Herb-Drug Interactions Caused by the Nuclear Receptor PXR

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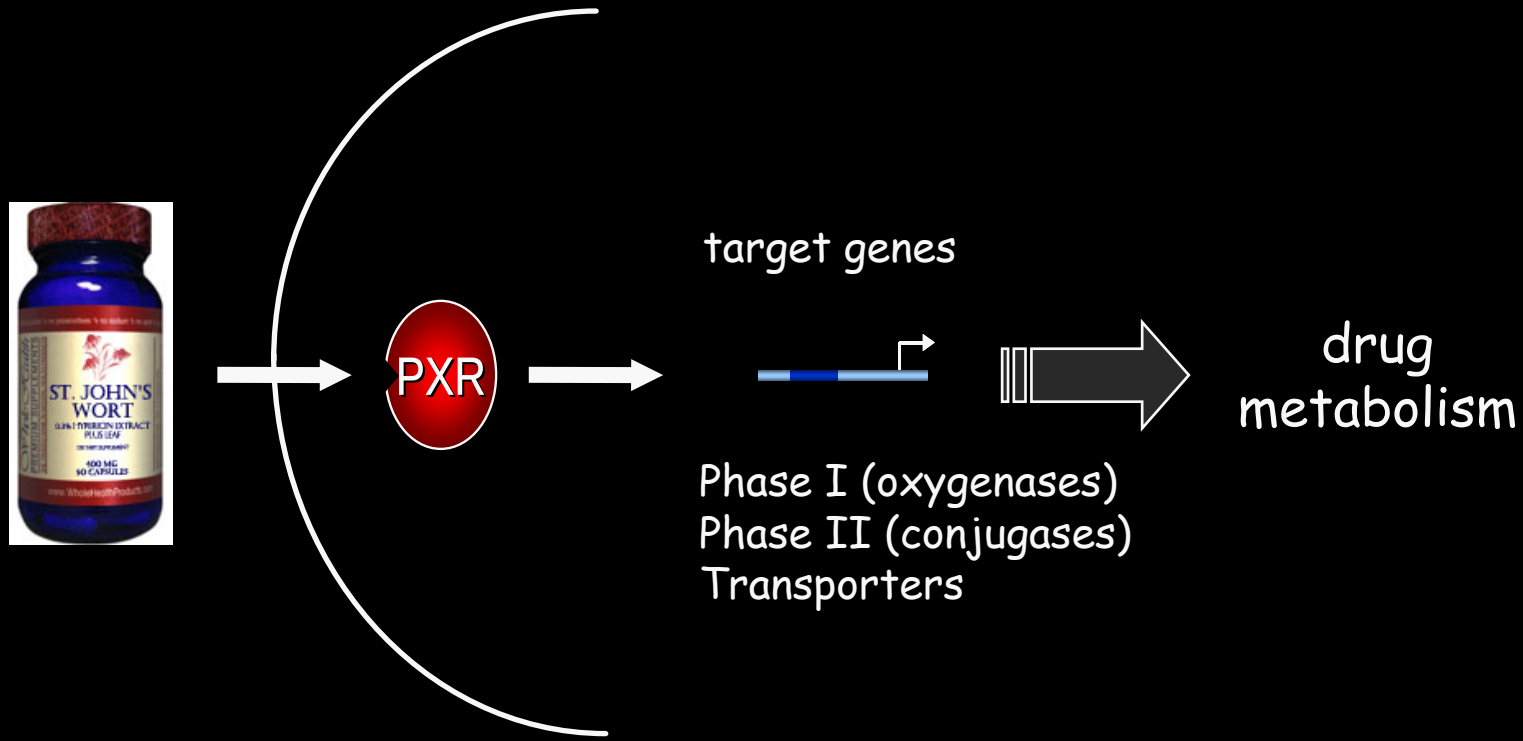
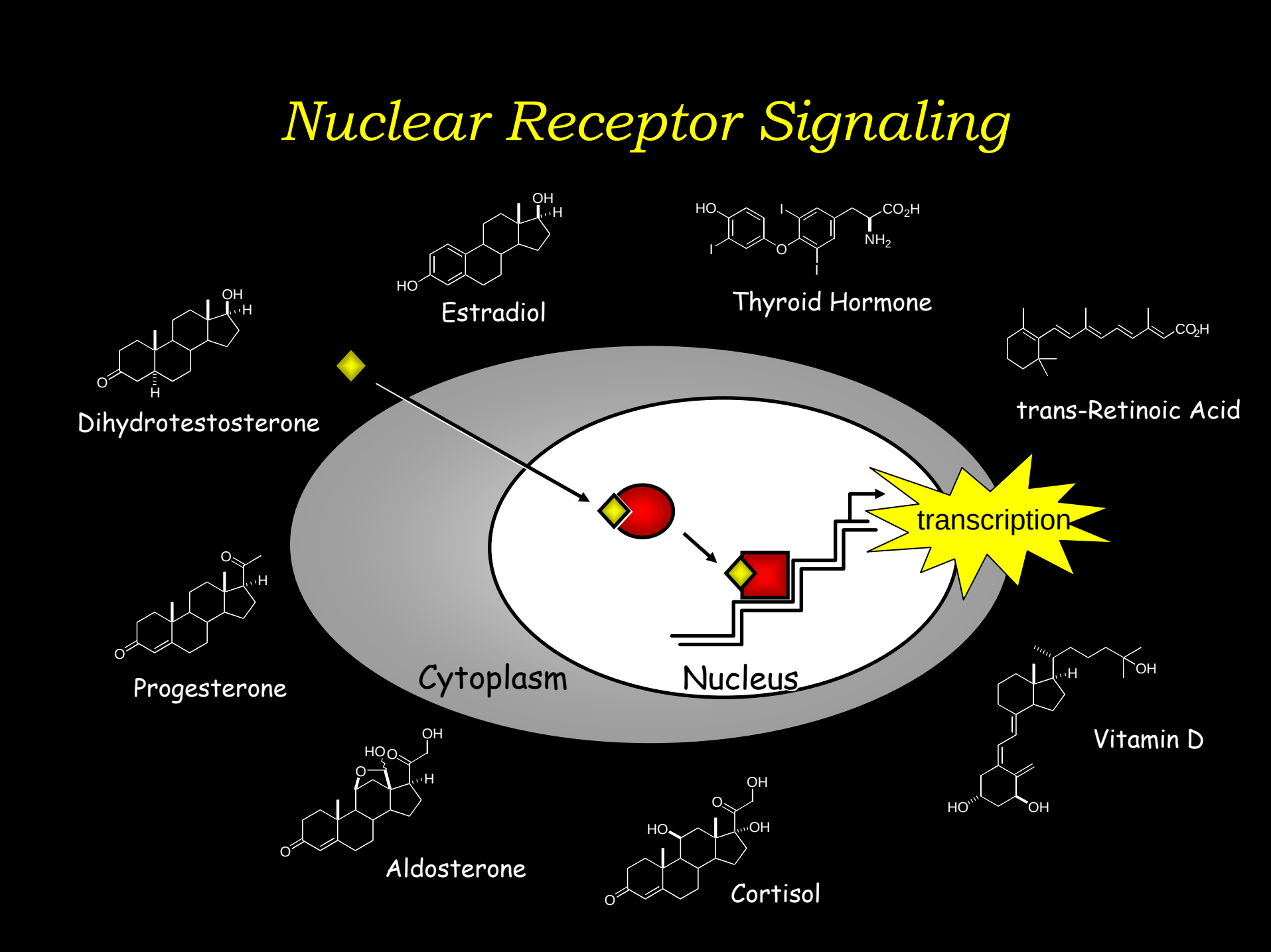
St. John's Wort Causes Drug Interactions

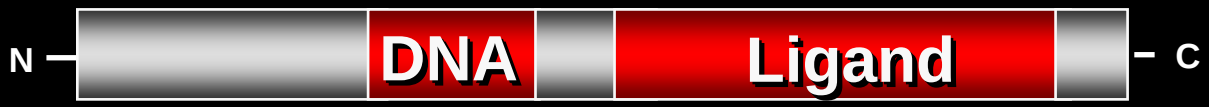


PXR screens can be used to prevent herb-drug interactions

Nuclear Receptor Signaling



Nuclear Receptor Superfamily



48 NRs in human genome

Classical Receptors (12)

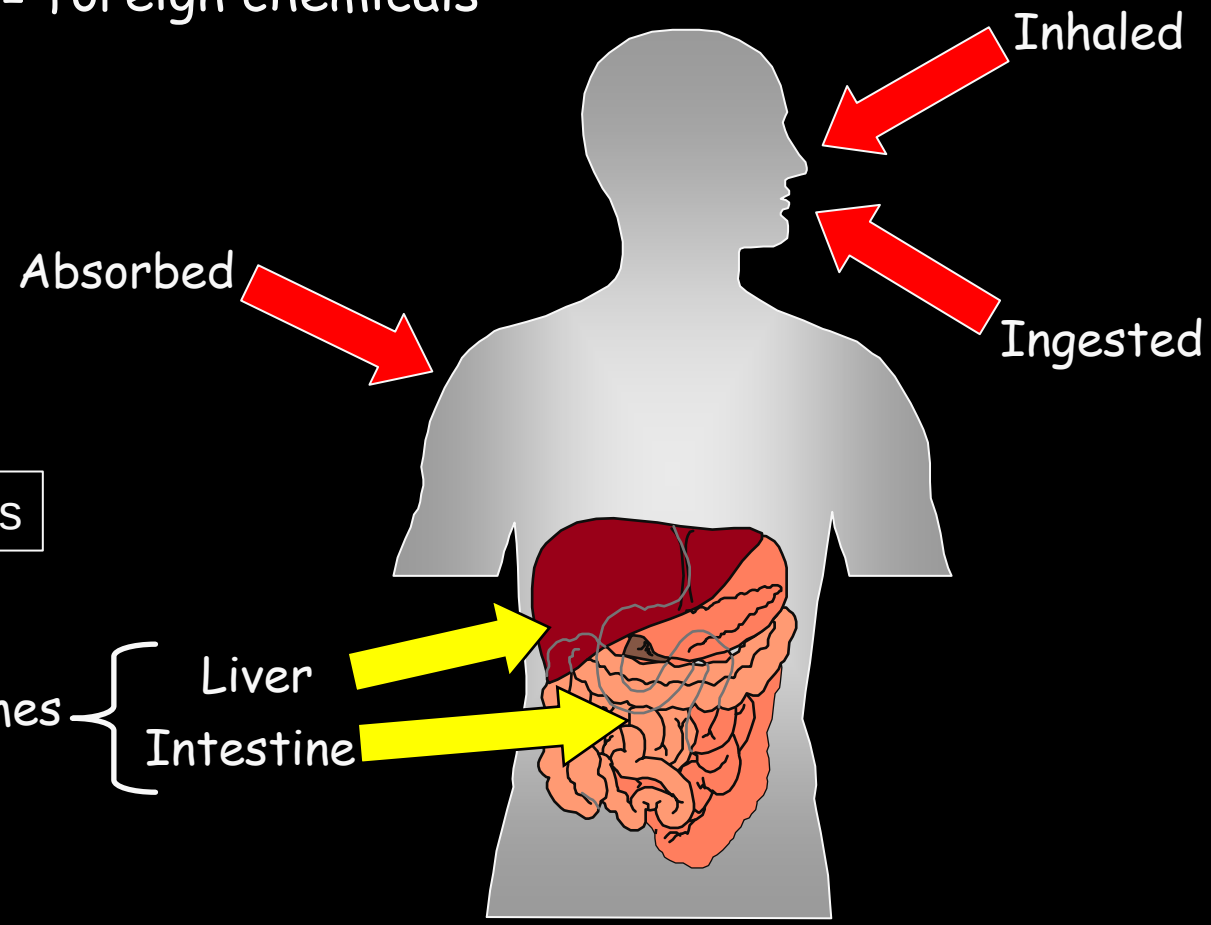
Glucocorticoid
Mineralocorticoid
Progesterone
Estrogen (α,β)
Androgen
Thyroid Hormone (α,β)
Vitamin D
all-*trans* Retinoic Acid (α,β,γ)

Orphan Receptors (36)

CAR
COUP (α,β,γ)
DAX
ERR (α,β,γ)
FXR
GCNF1
HNF4 (α,γ)
LXR (α,β)
NGFI-B (α,β,γ)
PNR
PXR
PPAR (α,γ,δ)
revErb (α,β)
RXR (α,β,γ)
ROR (α,β,γ)
SF1 (α,β)
SHP
Tlx
TR2 (α,β)

Xenoprotection

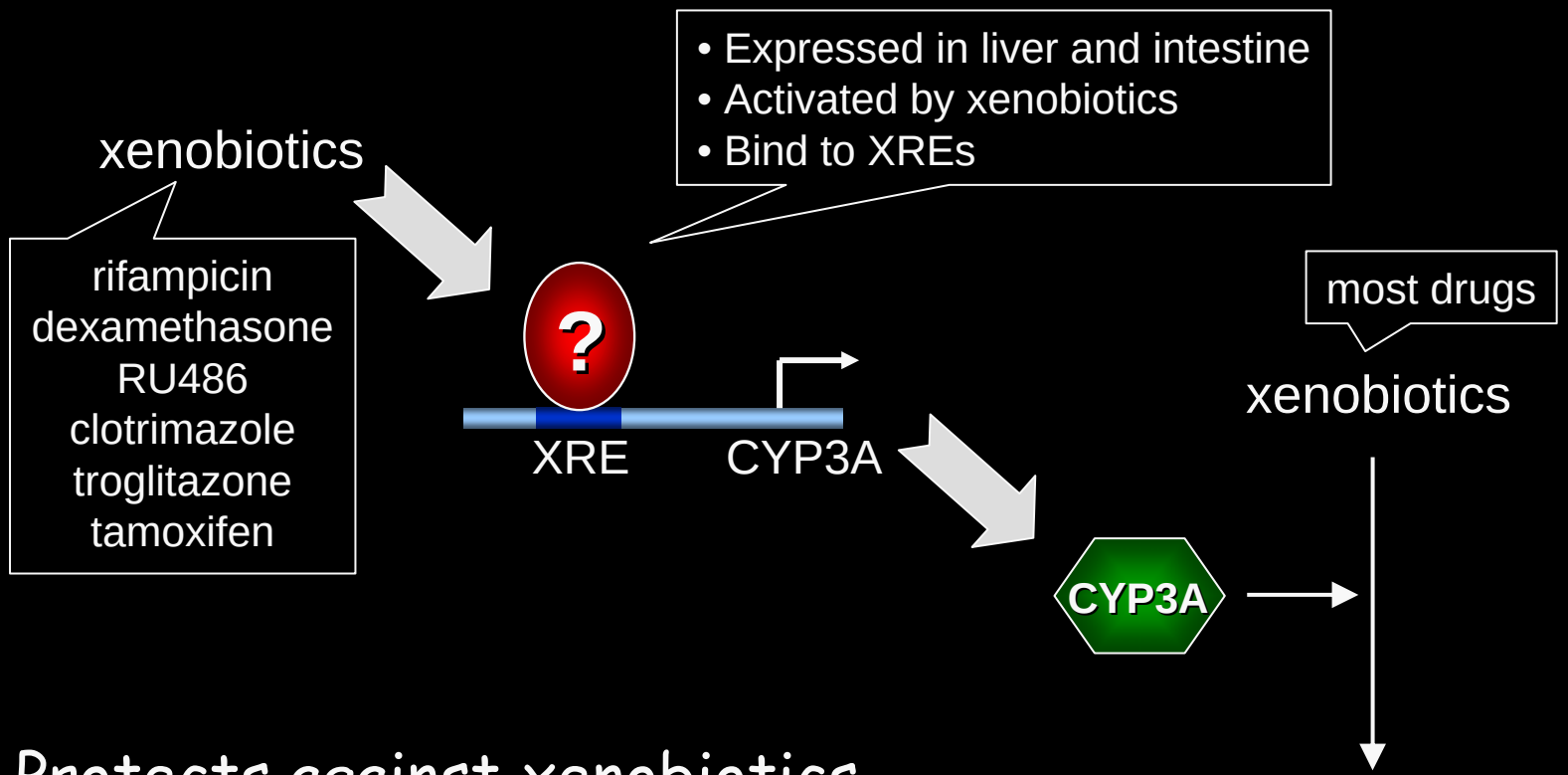
Xenobiotics = foreign chemicals



P450 enzymes

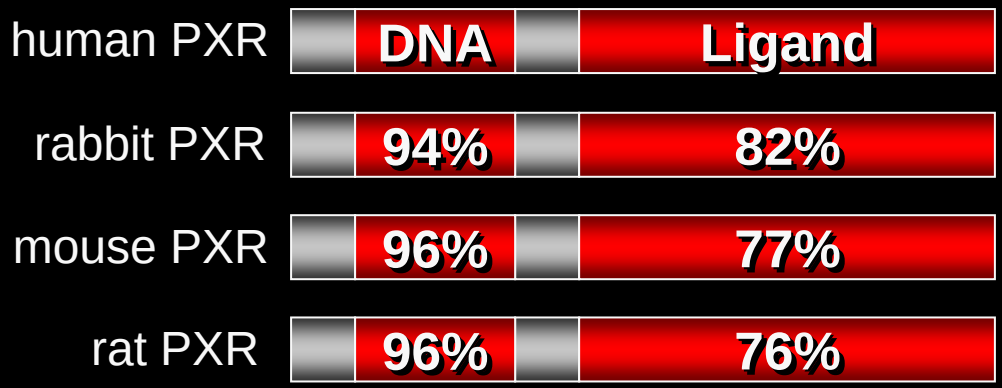
oxygenases
conjugation enzymes
transporters

CYP3A Induction



- Protects against xenobiotics
- Causes drug-drug interactions

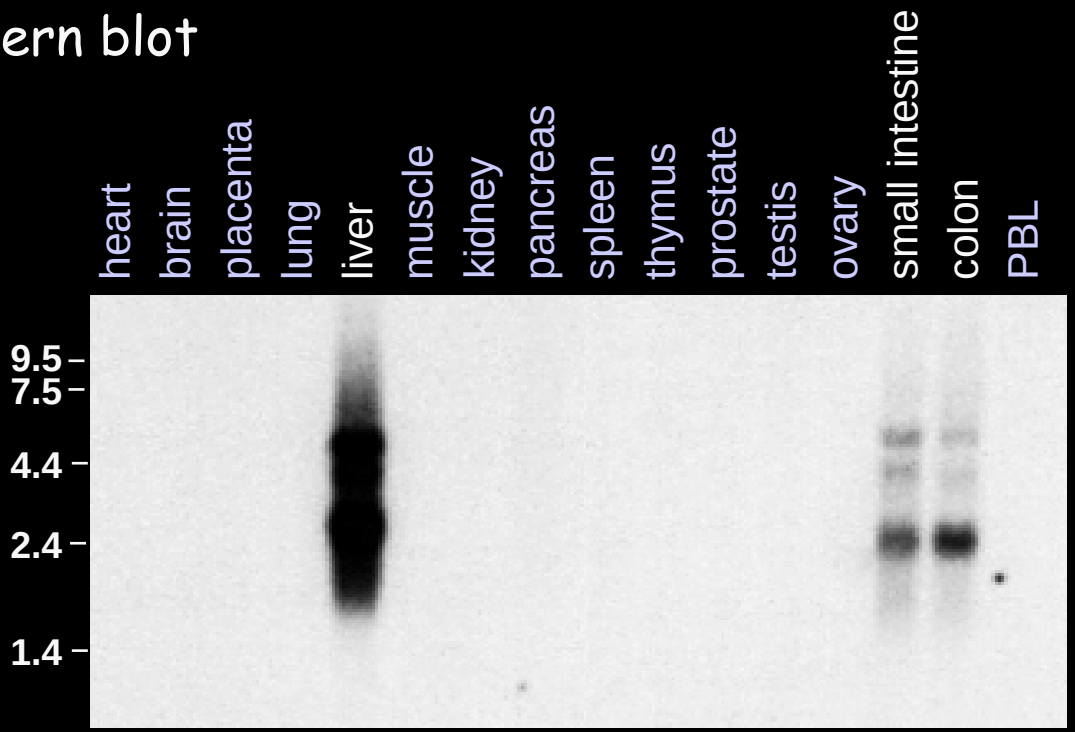
Pregnane X Receptor (PXR)



- Cloned due to homology with other nuclear receptors
- Named on basis of activation by natural and synthetic C21 steroids (pregnanes), including pregnenolone 16α-carbonitrile (PCN)

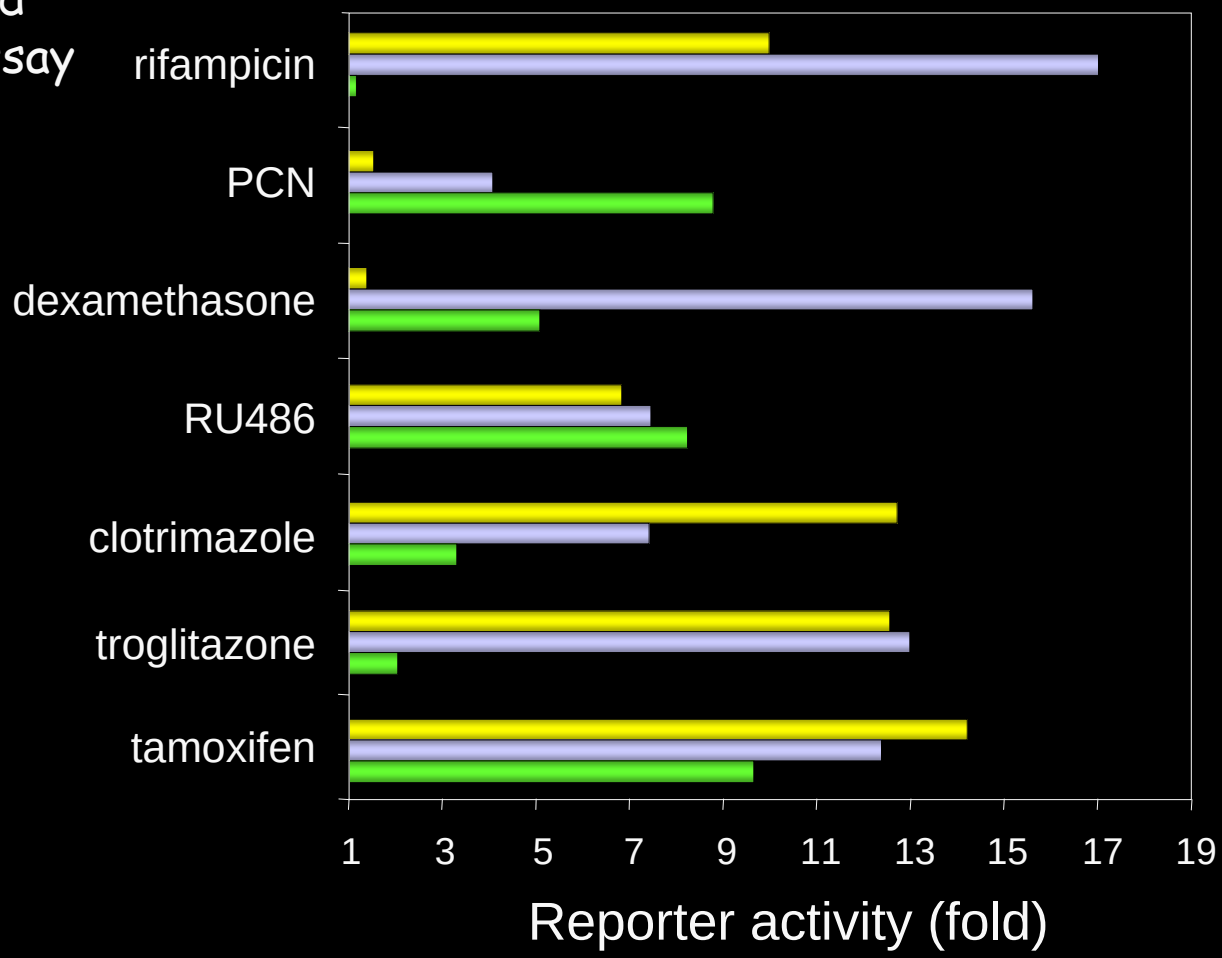
PXR Expression in Human

Northern blot

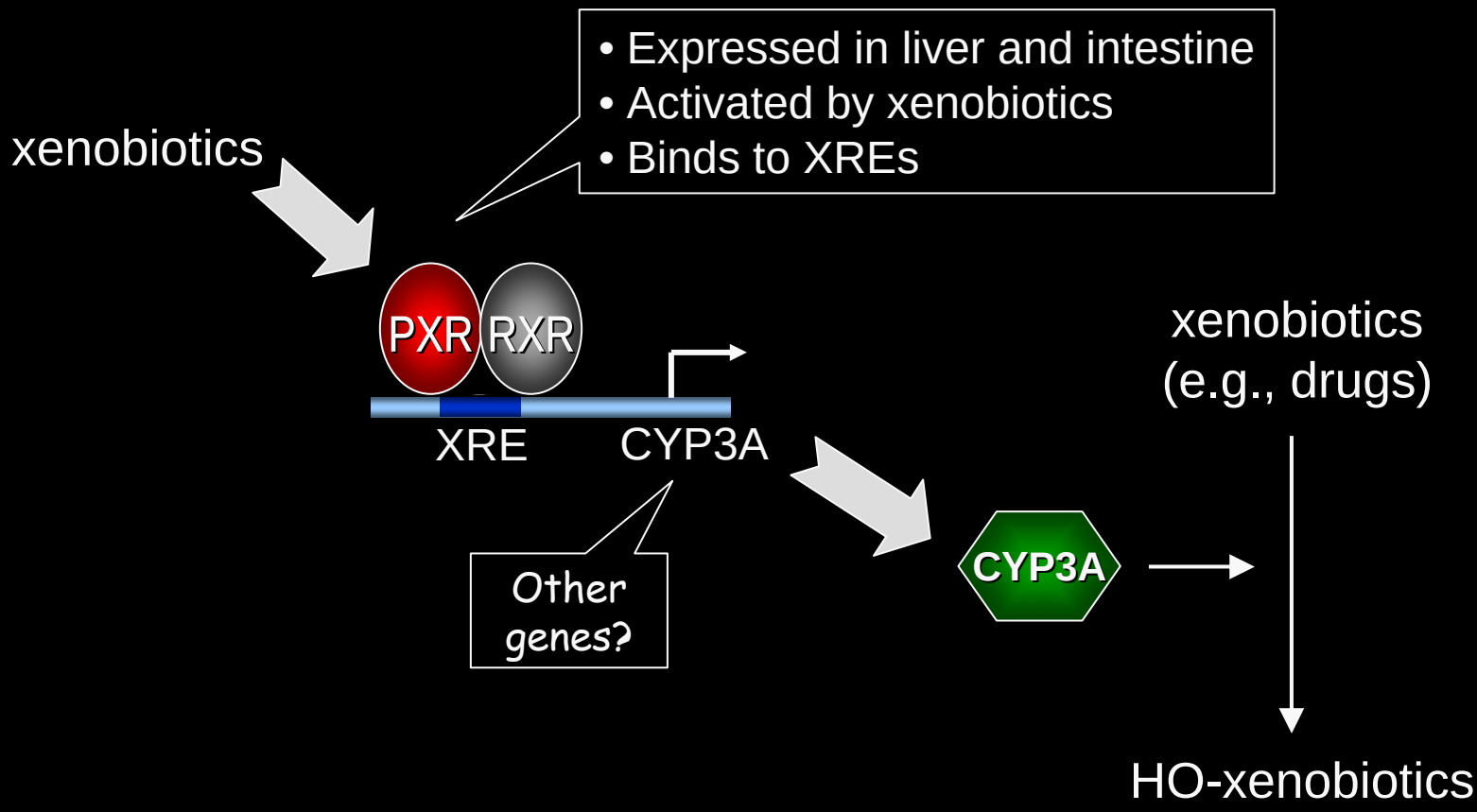


CYP3A Inducers Activate Human, Rabbit, and Rat PXR

Cell-based reporter assay



PXR Regulates CYP3A

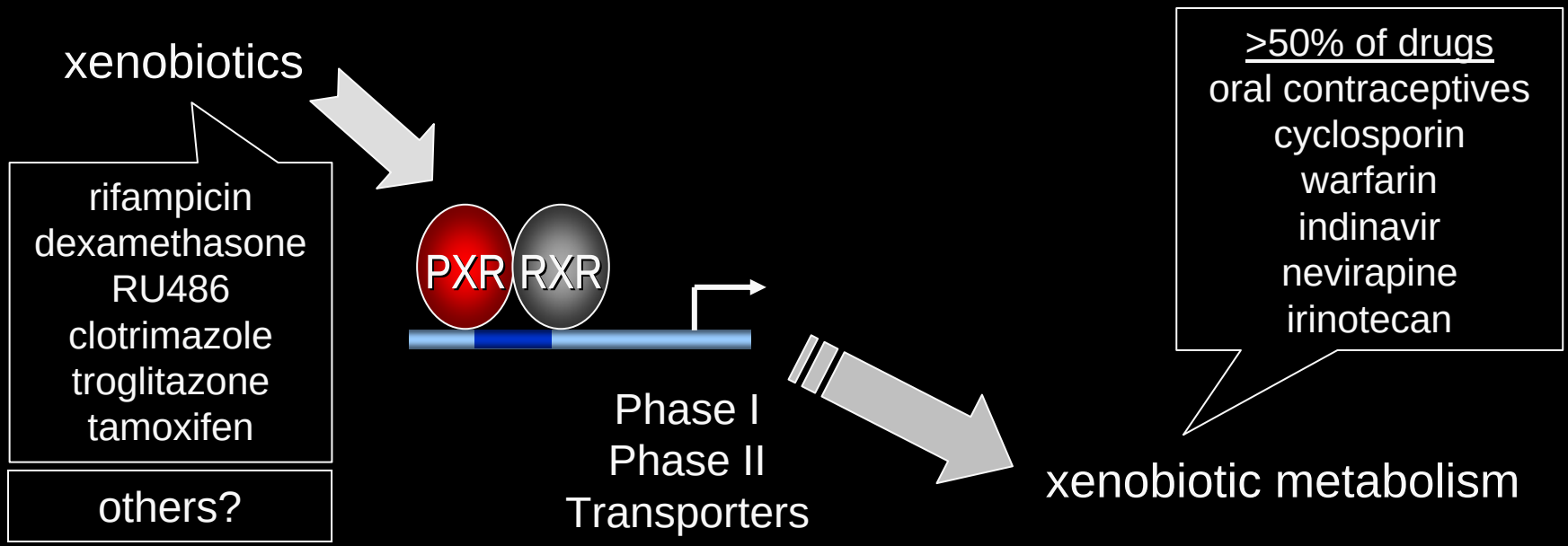


PXR Regulates Xenobiotic Metabolism

Liver RNA from mice treated with
- vehicle
- PCN

- Phase I (oxidation) enzymes
  - ⬆ *Cyp3a11 (3.5x)*
  - ⬆ *Cyp2b10 (12x)*
  - ⬆ *Aldh1a1 (2.1x)*
  - ⬆ *Aldh1a7 (1.6x)*
- Phase II (conjugation) enzymes
  - ⬆ *Ugt1a1 (2.8x)*
  - ⬆ *Gst-a1 (16x)*
- Transporters
  - ⬆ *Mdr1a (3.2x)*
  - ⬆ *Mrp3 (3.0x)*
  - ⬆ *Oatp2 (9.2x)*

PXR Protects the Body from Toxins, But…



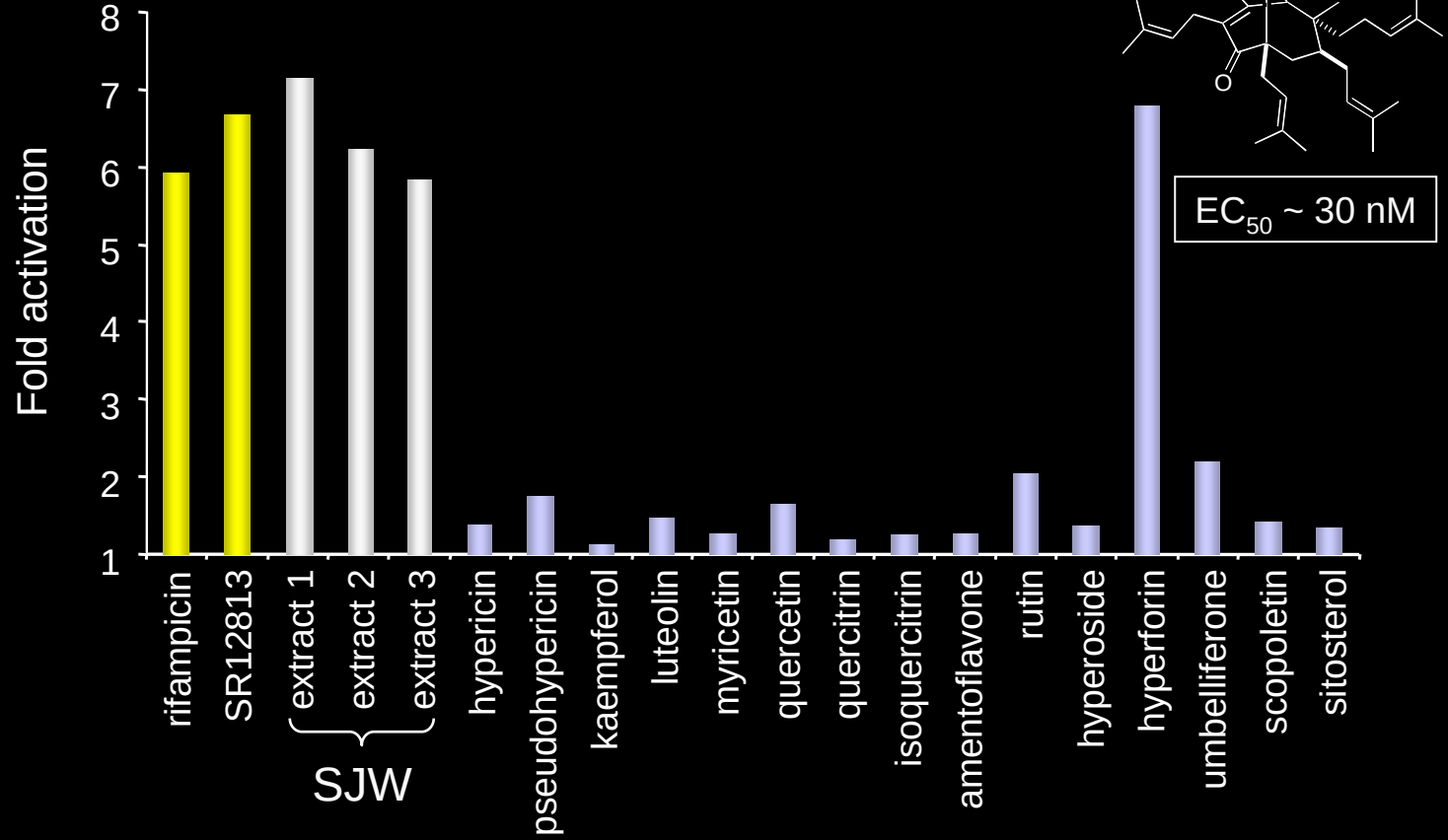
Causes Drug-Drug Interactions

St. John's Wort

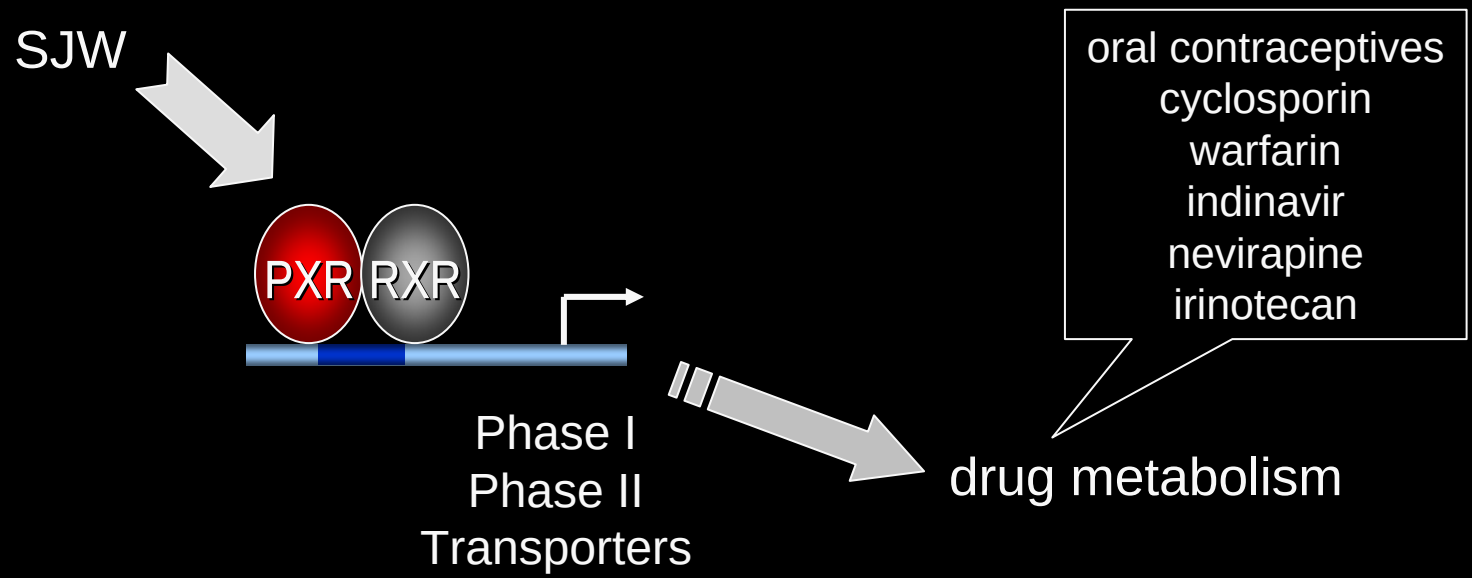
- Medicinal herb
- Widely used for depression
  - European sales of $6 billion (1998)
  - US sales of $210 million (2000)
- Complex mixture of > two dozen chemicals
- Drug interactions
  - oral contraceptives
  - cyclosporin
  - warfarin
  - indinavir
  - nevirapine
  - irinotecan

St. John's Wort Activates PXR

Cell-based reporter assay



SJW Interacts with Drugs



SJW is predicted to interact with most drugs

SJW Interacts with Drugs

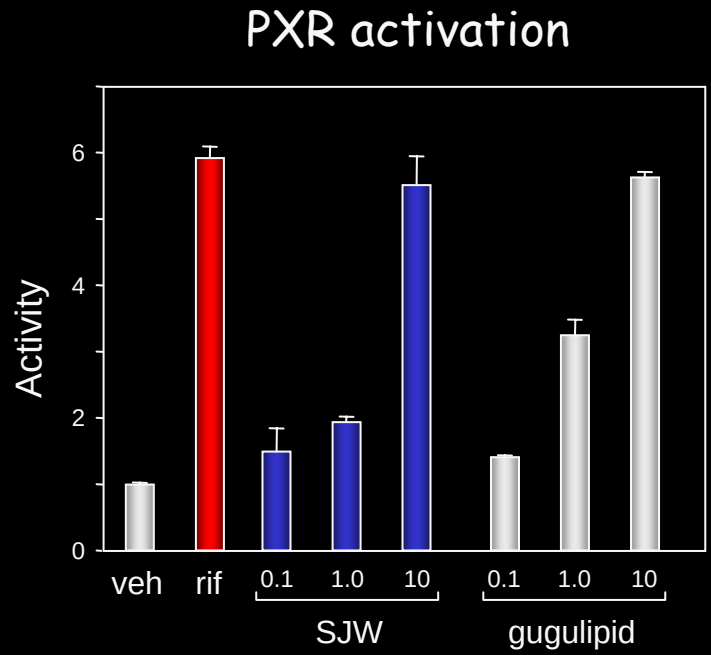
cyclosporin……immunosuppressant
tacrolimus……immunosuppressant
quazepine……sedative
warfarin……anticoagulant
verapamil……antihypertensive
nifedipine……antihypertensive
omeprazole……antiulcerative
theophylline……bronchodilator
ethinylestradiol…..oral contraceptive

midazolam……anesthetic
nevirapine……antiviral
indinavir……antiviral
irinotecan……antineoplastic
gleevec……antineoplastic
amitriptyline….antidepressant
simvastatin……anticholesterolemic
digoxin……cardiotonic
methadone……analgesic
alprazolam……anxiolytic

Do other herbs activate PXR?

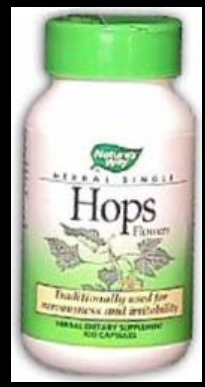
Gugulipid Activates PXR

- Derived from mukul myrrh tree
- Promoted for reducing cholesterol and treating obesity
- Accelerates the metabolism of two antihypertension drugs
  - diltiazem
  - propranolol

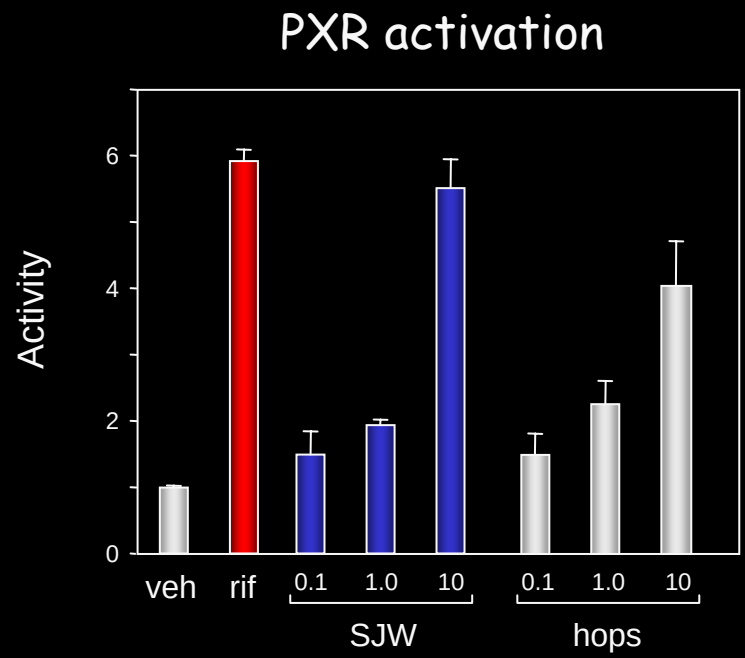


Gugulipid may counteract other drugs including statins

Hops Activates PXR

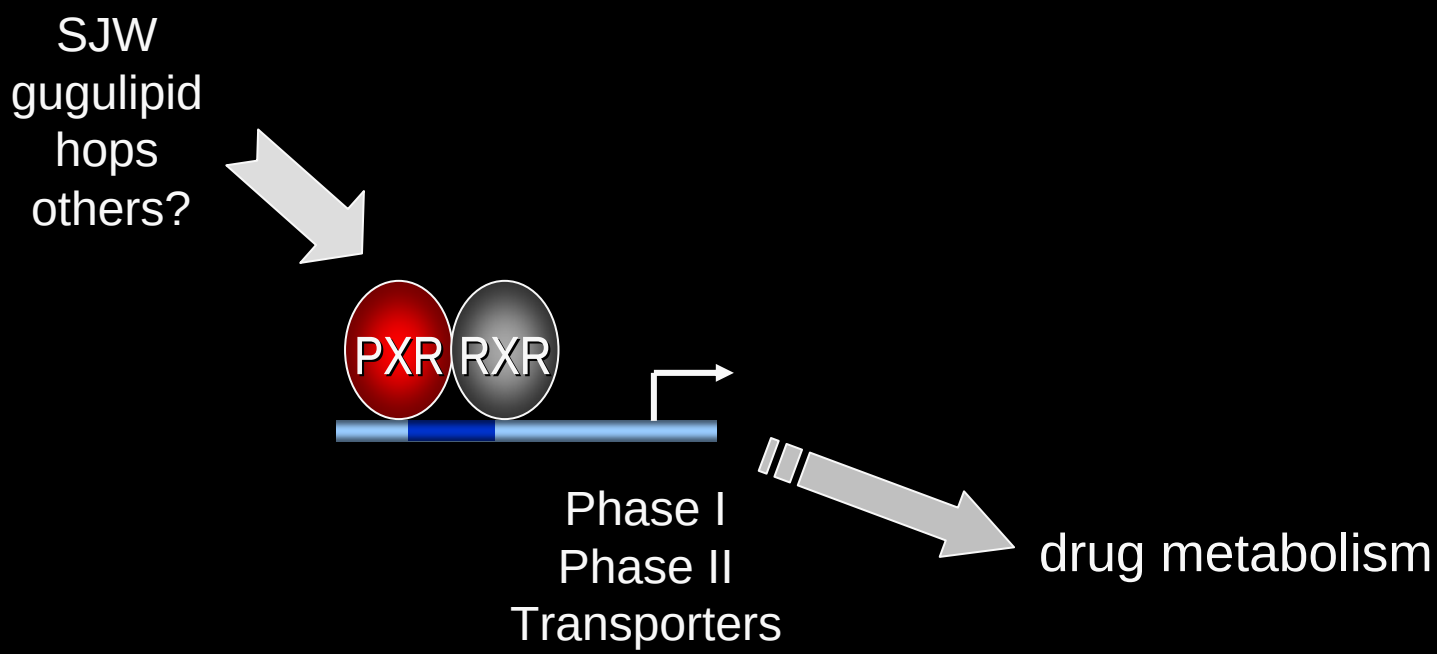


- Promoted for treating
  - insomnia
  - anxiety
  - indigestion
- Increases drug metabolizing enzymes in rodents



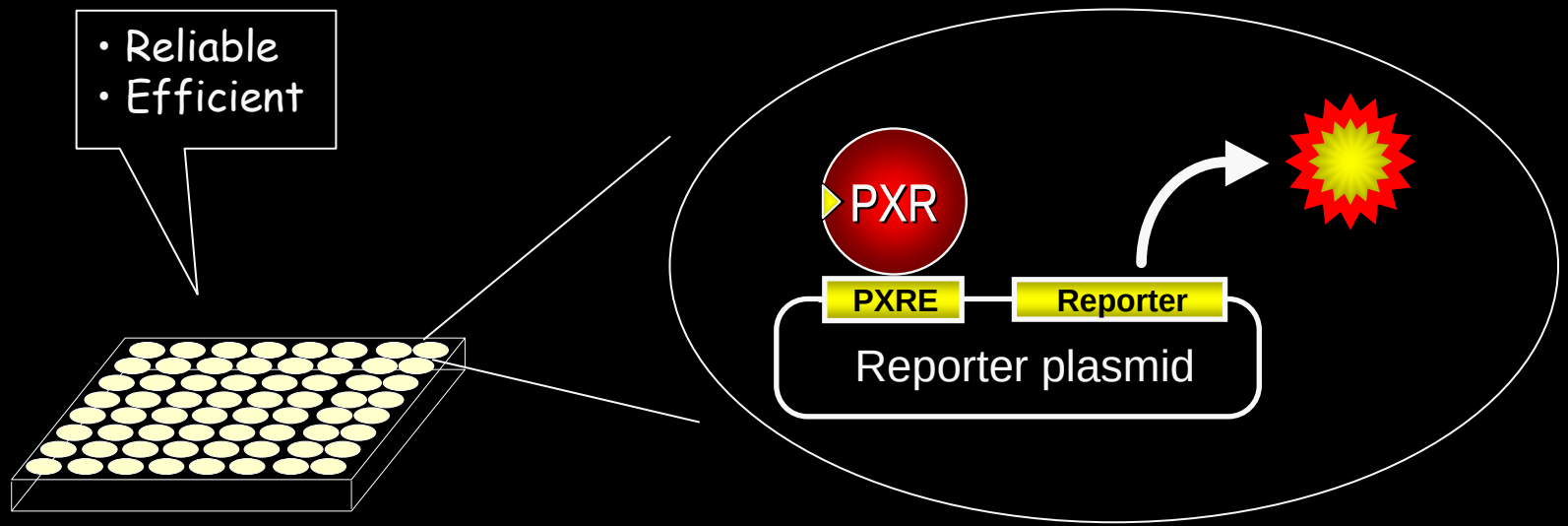
Hops is predicted to interact with most drugs

Herbs Activate PXR



These herbs are predicted to interact with many drugs

PXR Assays Predict Herb-Drug Interactions



Herb-drug interactions can be predicted and prevented

Acknowledgments

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