

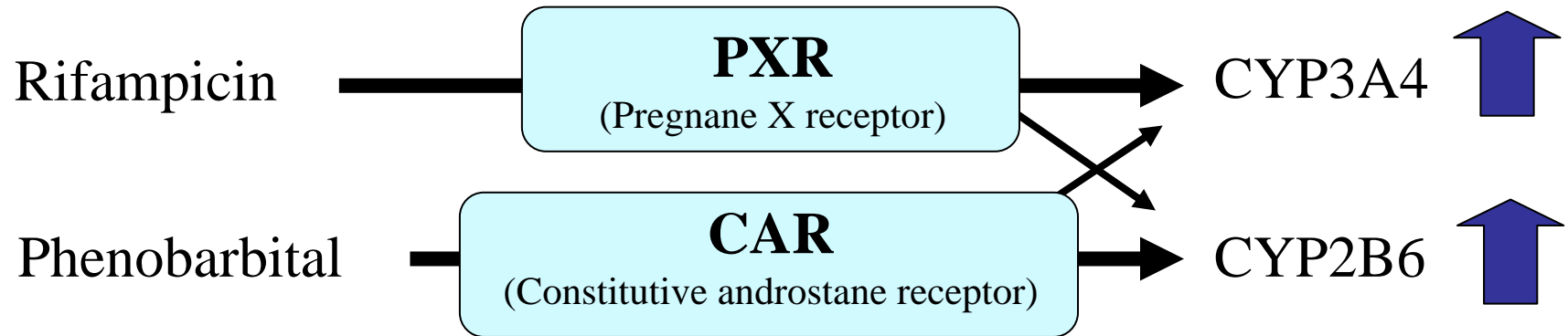
核内レセプターによる薬物代謝酵素の 発現調節機構に関する研究

千葉大学大学院薬学研究院
薬物学研究室

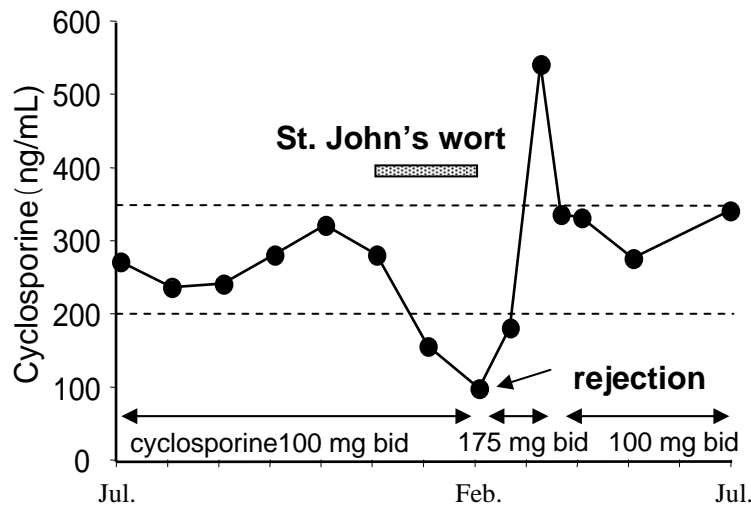
小林カオル

Induction of drug metabolizing enzymes

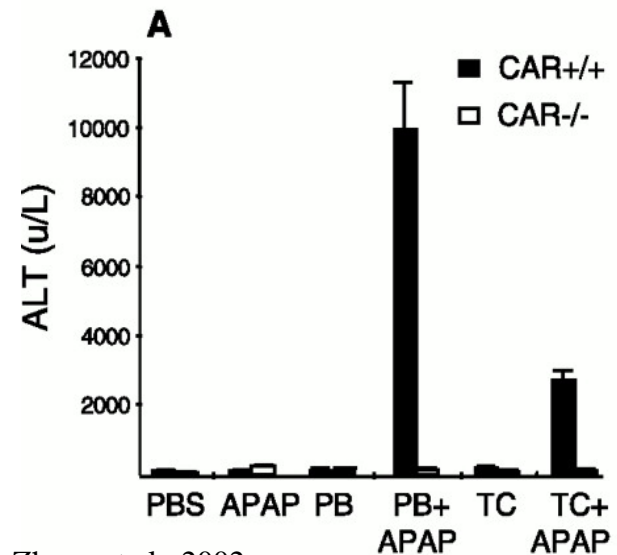
Effects on drug therapy and toxicity



CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP3A7, UGT1A1, SULT2A1, GSTs....etc.



Gary et al., 2000

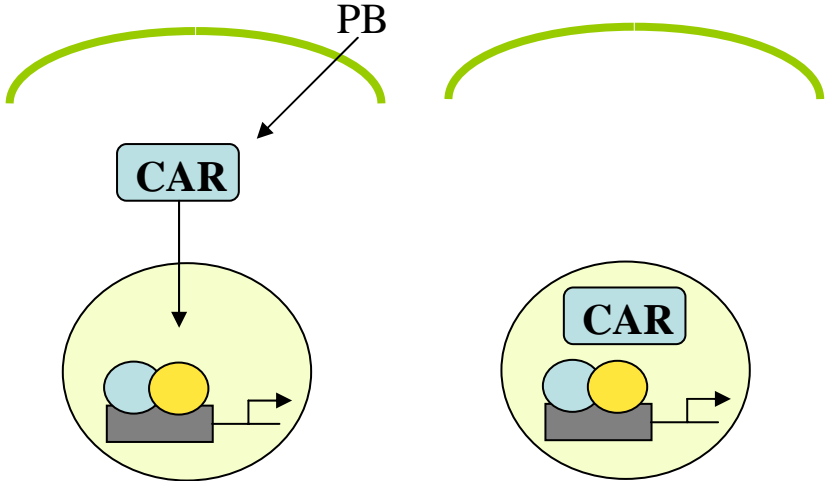


Zhang et al., 2002

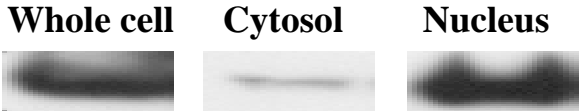
Intracellular localization of CAR

Hepatocytes

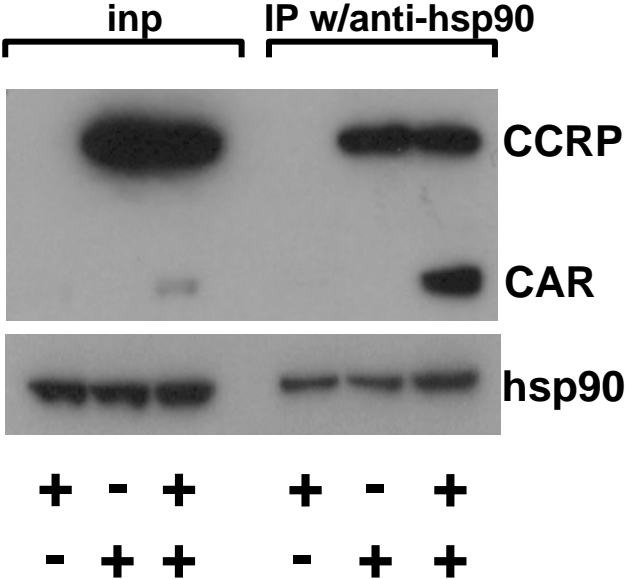
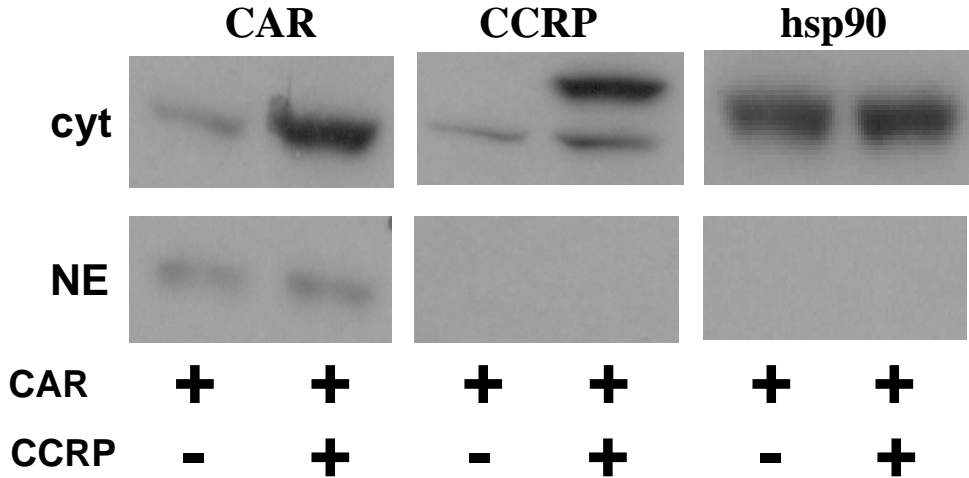
HepG2 cells



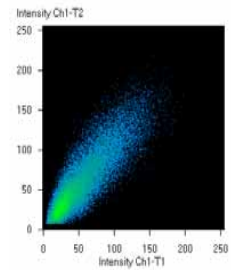
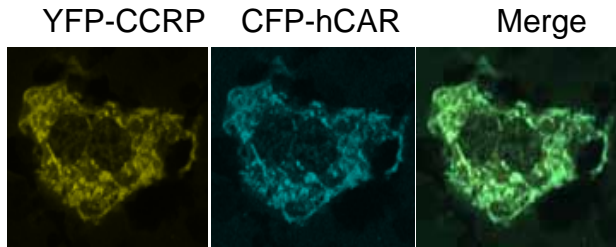
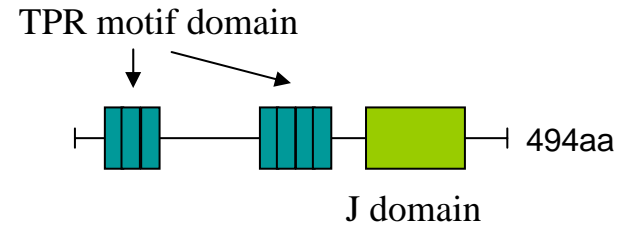
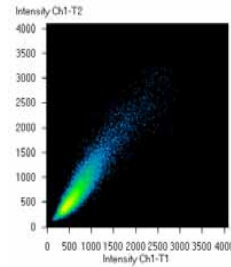
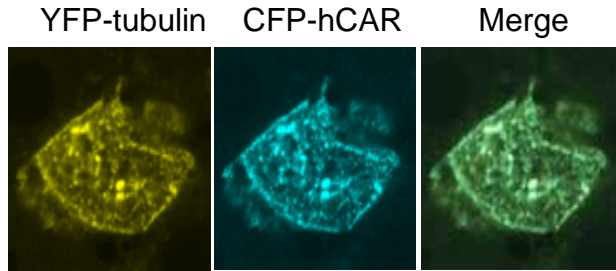
Exogenous CAR protein in HepG2 cells



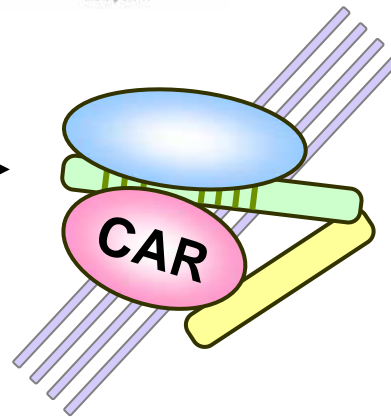
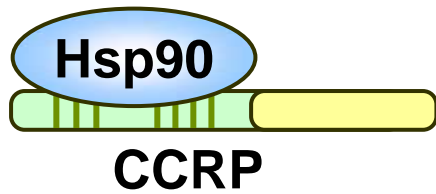
Cytoplasmic accumulation of CAR by CCRP



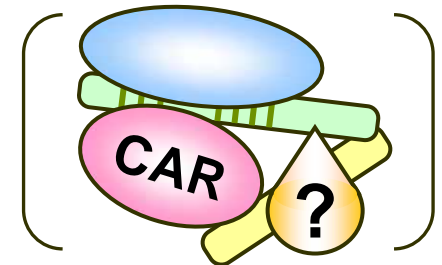
In vivo expression of fluorescent protein-tagged CAR and CCRP



Domains of CCRP

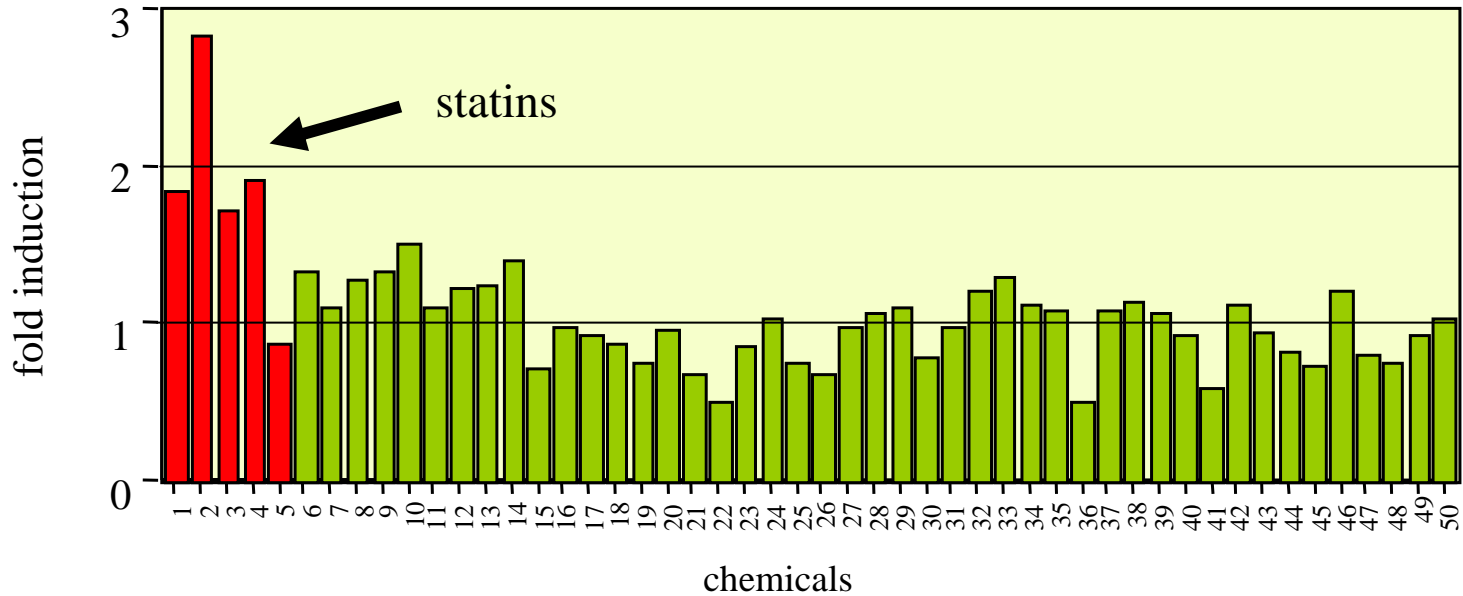


PB

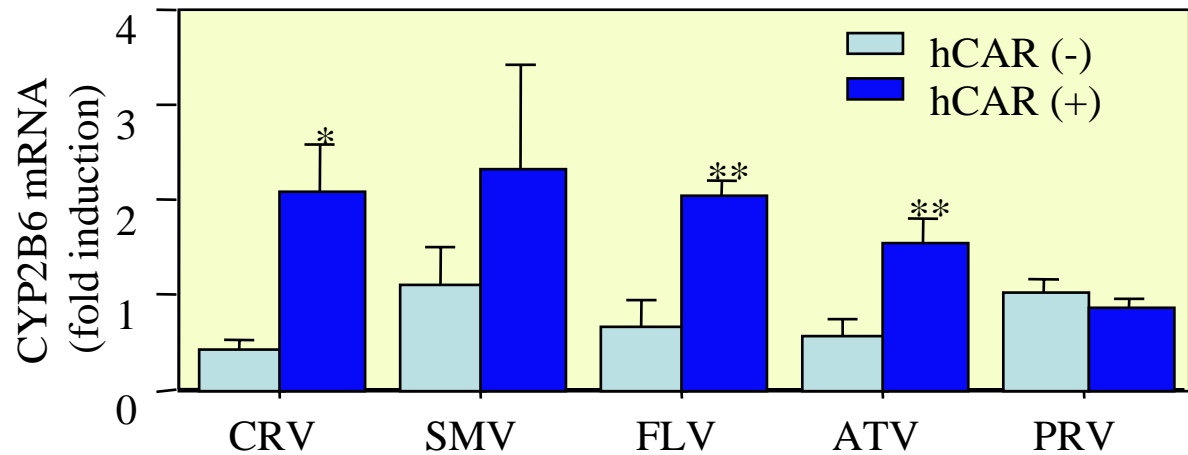


Identification of statins as human CAR activators

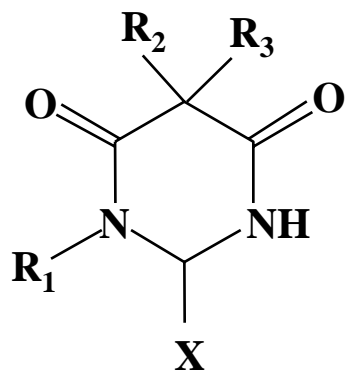
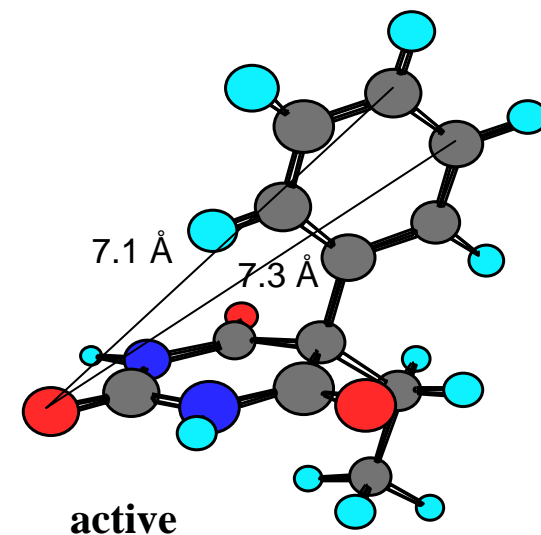
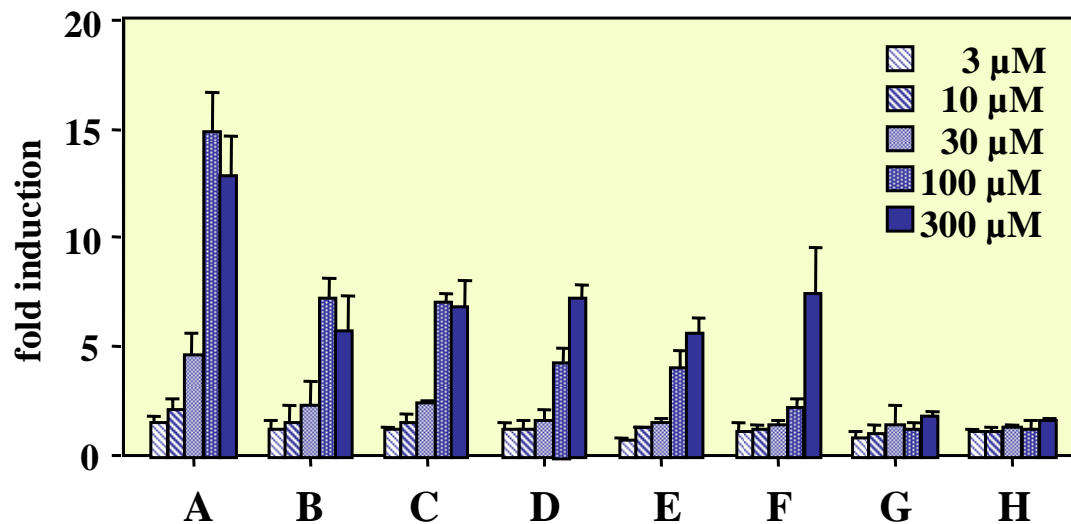
Reporter gene assay



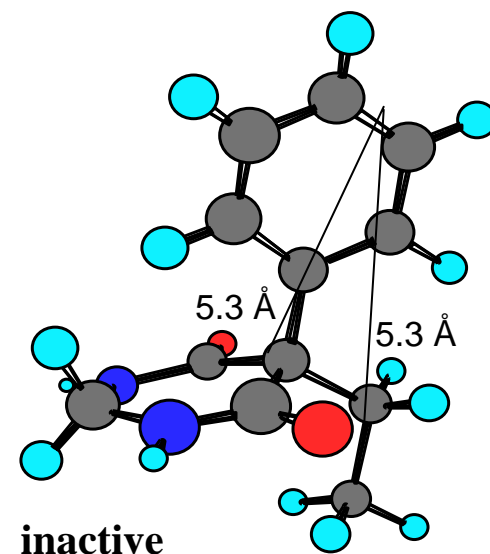
CYP2B6 mRNA



Effects of barbiturates on hPXR activation



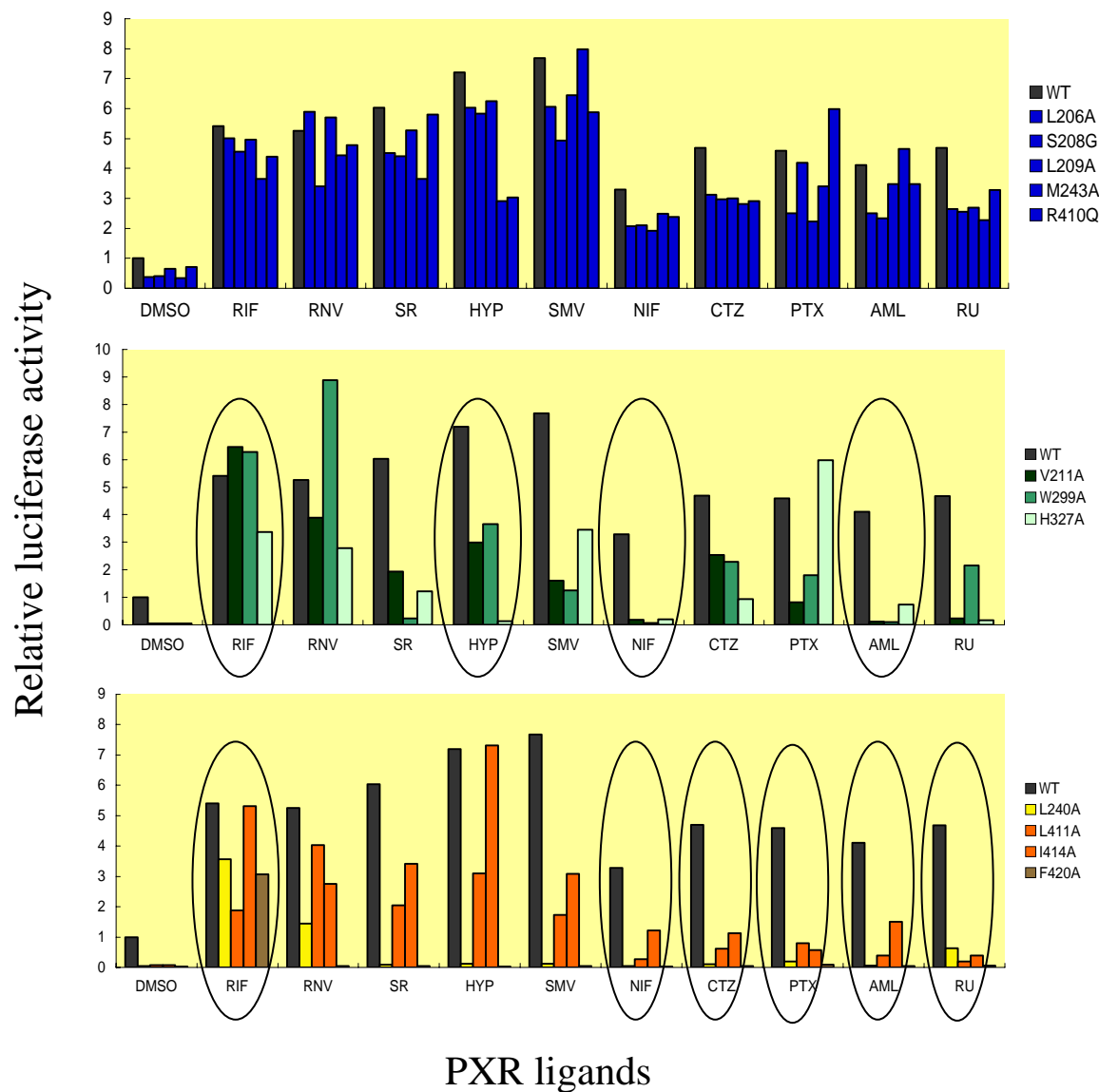
Compound	X	R ₁	R ₂	R ₃
A Mephobarbital	O	CH ₃	C ₂ H ₅	C ₆ H ₅
B Pentobarbital	O	H	C ₂ H ₅	C ₅ H ₁₁
C Hexobarbital	OH	CH ₃	CH ₃	C ₆ H ₉
D Cyclobarbital	O	H	C ₂ H ₅	C ₆ H ₉
E Amobarbital	O	H	C ₂ H ₅	C ₅ H ₁₁
F Phenobarbital	O	H	C ₂ H ₅	C ₆ H ₅
G Barbital	O	H	C ₂ H ₅	C ₂ H ₅
H Primidone	H	H	C ₂ H ₅	C ₆ H ₅



Effects of amino acid mutation on the PXR activation

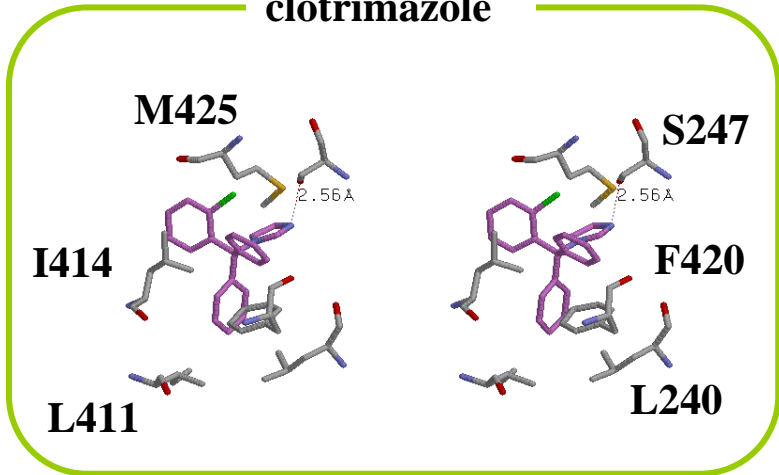
Amino acid sequence of PXR-LBD

141 QGLTEEQRMMIREL
 MDAQMKTFTDTFSH
 FKNFRLPGVLSGCG
 ELPESLQAPSREEA
 AKWSQVRKDLCSLK
 VSLQLRGEDGSVWN
 YKPPADSGGKEIFS
 LLPHMADMSTYMFK
 GIISFAKVISYFRD
 LPIEDQISLLKGAA
 FELCQLRFNTVFNA
 ETGTWECGRLSYCL
 EDTAGGFQQLLEP
 MLKFHYMLKKLQLH
 EEEYVLMQAISLFS
 PDRPGVLQHRVVDQ
 LQEQFAITLKSIE
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 IMAMLTELRSINAQ
 HTQRLLRIQDIHPF
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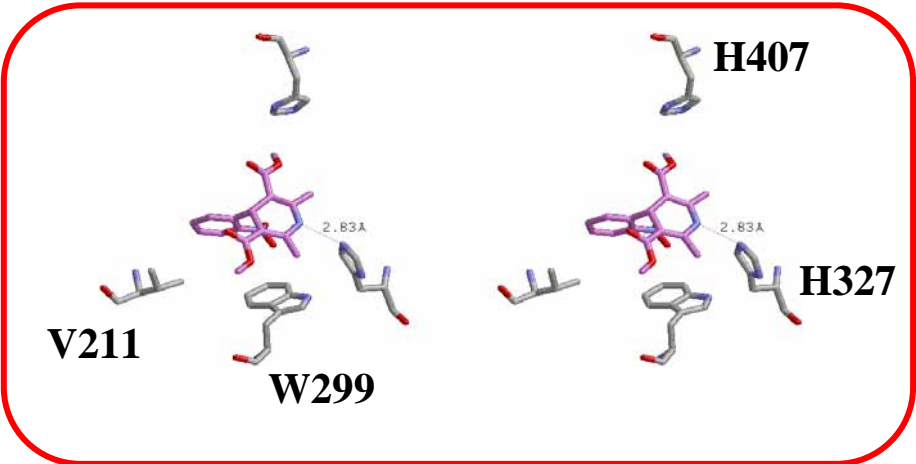
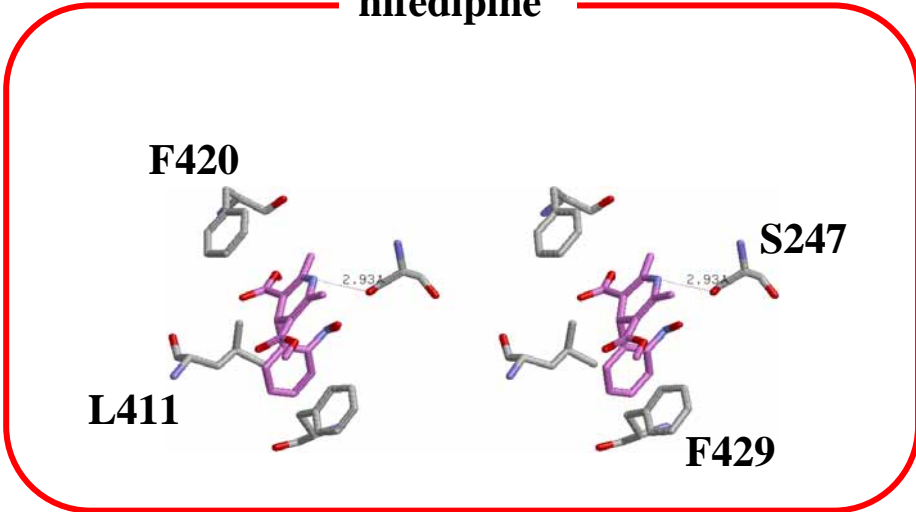


Proposed interaction between PXR and ligands

clotrimazole

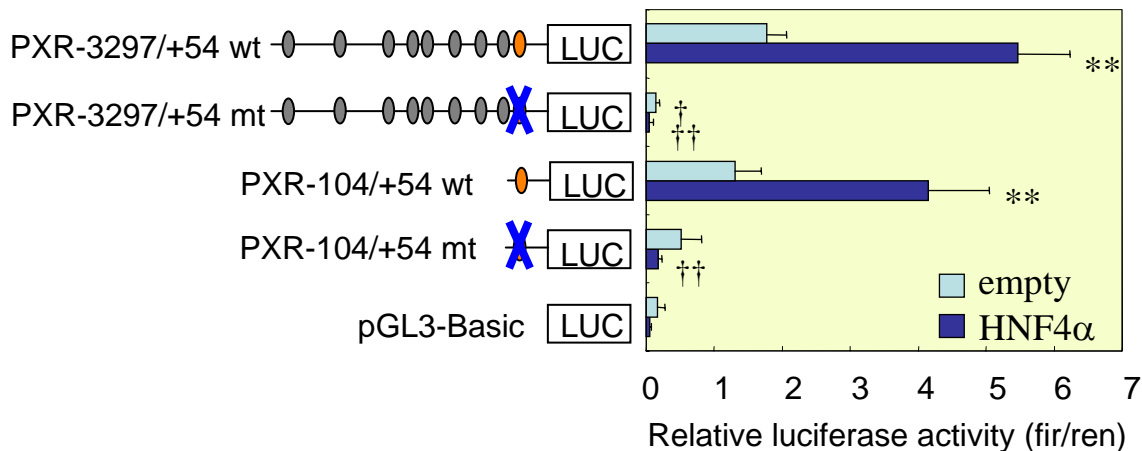


nifedipine



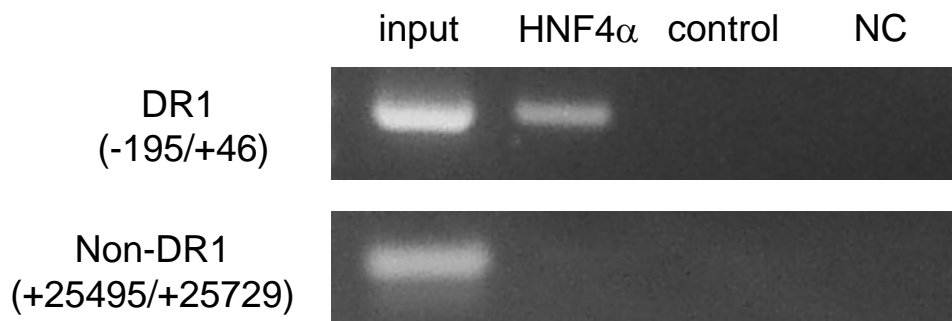
Involvement of HNF4 α in transcriptional regulation of human *PXR* gene

Mutation assay

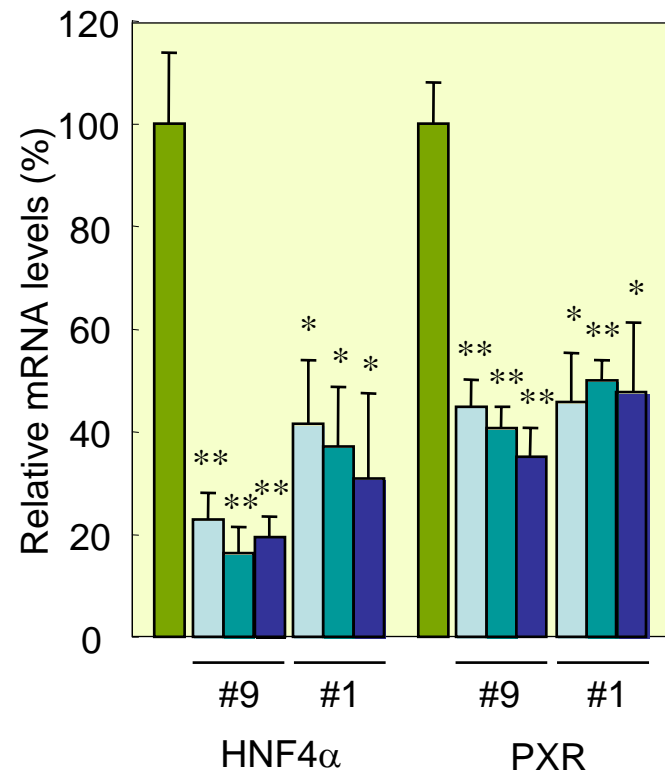


Human -88 TGGACTTGGGACT -76
 |||||
 Mouse -44 TGCTGGACTTGGGACTTGG -26

ChIP assay



RNAi for HNF4 α



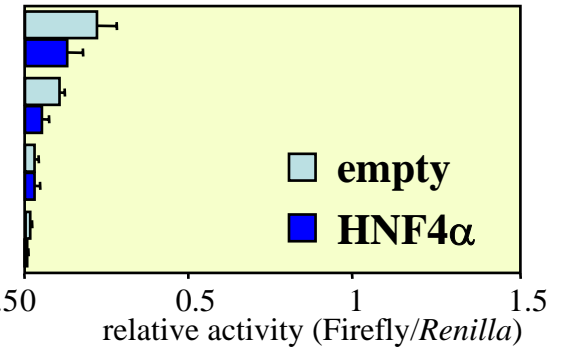
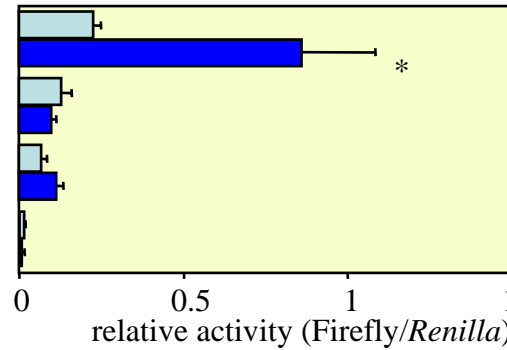
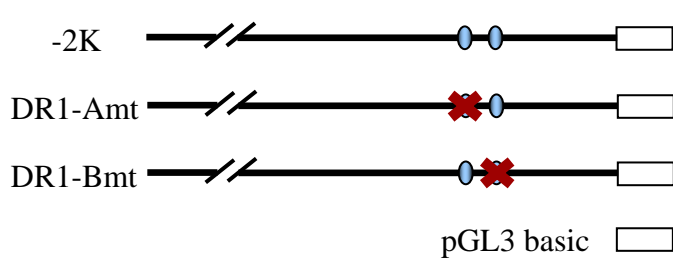
Involvement of HNF4 α in the different expression levels between *CYP2C9* and *CYP2C19* in the human liver

Mutation assay

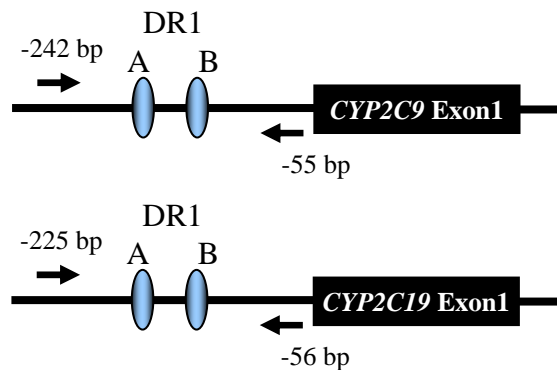
DR1
A B

CYP2C9

CYP2C19



ChIP assay

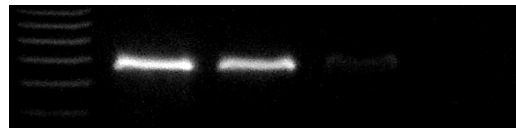


CYP2C9

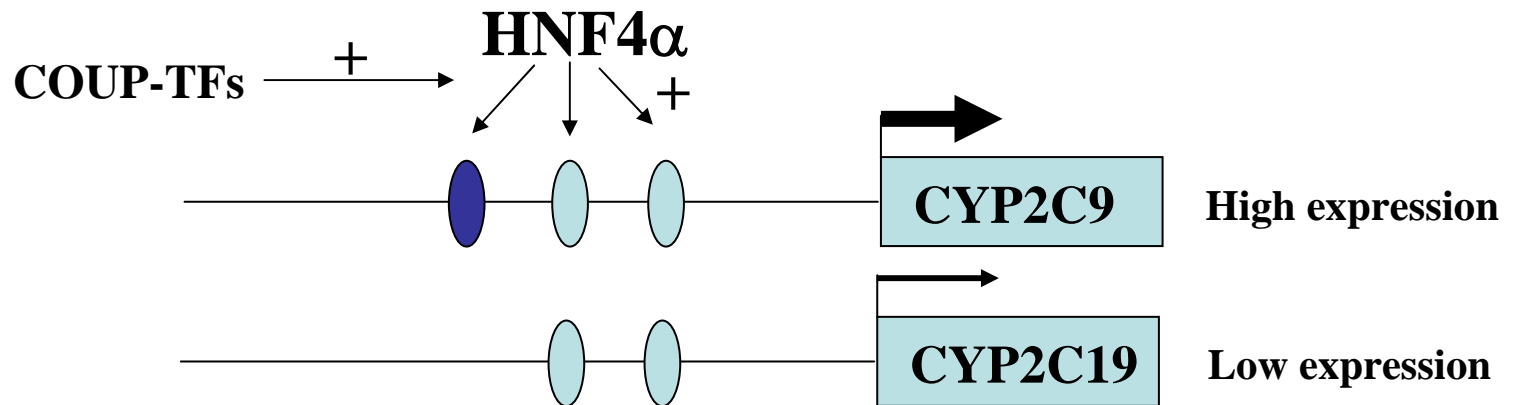
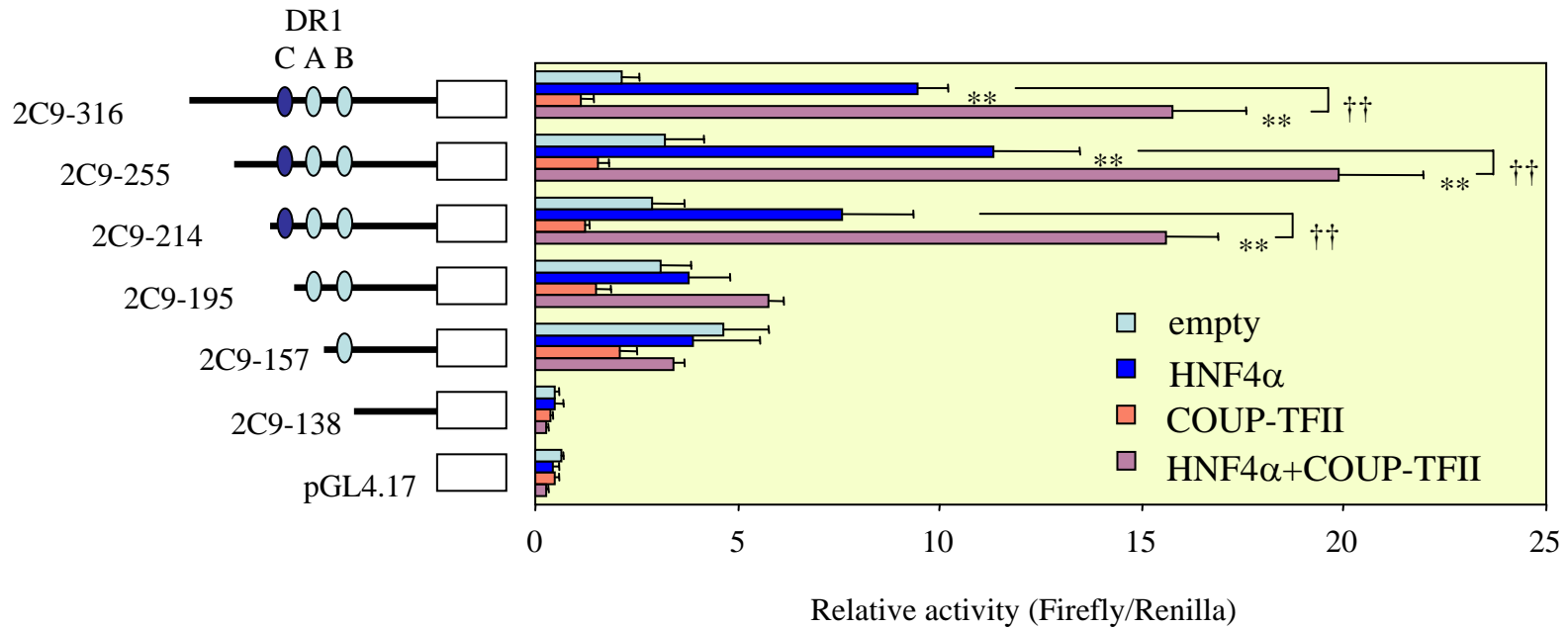
CYP2C19

Input HNF4 α Cont NC

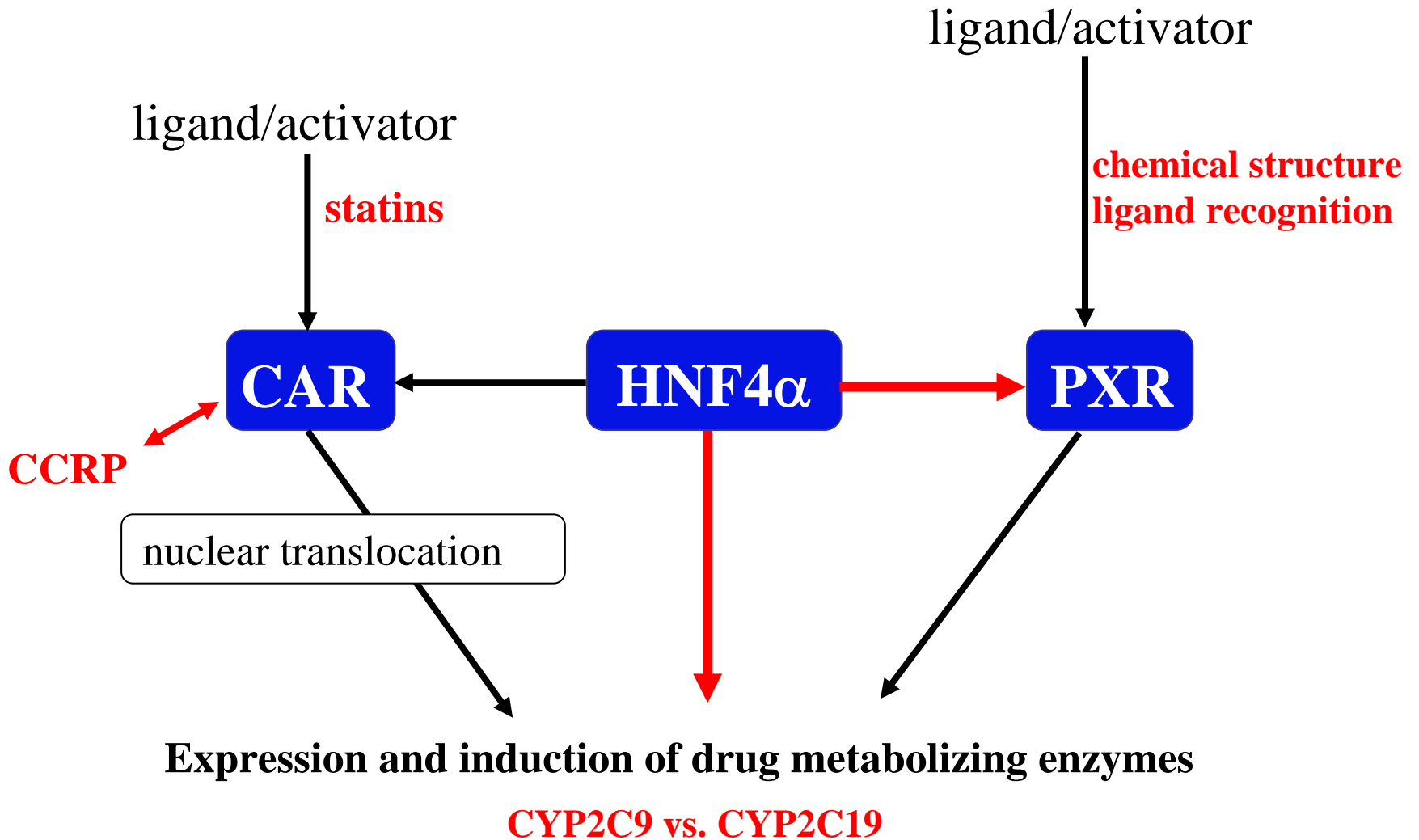
Input HNF4 α Cont NC



Effects of HNF4 α and COUP-TFII on the promoter activity of *CYP2C9* gene



Outline of our studies



Acknowledgements

千葉 寛 教授
細川正清 教授(現 千葉科学大学)
降幡知巳 助教
森本かおり 博士(現 高崎健康福祉大学)
清水俊之 博士
樋口智明 修士
高間香織 修士
山上紗絵子 修士
山中陽介 修士
川島さち代 修士
岩崎紀彦 修士
三家本雅樹 修士
齊藤公亮 修士
井上直樹 修士
平野 舞 修士

畑 晶之 博士
(現 松山大学)

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NIEHS/NIH



National Institute of Environmental Health Sciences (NIEHS) / NIH