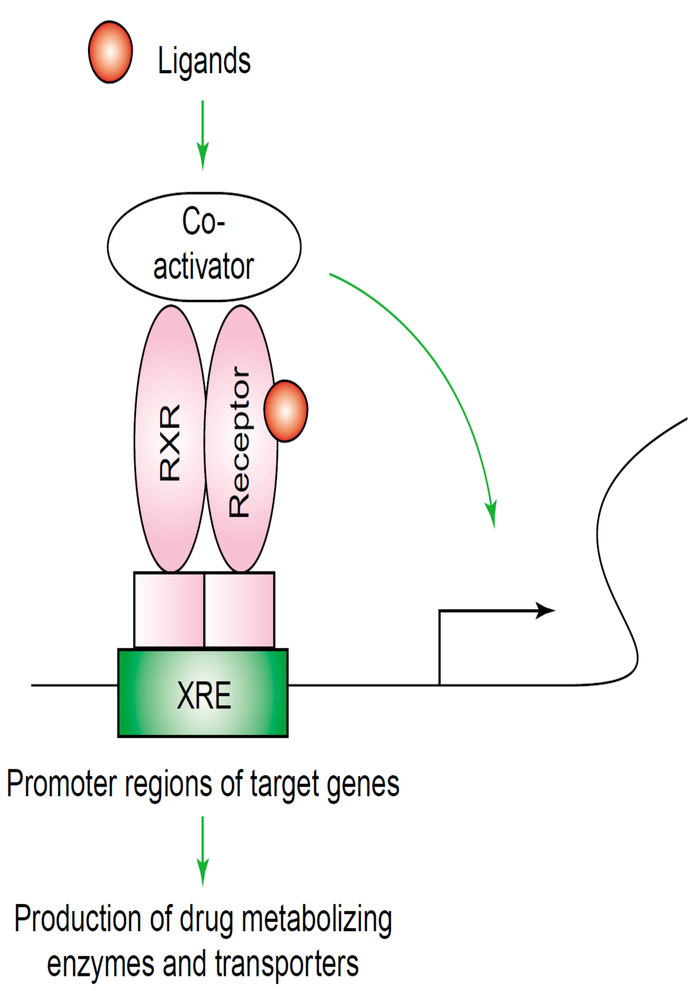
Regulation of DMEs by Nuclear Receptors

Ligand

Activates the expression of nuclear receptors and their dimerization

Heterodimers bind to xenobiotic response elements of target gene promoters

Expression of drug metabolizing enzymes



Objectives

- Identification of expression pattern of orphan nuclear receptors in the pig
- To identify splice variants of orphan nuclear receptors and their comparison to human

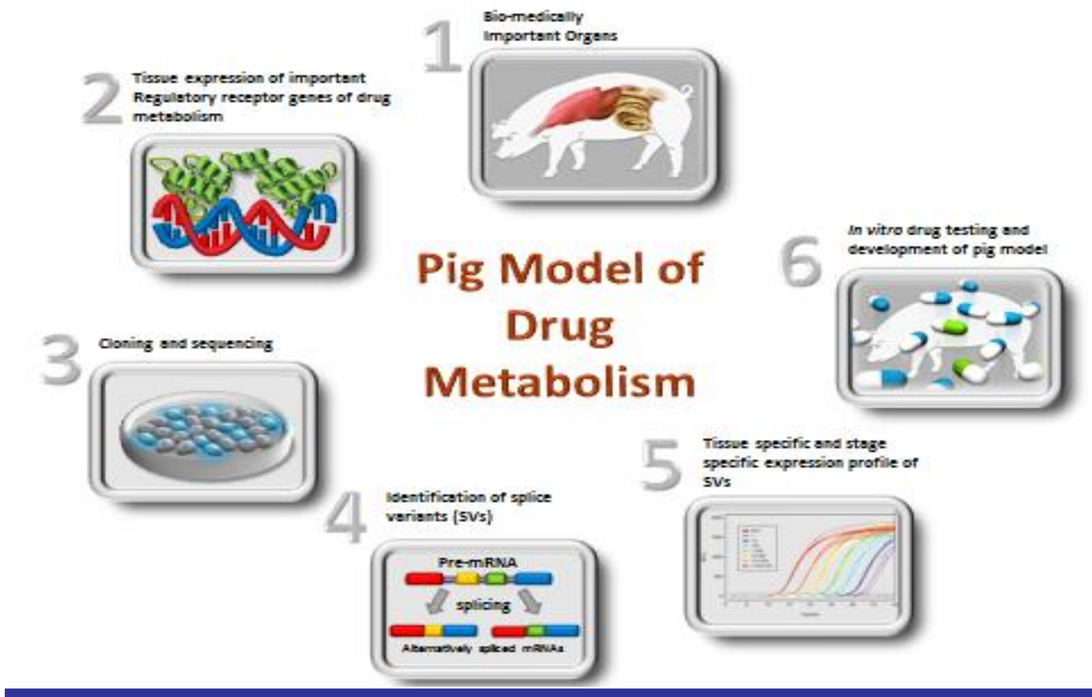
Materials and Methods

- Bio-medically important organs were surveyed for expression of CAR, LXR-α, LXR-β, PPAR-α, PPAR-β, and PPAR-γ.
- Cloning and sequencing is underway to identify splice variants and expression patterns to determine comparison to human patterns.

References

Xie et al., Orphan nuclear receptor-mediated xenobiotic regulation in drug Metabolism, Nature reviews, Vol 9, 2004

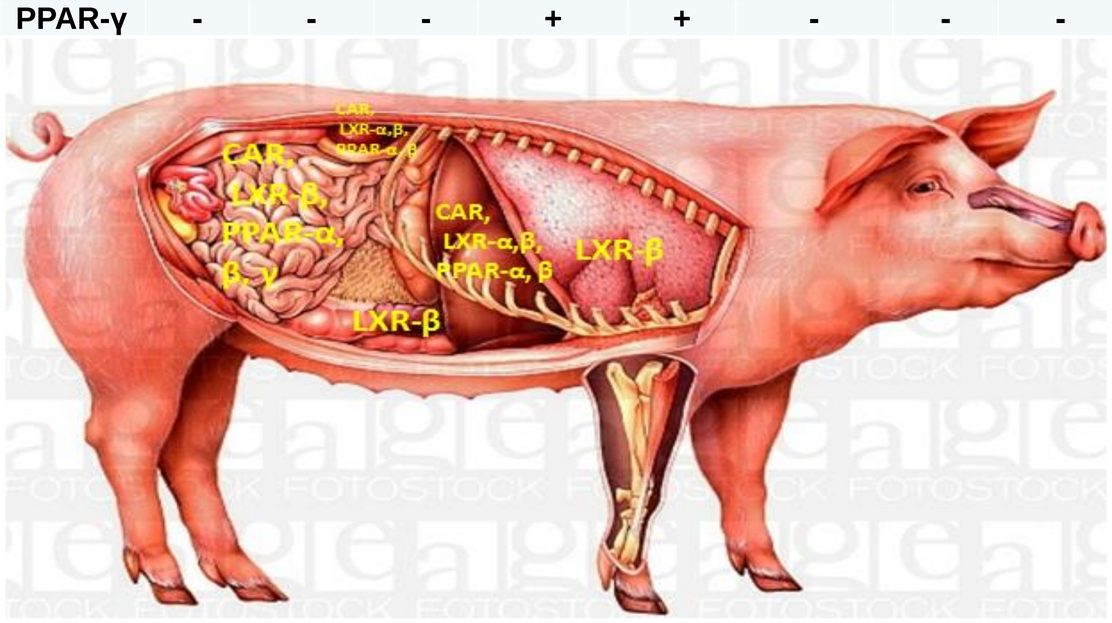
Overall Approach



Preliminary Results

Tissue Expression of different Nuclear Receptors

	Liver	Kidney	Lung	Small Intestine	Splee n	Pancreas	Heart	Brain
CAR	+	+	-	+	-	-	-	-
LXR-α	+	+	-	-	+	-	-	-
LXR-β	+	+	+	+	+	+	+	-
PPAR-α	+	+	-	+	-	-	+	
PPAR-β	+	+	-	+	-	-	+	+
PPAR-γ	-	-	-	+	+	-	-	-



- CAR was cloned from pig liver and kidney tissues by TOPO TA cloning method and clones were sequenced.
- Three alternatively splice variants were observed in liver and two variants in kidney tissues were identified with each predicted to generate a truncated protein product.
- Among the splice variants in liver, splice variant 1 and variant 2 were found predominantly and variant 3 were very rare
- Among kidney splice variants, variant 1 was predominant

Conclusion and Future Directions

- Tissue expression of different nuclear receptors were similar to human
- Further characterization of nuclear receptors and in vitro drug testing for development of a swine model of drug metabolism will be done in future

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