The 2012 FDA Draft Guidance on Drug-drug Interactions: Enzyme Induction and Beyond

Michael Sinz, Ph.D.

Research Fellow
Research and Development
Bristol-Myers Squibb
Wallingford, CT USA

Bristol-Myers Squibb

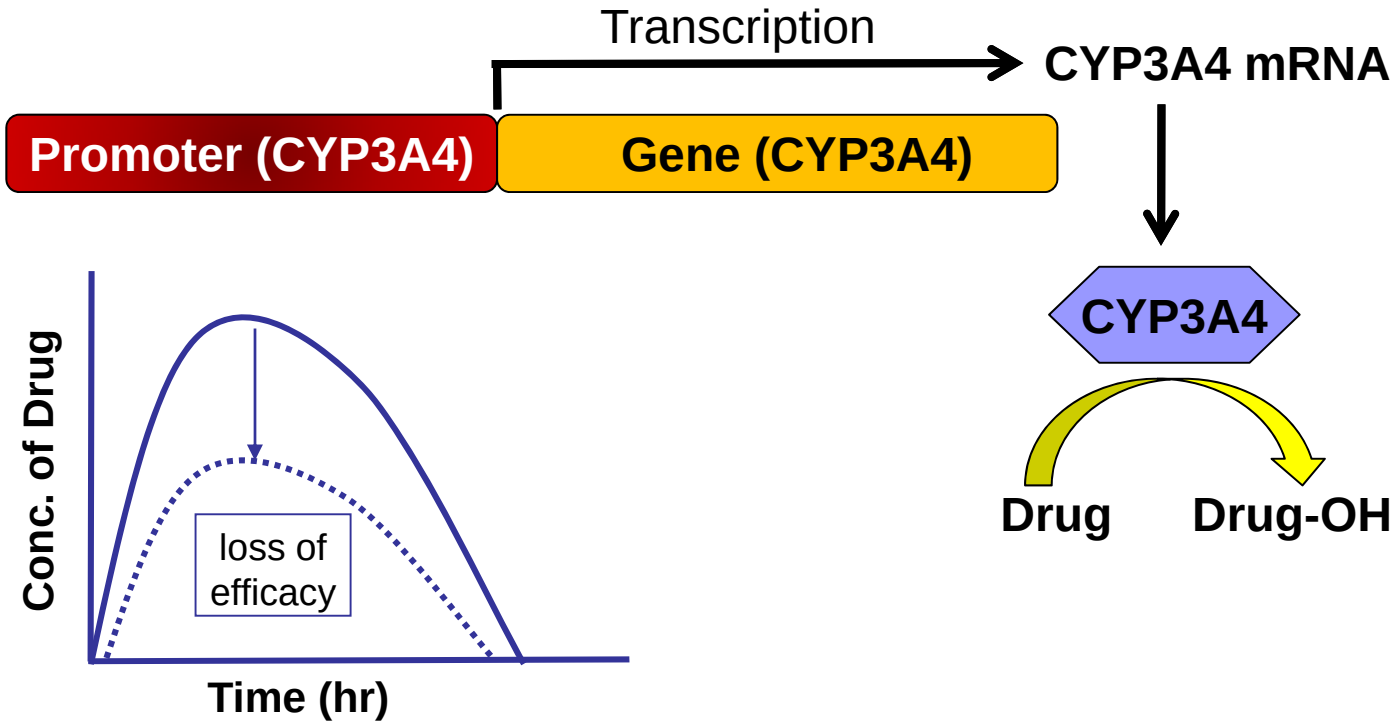
NJDMDG Symposium April 26, 2012

The “Guidance for Industry”

Guidance for Industry

Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations

Reaction phenotyping
DDI (inhibition & induction)
In vivo clinical studies
Labeling



General Scheme of Model-based Prediction: Investigational Drug Interacting with CYP Enzymes

CYP inhibition
(reversible and time-dependent)

- Measure enzyme activity in human liver microsomes
- Estimate DDI parameters

CYP induction

- **Measure mRNA change by investigational drug in cultured human hepatocytes from 3 or more donors**
- **Estimate DDI parameters**

Basic Models

Is the calculated R value >1.1
Reversible inhibition, $R_1=1+[I]/Ki$
TDE, $R_2=(Kobs+Kdeg)$ & $Kobs=kinact x [I]/(KI+[I])$

Is increase in mRNA > a predefined threshold?
Or
Is the calculated R value < 0.9?
$R_3 = 1/(1 + d \times E_{max} \times [I] / (EC_{50} + [I]))$

Mechanistic Models

Is AUCR>1.25 (inhibition) or <0.8 (induction)

Mechanistic Static Model

$$AUCR = \left(\frac{1}{(A_g x B_g x C_g)x(1-F_g)+F_g}\right) x \left(\frac{1}{(A_h x B_h x C_h)x F_m+(1-F_m)}\right)$$

OR, **Dynamic Model (PBPK)**

Yes

Conduct a clinical study using an appropriate probe substrate

Basic Induction Model

$$R_3 = \frac{1}{1 + \left(\frac{d \times E_{max} \times [I]}{EC_{50} + [I]}\right)}$$

Is increase in mRNA > a predefined threshold?
or
Is the calculated R<0.9

d = 1

[I] = maximum total (free+unbound) systemic concentration

E_{max} is the maximum induction response
EC_{50} is the concentration causing half maximal effect

What if due to solubility or cytotoxicity issues the E_{max} and EC_{50} can not be determined?

Options ? →

AUC/F2 Method ?

Basic equation is designed to eliminate false negatives, but unfortunately leads to increased false positives, hence the need to move to the mechanistic models

Mechanistic Static Induction Model

$$AUCR = \left(\frac{1}{(A_g x B_g x C_g) x (1-F_g) + F_g} \right) x \left(\frac{1}{(A_h x B_h x C_h) x F_m + (1-F_m)} \right)$$

Gut | Liver

$$C = 1 + \frac{d \times E_{max} \times [I]}{[I] + EC_{50}}$$

$$[I]_g = F_a \times K_a \times Dose/Q_{en}$$

$$[I]_h = f_u \times (C_{max} + (F_a \times K_a \times Dose/Q_h))$$

A – reversible inhibition
B – irreversible inhibition
d = 1 (?), likely to be < 1 in the mechanistic model (0.3-0.8; ~0.5)
F_a = 1 (if unknown)
K_a = 0.1/min (if unknown), a value of 0.03/min is probably more reasonable
F_g – fraction available after intestinal metabolism
F_h – fraction of systemic clearance of substrate

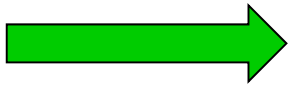
Interpretation: Is AUCR>1.25 (inhibition) or <0.8 (induction)

Basic to Mechanistic Model

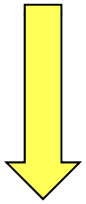
d = 1
[I] = 2.3 uM
E_{max} = 25
EC_{50} = 5.3 uM

Basic Model

R_3 = 0.12
(R_3< 0.9 implies induction)



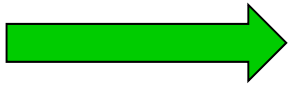
Induction Expected



d = 0.5
F_a = 1
K_a = 0.03/min
Dose = 81 uM
[I] = 2.3 uM
Fu = 0.012
E_{max} = 25
EC_{50} = 5.3 uM
$K_{deg,g}$ = 0.00032/min
$K_{deg,h}$ = 0.00048/min
$F_{g,h}$ (midazolam)

Mechanistic Static Model

AUCR = 0.21
(AUCR<0.8 implies induction)



Induction Expected
'Moderate Inducer'

Model System for Evaluating Induction

- Primary cultures of human hepatocytes (fresh or cryopreserved)
  - What about immortalized hepatocytes or NHR assays? "At present, data generated from other in vitro systems are considered complementary and may be reviewed along with data generated with cultured hepatocyte systems."
  - EMA, "very well justified" immortalized cell lines acceptable
- Evaluate 3+ donors to account for interindividual variability
  - If one donor is positive in Basic model, the drug is considered an inducer and "follow-up evaluation is needed" (ie. Mechanistic)
- Need to determine performance of hepatocytes in identifying enzyme induction potential with 'sufficient' number of clinical inducers (how many?)

Model System for Evaluating Induction

- "The changes in the mRNA level of the target gene should be used as an endpoint"
  - Not consistent with EMA guidance (activity & RNA)
  - Activity should be an option in cases when the test compound is not an inhibitor
- Inclusion of negative controls
  - Could provide value in distinguishing real induction from the 'noise' of the assay, but no guidance given on what to use or at what concentration.
- Evaluate CYP1A2, 2B6, and 3A
  - If CYP3A is positive, then evaluate CYP2Cs (2C8, 2C9, and 2C19)
    - Generally, CYP2C induction is less than CYP3A and mediated by factors beyond PXR and CAR (Fahmi et al, DMD 2010 & Chen/Goldstein, CDM 2009)

In Vitro CYP Inducers (Table 2)

CYP	In vitro inducer as positive controls	Recommended concentration (uM) of positive controls	Reported fold induction in enzyme activity
1A2	Omeprazole Lansoprazole	25-100 10	14-24 10
2B6	Phenobarbital (CITCO-EMA)	500-1000 (<100 nM)	5-10
2C8	Rifampin	10	2-4
2C9	Rifampin	10	4
2C19	Rifampin	10	20
2D6	None identified		
3A4	Rifampin	10-50	4-31

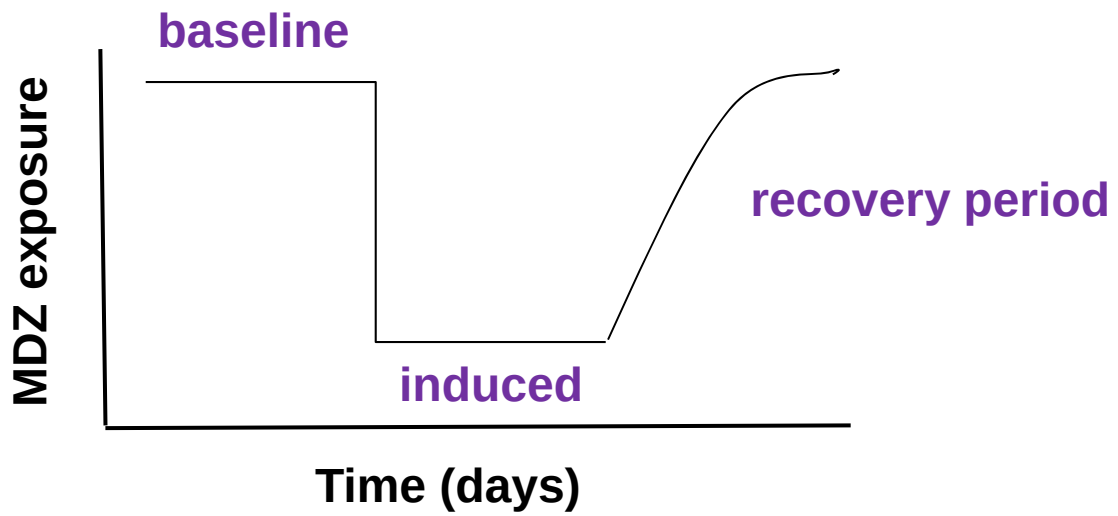
No information on 'reported fold induction in mRNA response'

Classification of In Vivo Inducers (Table 4)

CYP	Strong Inducers >80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
1A2		Montelukast, phenytoin, smokers	Moricizine, omeprazole, phenobarbital
2B6		Efavirenz, rifampin	Nevirapine
2C8		Rifampin	
2C9		Carbamazepine, rifampin	Aprepitant, bosentan, phenobarbital, St. John's wort
2C19		Rifampin	Artemisinin
3A4	Avasimibe, carbamazepine, phenytoin,rifampin, St. John's wort	Bosentan, efavirenz, etravirine, modafinil, nafcillin	Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib
2D6	None known	None known	None known

Change in Clinical Section

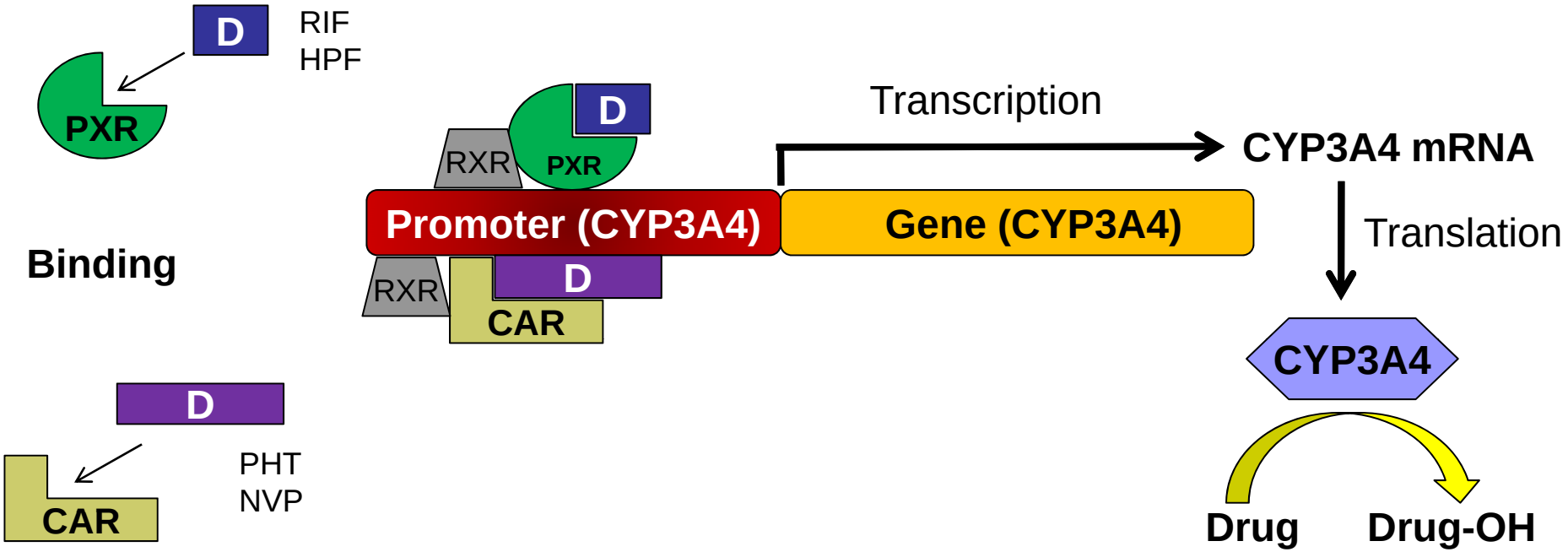
"… it is critical to evaluate the time it takes for the enzyme activities to return to normal when induction or TDI is involved so that a third crossover period in which the interacting drug is removed"



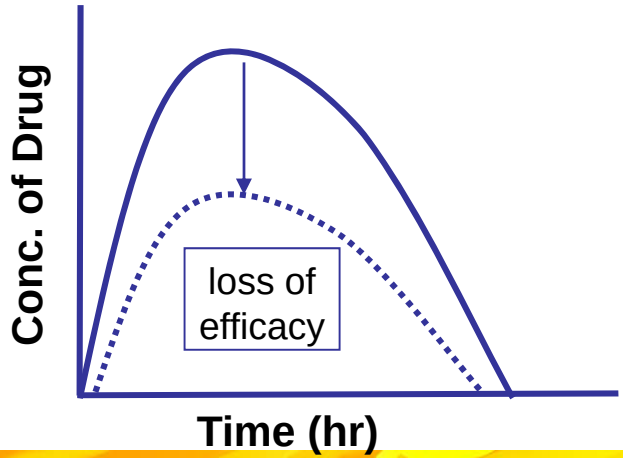
……AND BEYOND

A Novel Mechanism of Enzyme Induction: Non Classical PXR or CAR-Mediated Induction

CYP3A4 Gene Activation by PXR and CAR



Both PXR and CAR can cause CYP3A4 gene activation and enzyme induction leading to <u>significant drug interactions</u>



Comparative PXR Binding and Transactivation Results

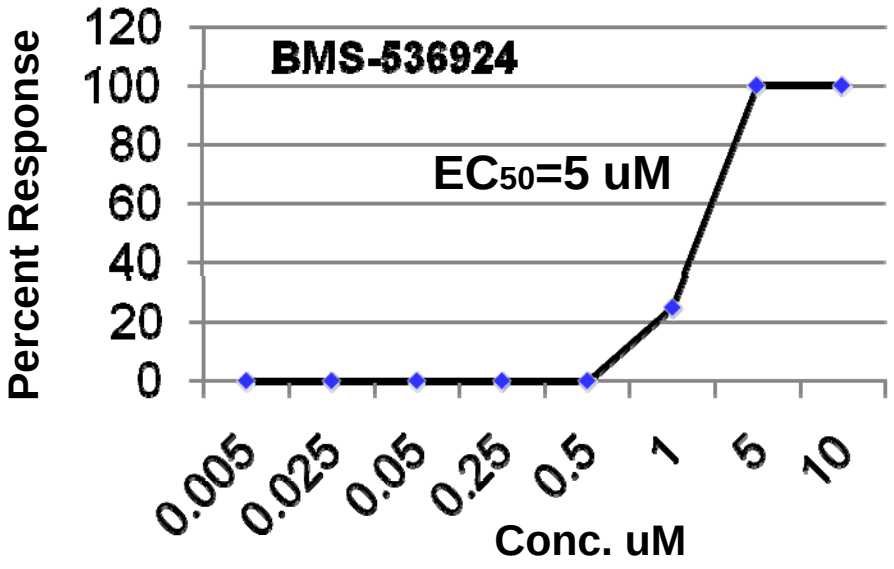
PXR Binding Assay

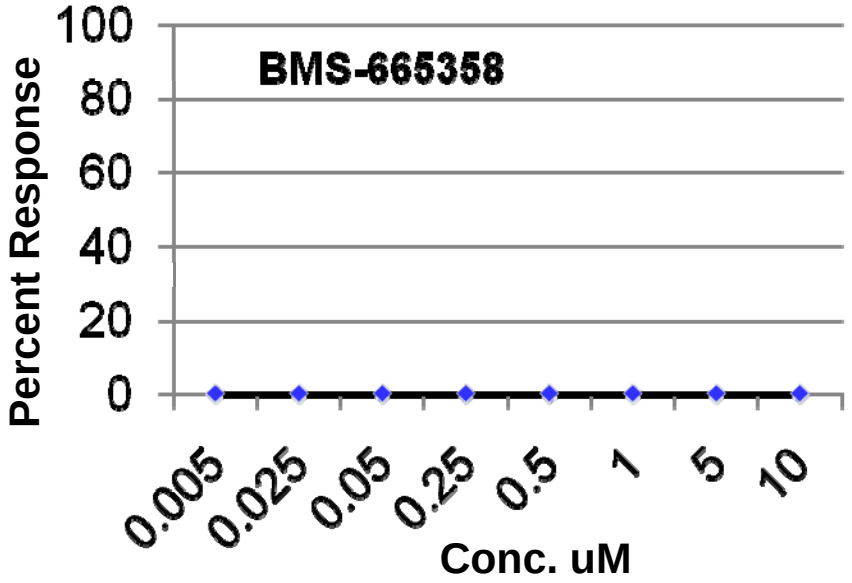
BMS-536924 binds to PXR:
IC_{50} = 1.0 uM

BMS-665351 does not bind to PXR:
IC_{50} = 30 uM

SAR

PXR Transactivation Assay



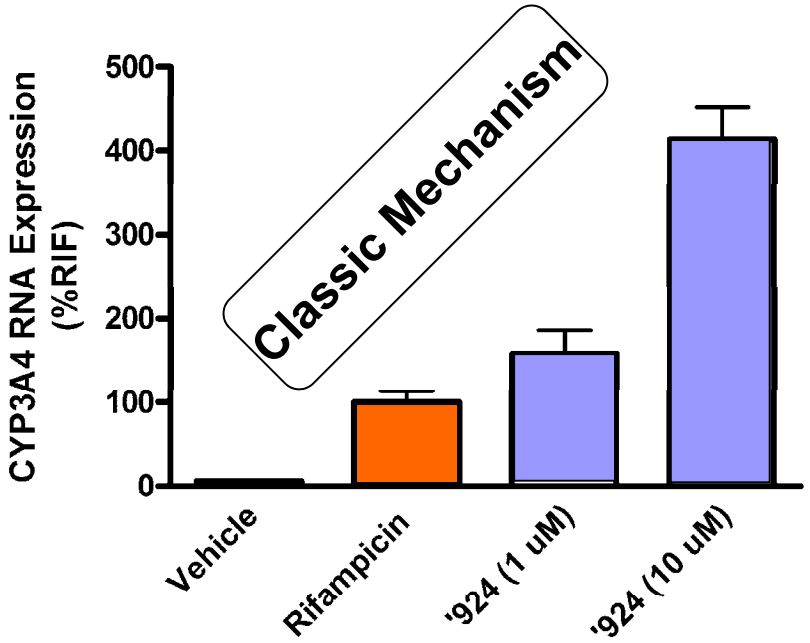


PXR and Hepatocyte Data on Both Sets of Compounds

BMS-536924

Binds to PXR
Activates PXR

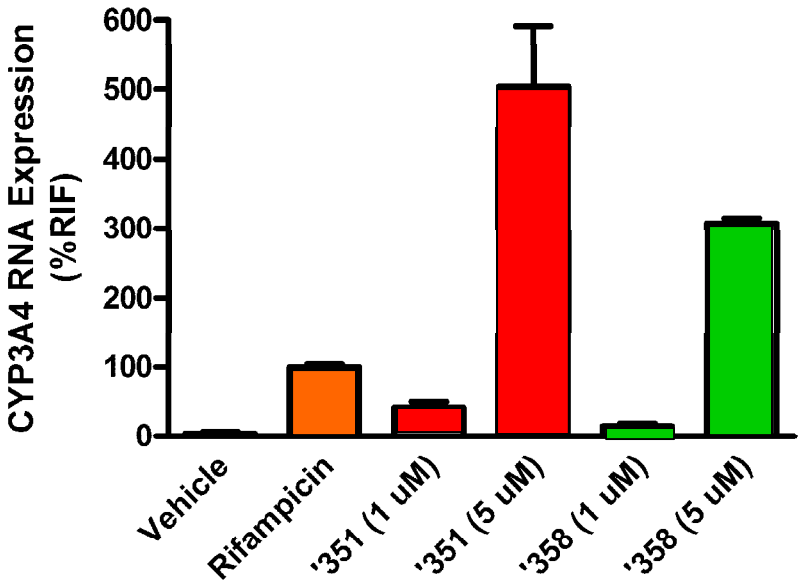
Induces CYP3A4 in Primary Human Hepatocytes



BMS-665351

Do Not Bind to PXR
Do Not Activate PXR

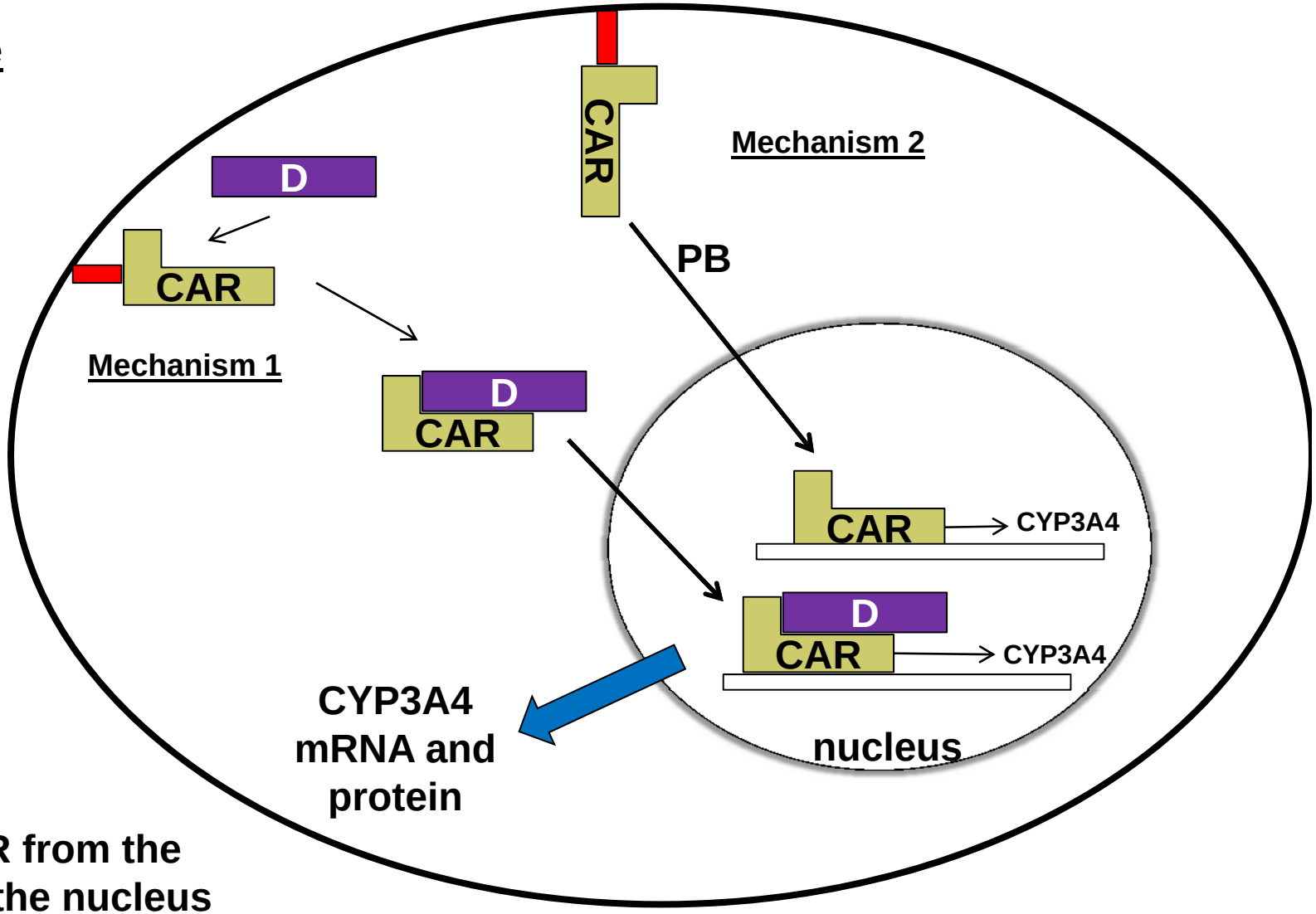
Induces CYP3A4 in Primary Human Hepatocytes



Rifampicin-positive control for PXR

Two Mechanisms of CAR-Mediated Enzyme Induction

Constitutive Androstane Receptor

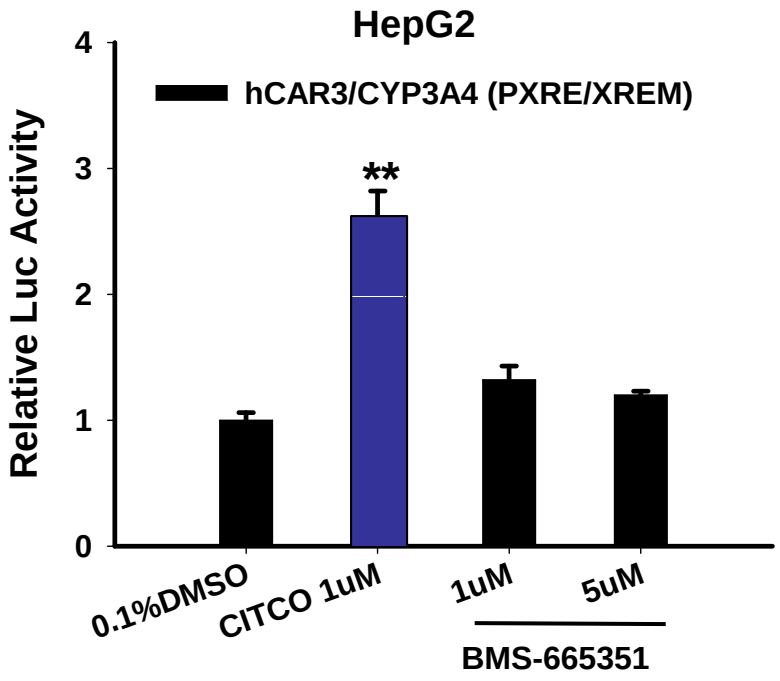


Transit of CAR from the cytoplasm to the nucleus by any mechanism is termed Translocation

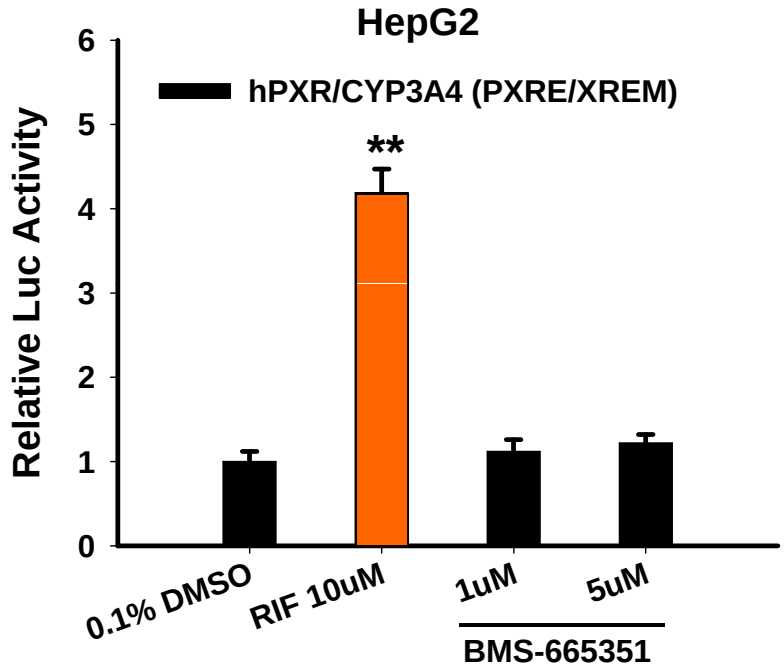
PB-phenobarbital

Activation of CAR and PXR in HepG2 Cells

CAR3 Expression Assay



PXR Expression Assay

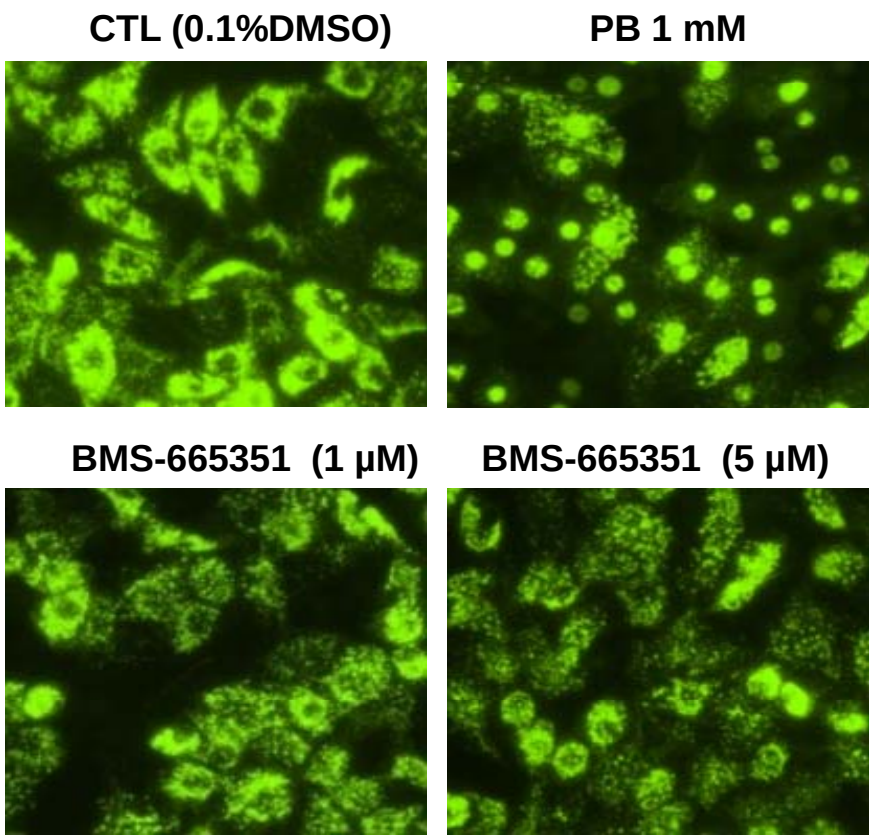


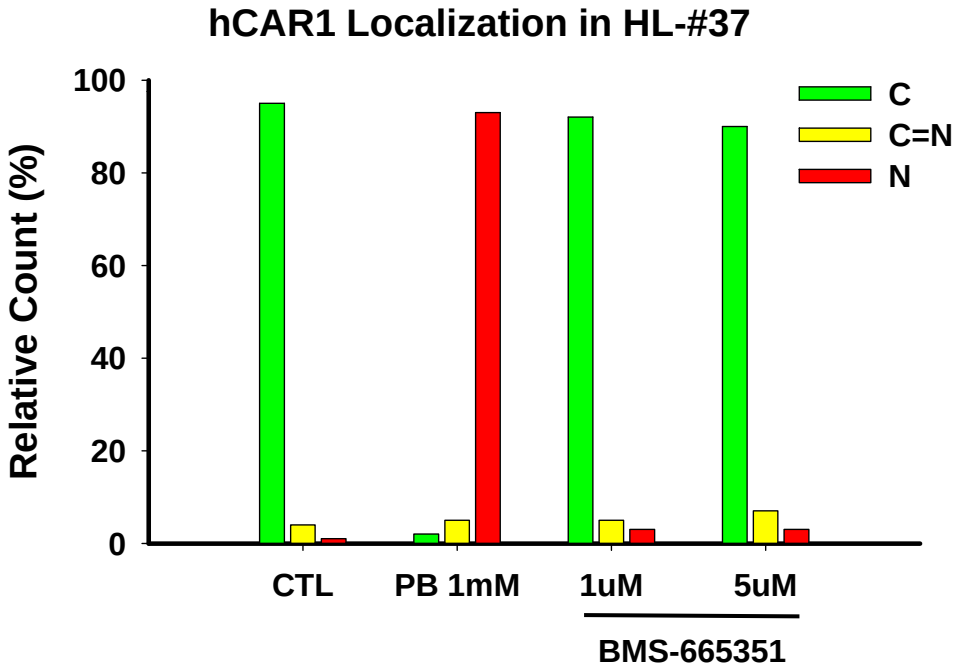
BMS-665351 does not activate human CAR or PXR

CITCO-positive control for CAR

CAR Translocation Assay: BMS-665351

Human hepatocytes infected with adenovirus fluorescently tagged with CAR (AD/EYFP-hCAR)



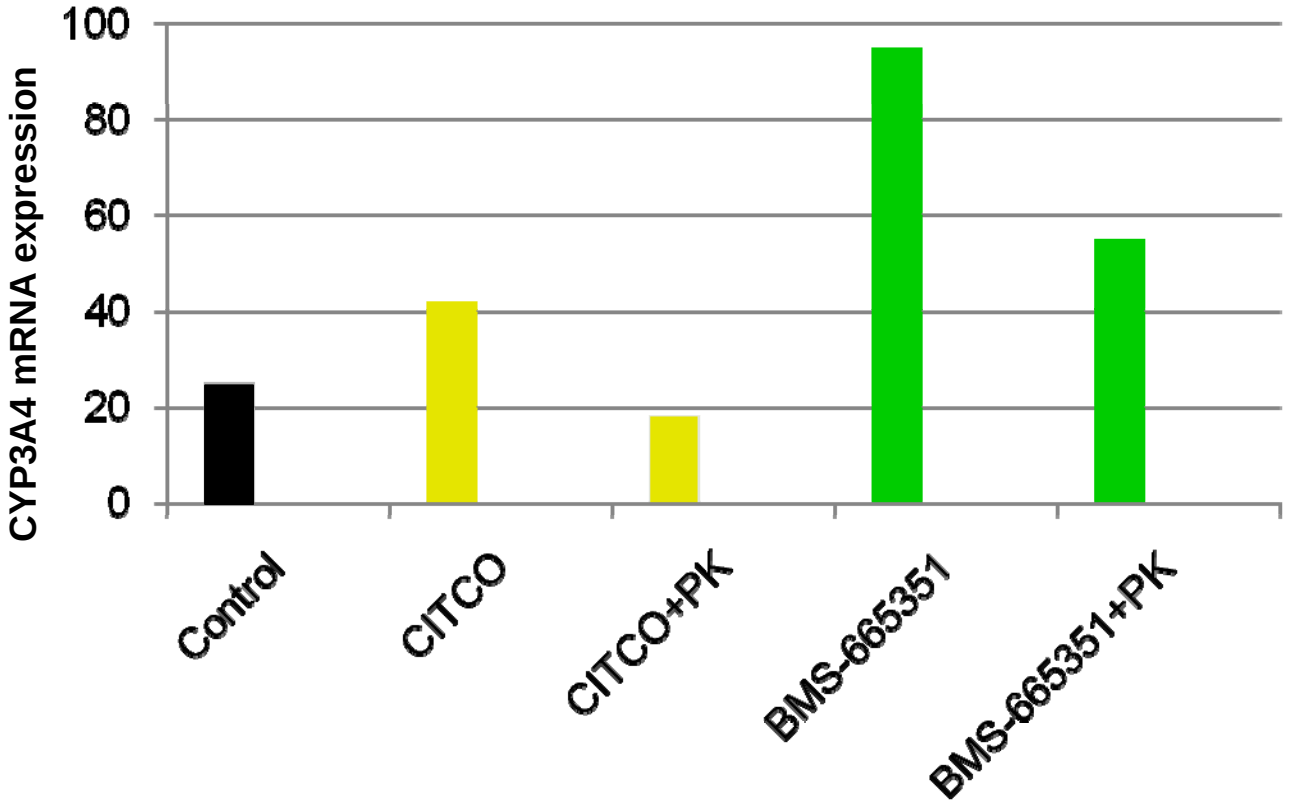


BMS-665351 does not translocate CAR

C-cytoplasm
N-nucleus

Does the Induction Have Anything to do with CAR?

CAR3 Over Expression System (HepG2)

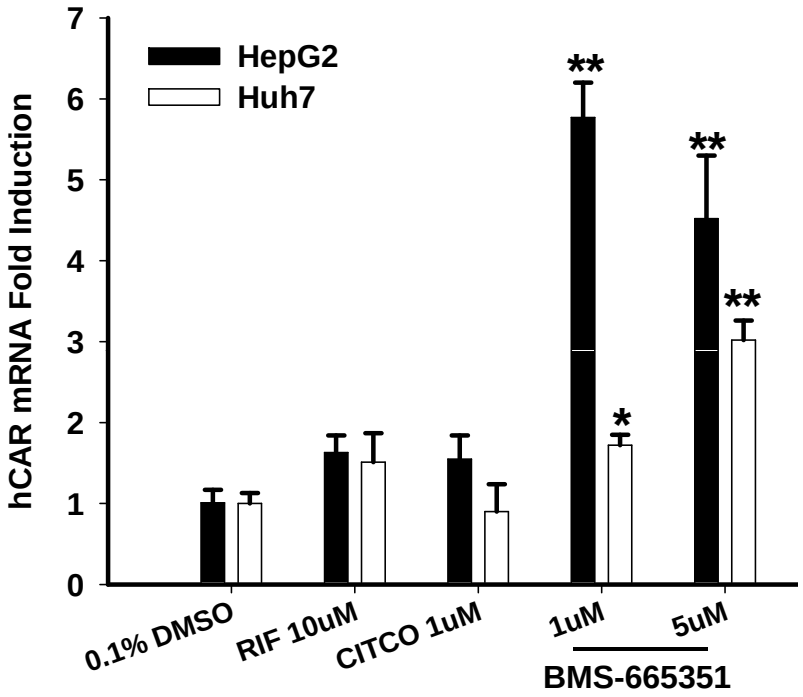


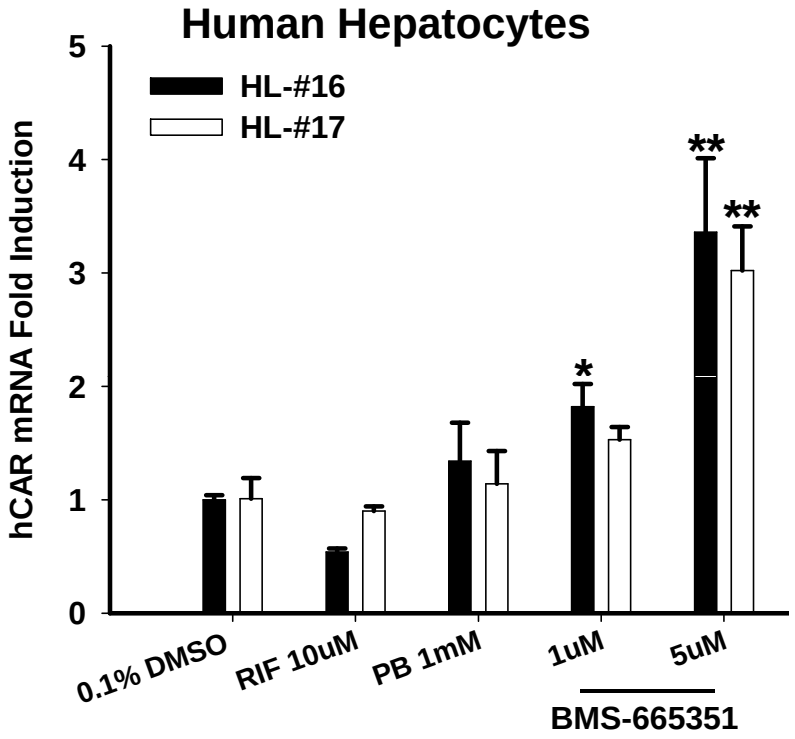
CAR is involved in the CYP3A4 induction response

BMS-665351: 10 uM
CITCO: 1 uM
PK11195: 10 uM

PK11195 – a selective CAR deactivator

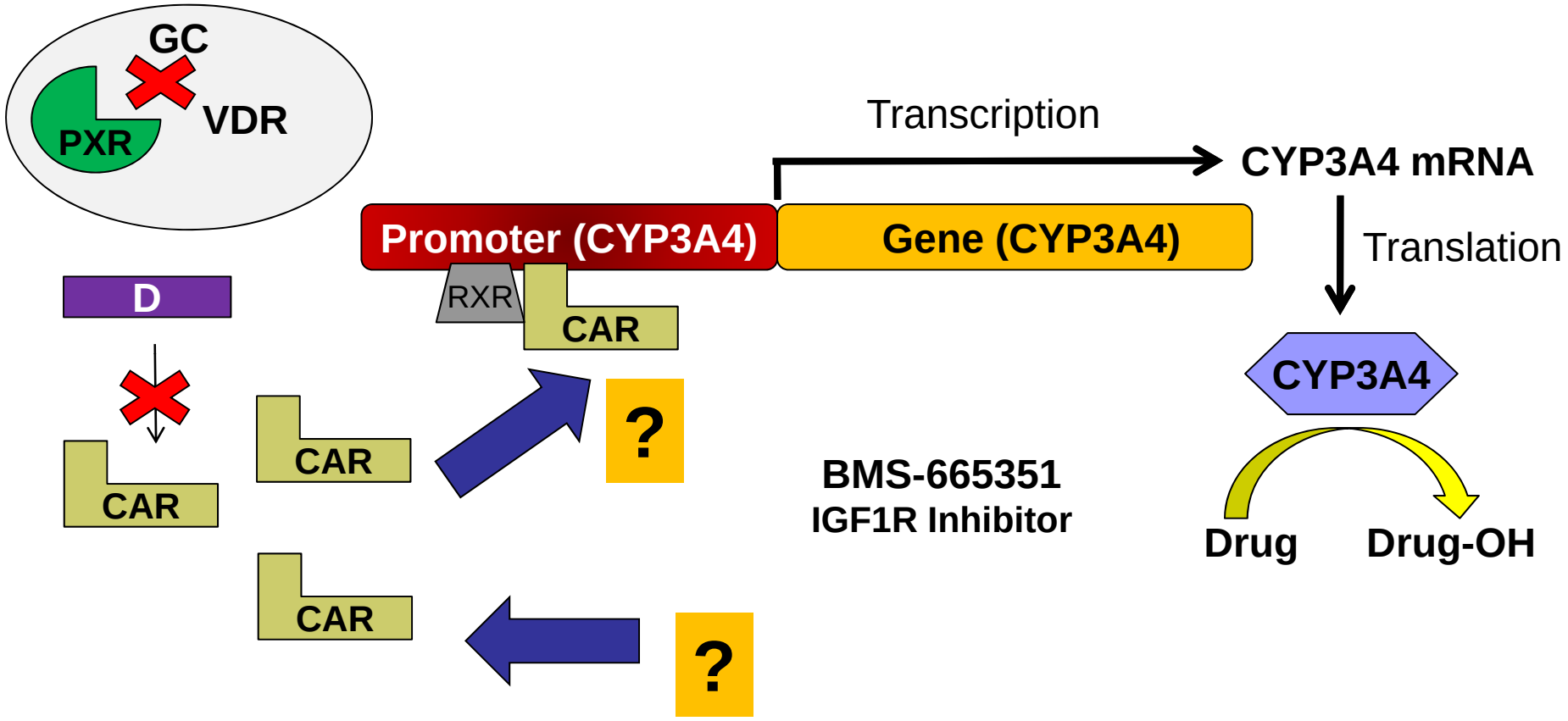
Does BMS-665351 Induce the Expression of CAR?





BMS-665351 induces the expression of CAR in cell lines and human hepatocytes
Does not induce the expression of PXR

Summary



- Further studies necessary to link the increase in CAR expression to the increased expression of CYP3A4
  - CAR promoter-reporter assay and siRNA CAR knock-down
  - Does this mechanism of CYP3A4 induction translate to an in vivo DDI?

Acknowledgements

Bristol Myers Squibb
Sean Kim
Mark Wittman
Kurt Zimmermann
Joan Carboni
BMS IGF1R Team

University of Baltimore
Linhao Li
Hongbing Wang