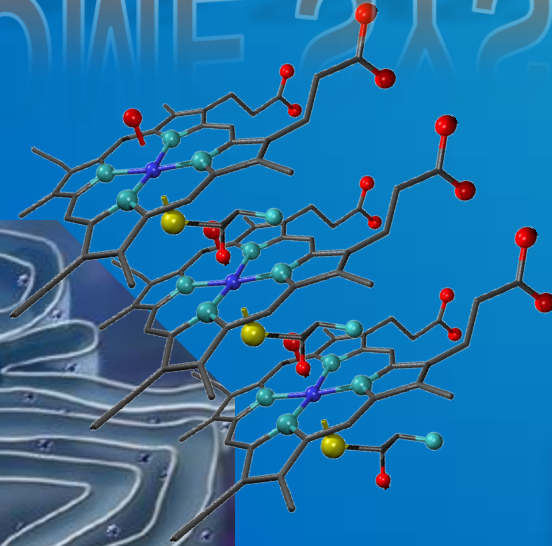
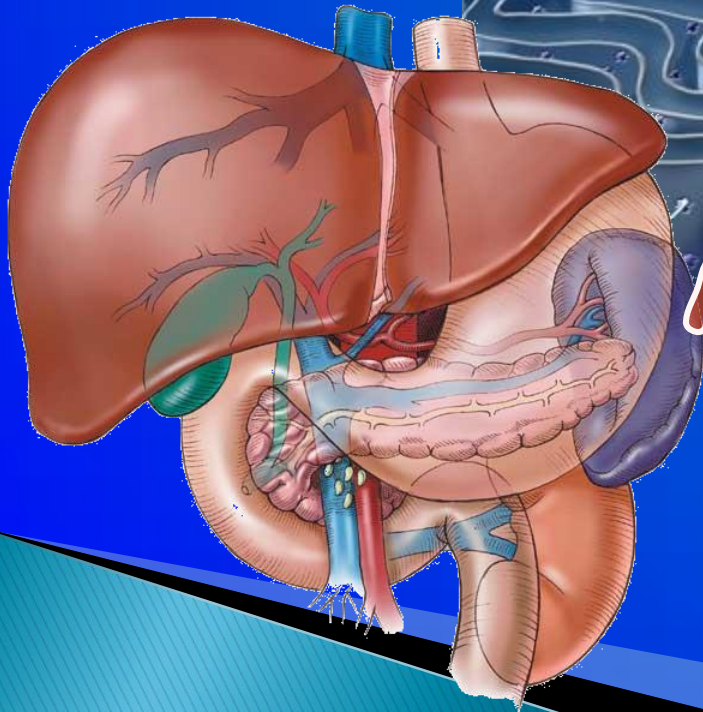


# CYTOCHROME SYSTEM

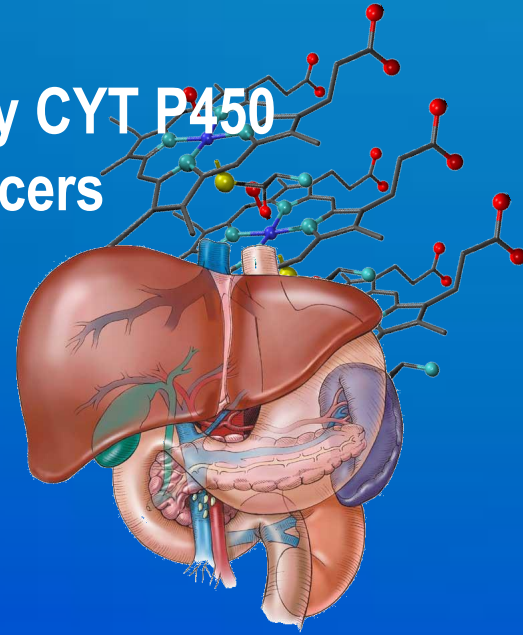
&

DRUG  
METABOLISM



# CYTOCHROME SYSTEM & DRUG METABOLISM

- Revise the aim and phases of drug metabolism
- Define the role of cytochrome system in relation to drug metabolism
- Expand on the nature, location, nomenclature, structure, distribution & function of CYT P450
- Focus on its regulation; directly & indirectly, its induction & inhibition its relevance to drug interactions
- Interpret the molecular mechanism of interactions by CYT P450
- Classify its different isoforms, their substrates, inducers & inhibitors
- Delineate some of its genetic variations



RENAL  
Elimination



Polar product

Non-Polar product



BILIARY  
Elimination

Being mostly lipophylic → The liver subjects them to chemical transformation **(METABOLISM)** → to become inactive & easily EXCRETED.

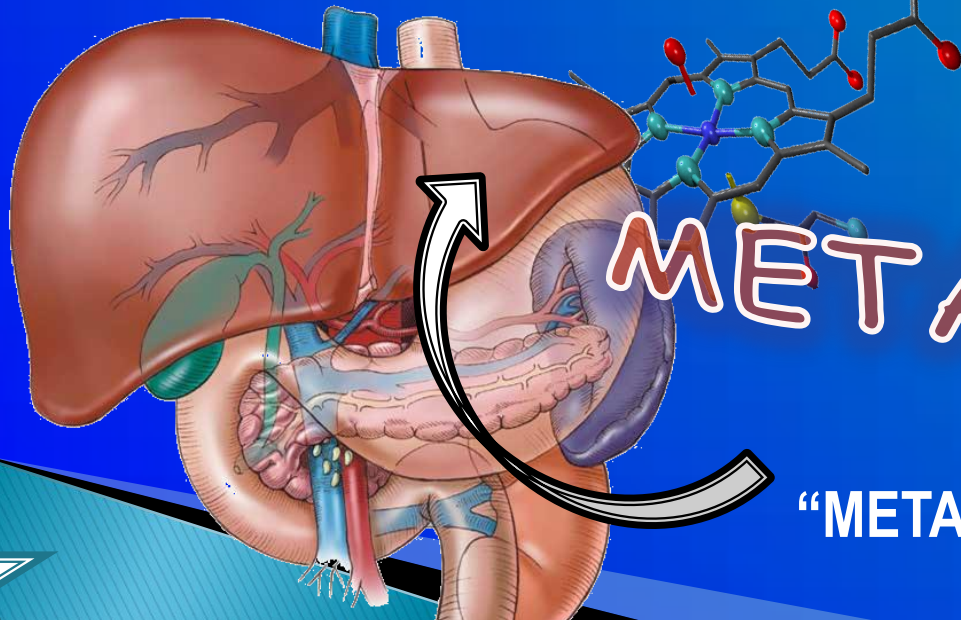


Identified as foreign substances that body must get rid of



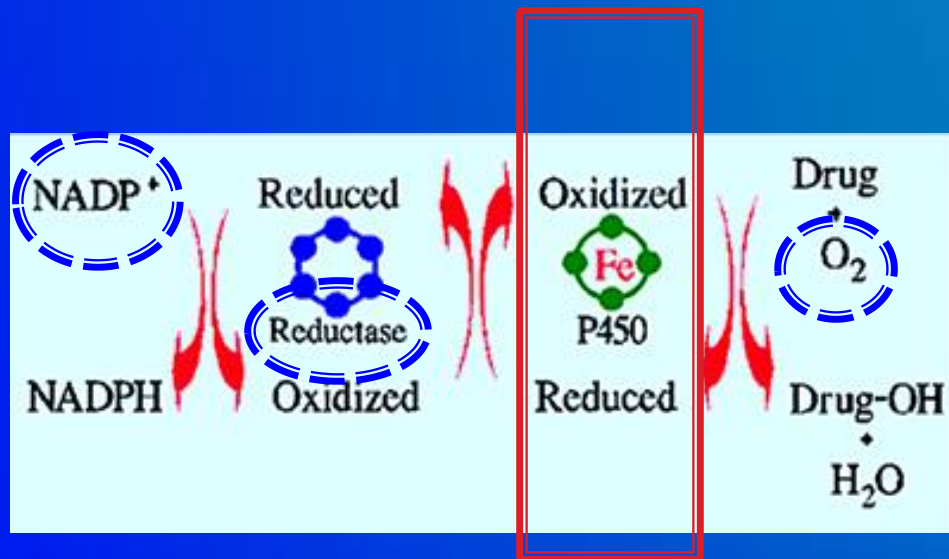
DRUG  
METABOLISM

Occurs mainly in the  
"METABOLIC CLEARING HOUSE"



“ **Cytochrome P450**“ “ **CYT 450**”  
 superfamily is the terminal rate limiting oxidase of this system

- ✿ Inactive product
- ✿ Active metabolite;
- ✿ Similar to parent
- ✿ More active than parent
- ✿ A product with different effect
- ✿ Toxic metabolite



Its enzymes are part of a cascade  
 → transfers electrons from molecular oxygen to oxidize the drugs

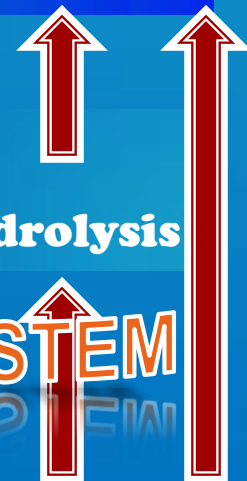
**Phase II**  
**CONJUGATION**

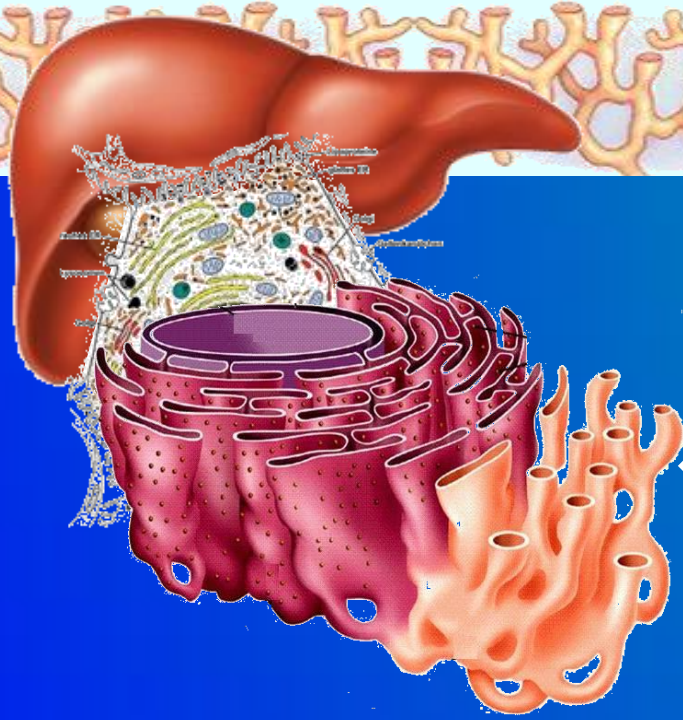
Create a conjugation site

**Phase I**  
**OXIDATION / Reduction / Hydrolysis**

**CYTOCHROME SYSTEM**

**DRUG METABOLISM**





## CYTOCHROME P450 FAMILY OF ENZYMES.

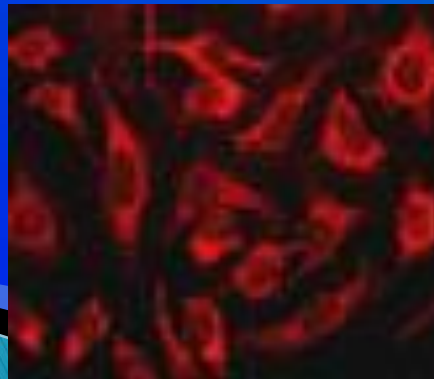
They are located mainly attached to the smooth endoplasmic reticulum (SER) of hepatocytes.



They are isolated in the subcellular fraction termed the **MICROSOMES**  
→ **Liver microsomal enzymes**

“**Cytochrome**” = colored cells  
They color the liver cells dark red as they contain iron

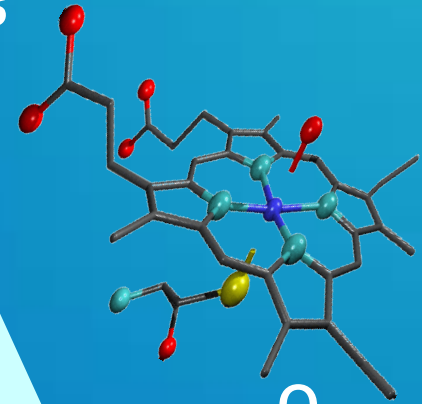
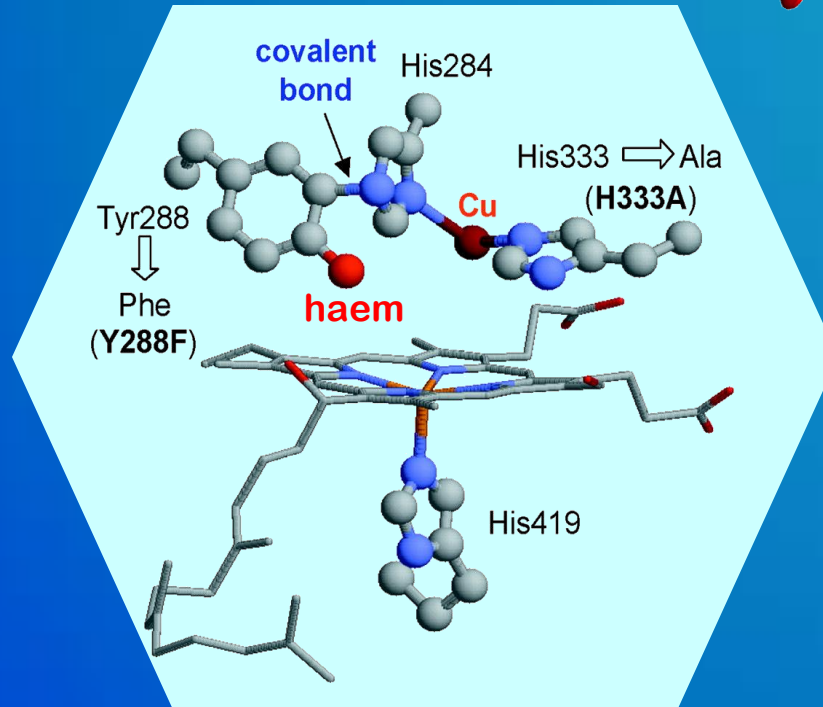
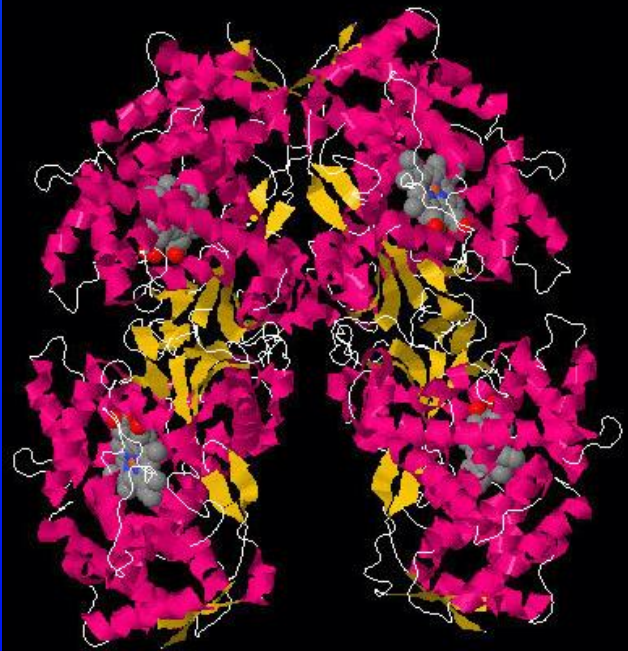
“**P450**” absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.



## STRUCTURE

They are heme-containing isoenzymes

Human Cytochrome P450  
from the  
Endoplasmic Reticulum



O<sub>2</sub>  
N<sub>3</sub>  
Su  
Fe

## DISTRIBUTION

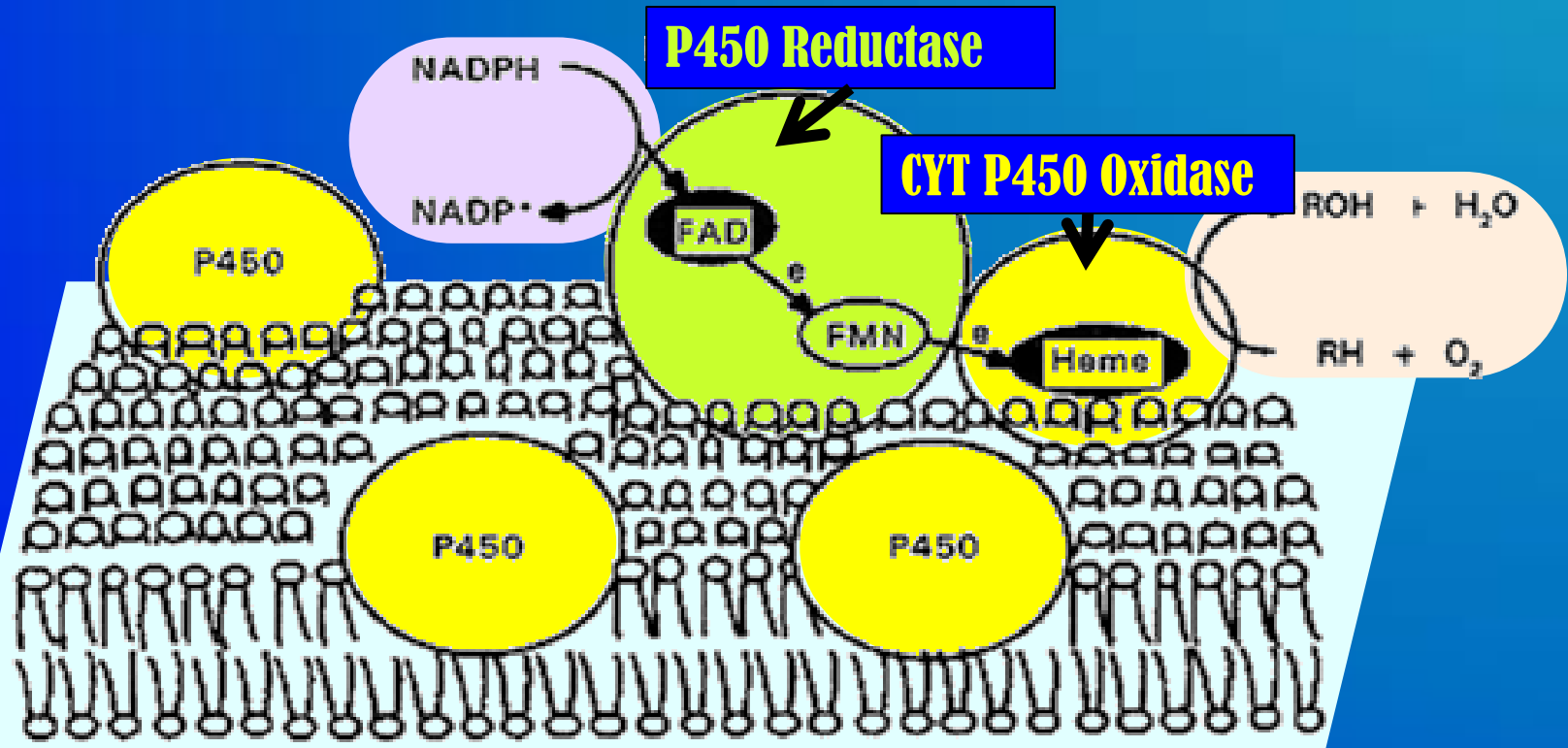
- Highly concentrated in hepatocytes
- Enterocytes of the small intestine present their principal extra-hepatic source
- Very small quantities in kidneys, lungs, & brain.

## Function

Responsible for most of the **OXIDATIVE METABOLISM** of:

- Endogenous substances: steroid hormones, prostaglandins, lipids, & fatty acids
- Exogenous compounds: diet( food & beverages) / Drugs/ environmental xenobiotics.

Substrates

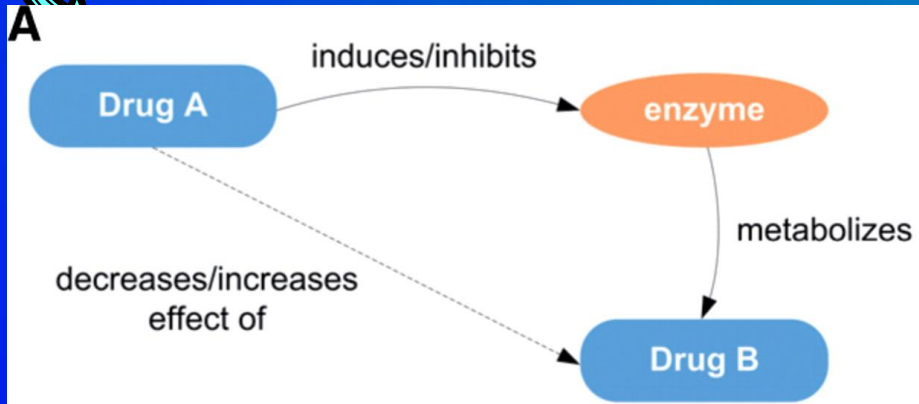


# Regulation

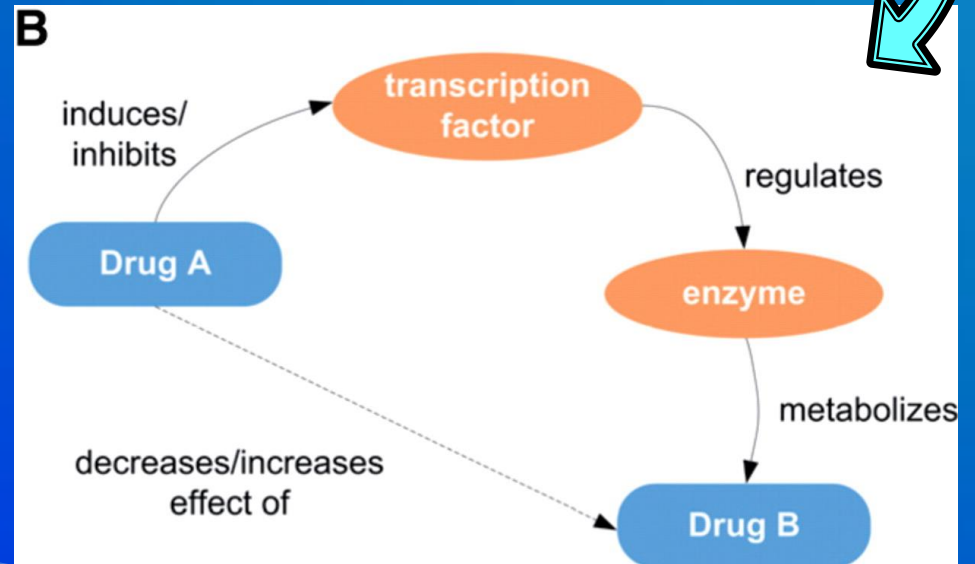
Activation or Inactivation of the CYT P450 can be achieved either

A: Directly

B : Indirectly by expression or repression of its relevant genes by activation or inhibition of the responsible transcription factors



Activation or Inactivation can be processed by any food, intrinsic products or extrinsic xenobiotics as drugs ( usually the lipophylic ) that have to be metabolized





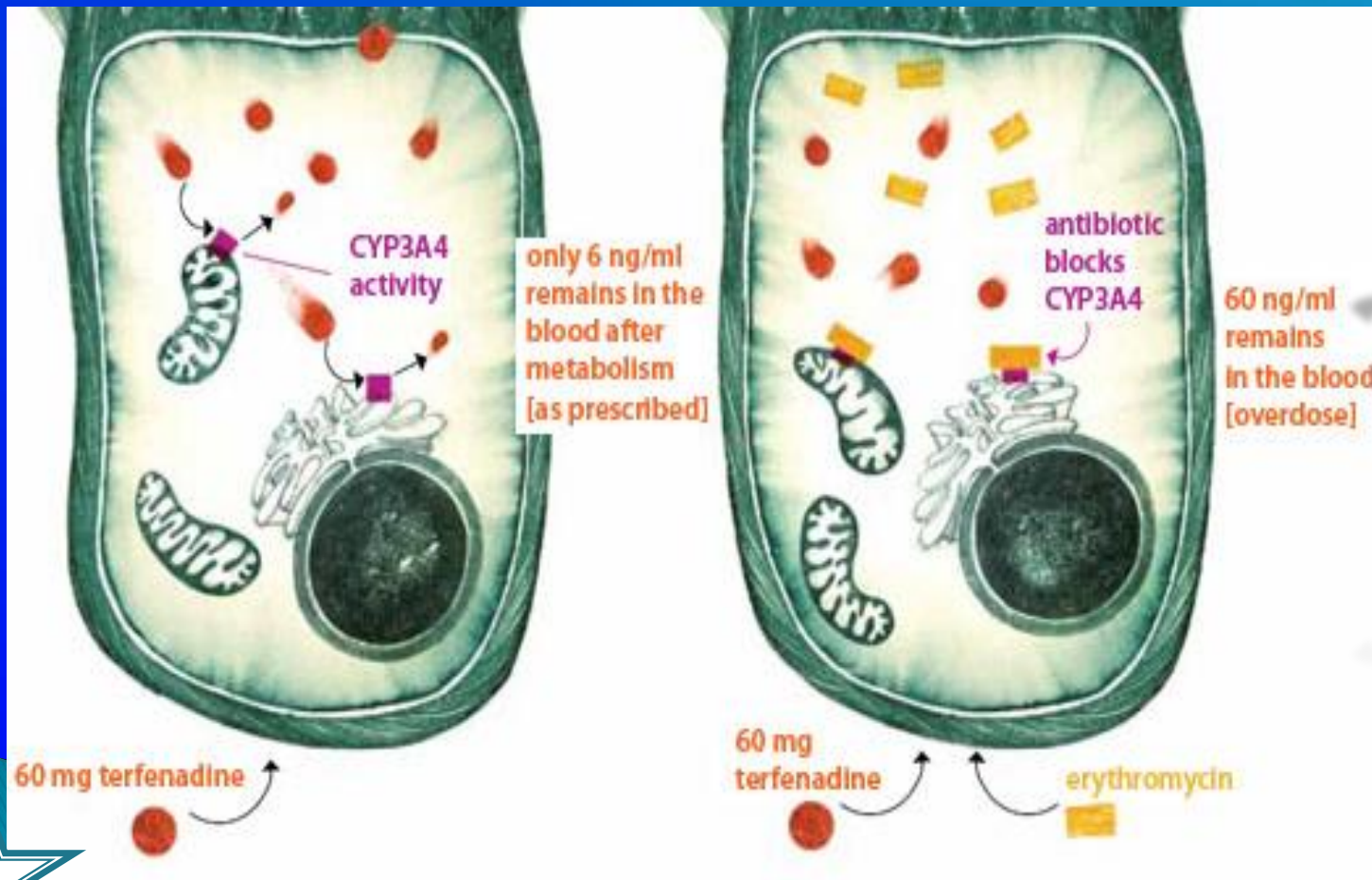
# Regulation

When drugs play a role in regulation of the CYT P450 → they are termed

● Enzyme Inducers if **Activate** the enzyme

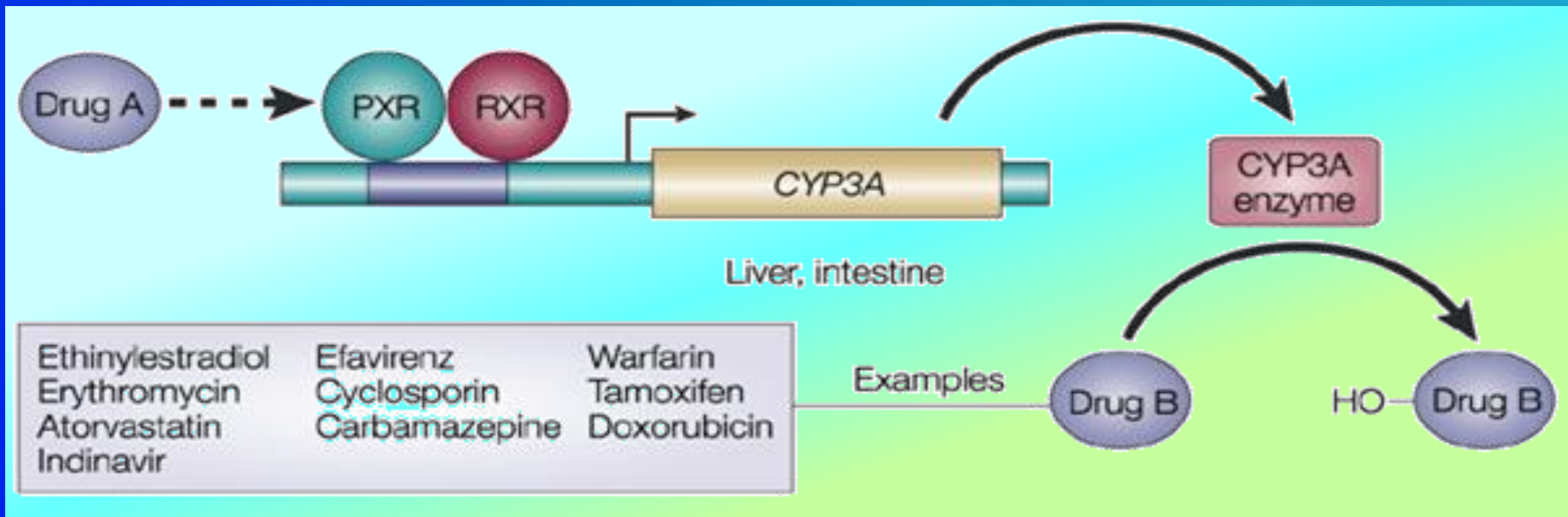
● Enzyme Inhibitors if **Inactivate** the enzyme

→ PHARMACOKINETIC  
DRUG-DRUG  
INTERACTION



# Molecular Basis Of Drug–drug Interaction

# Regulation



The orphan nuclear receptor **PXR** is a **TRANSCRIPTION FACTOR** that regulates the expression of the *CYP P450* genes.

If **Drug A** is **INDUCER** → it binds & activates **PXR** → which translocates in nucleus → dimerize with **RXR** → the heterodimer **PXR / RXR** will induce **EXPRESSION** of *CYT P450* isoenzymes to → ↑ metabolism of **Drug B**

If **Drug A** is an **INHIBITOR**, its binding will prevent activation → **REPRESSION** of *CYT P450* isoenzymes to → ↓ metabolism of **Drug B**

*PXR, pregnane X receptor  
RXR, retinoid X receptor.*



# Outcome Of Drug-drug Interactions Mediated By CYT P450

## Regulation

### IN RELATION TO ENZ INDUCERS

- ↑ → metabolism of the inducer + ↓ → its pharmacological action.  
*Tolerance or complete nullification*
- ↑ → metabolism of co-administered drugs

↓ EFFICACY

### IN RELATION TO ENZ INHIBITORS

- ↓ / Retard metabolism & excretion of inhibitor & co-administered drugs.
- ↑ / prolong action of the inhibitor & co-administered drugs.

↑ TOXICITY



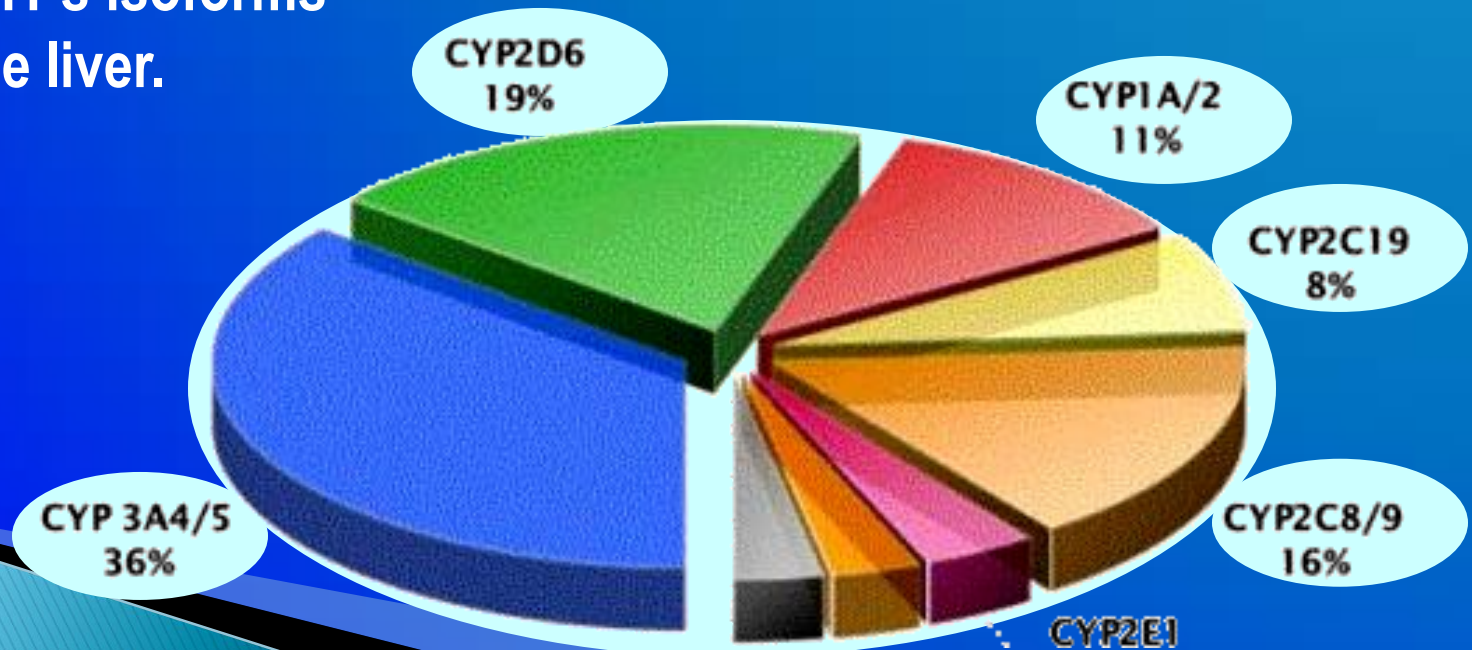
# Classification

- CYT P450 has been classified into
- Families designated by Numbers
  - Sub families designated by Letters

## Cytochrome P450 Isoforms

- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

Distribution of  
different CYPs isoforms  
in the liver.



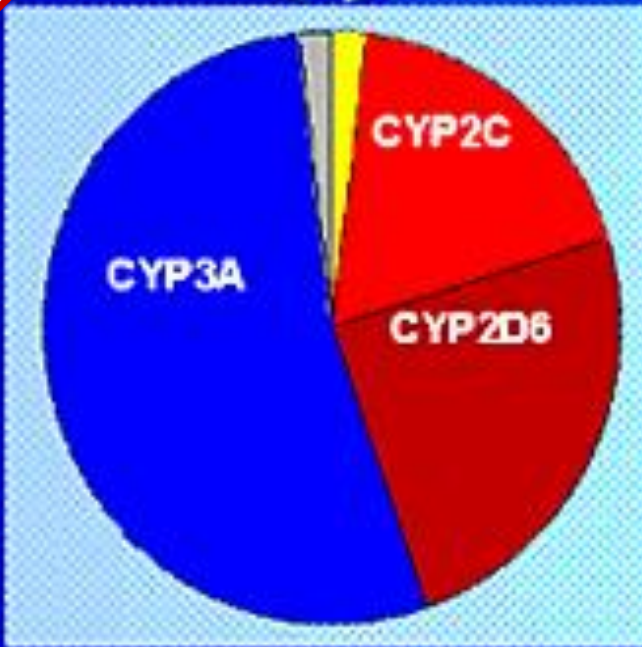
# CYP450 → Major Contributor to Phase I Metabolism



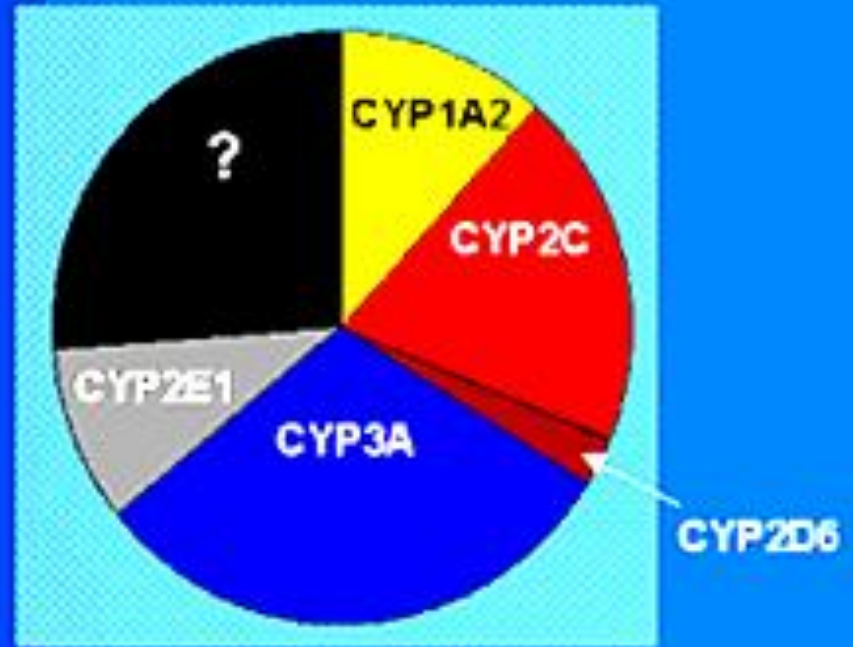
Relative Importance of P450s in Drug Metabolism

CYP2E1

CYP1A2

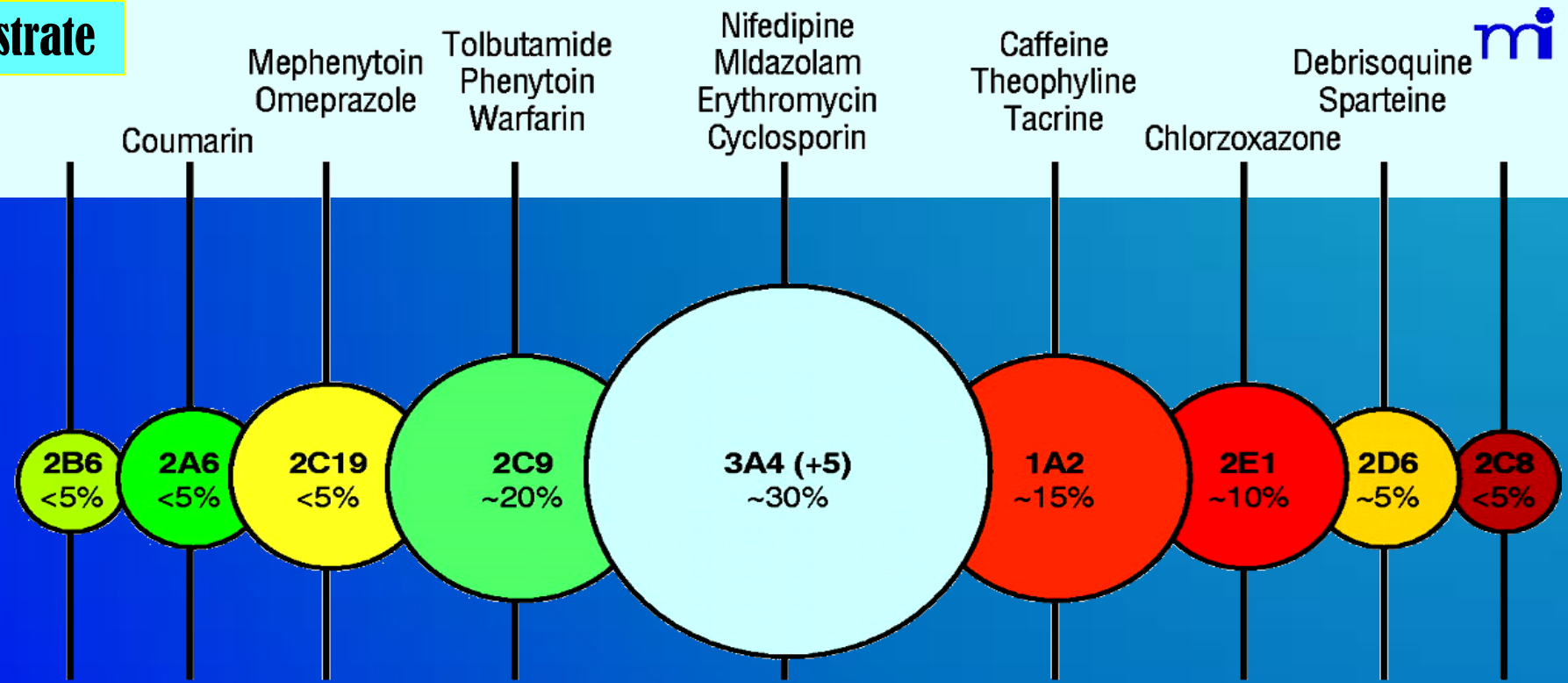


Relative Quantities of P450s in Liver





# Substrate



# Inhibitors

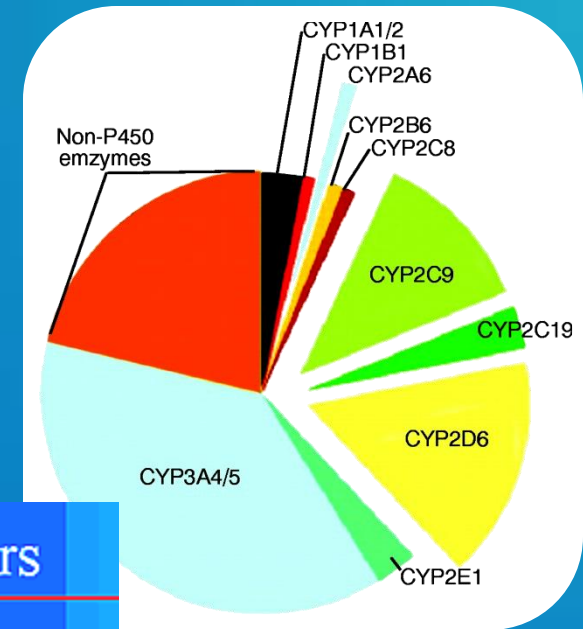
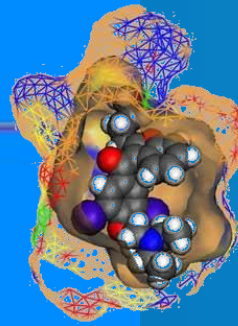
Fluconazole, Methoxsalen, Sulfaphenazole, Ketoconazole, Gestodene, Furafylline, Fluvoxamine, Disulfirma, Quinidine

# Inducers

Barbiturates, Rifampicin, Barbiturates, Rifampicin, Barbiturates, Rifampicin, Dexamethasone, Carbamazepine, Omeprazole, Tobacco smoke, Ethanol, Isoniazid

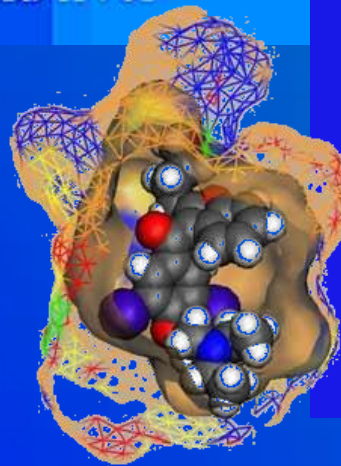
# Cytochrome P450 3A

- Responsible for metabolism of:
  - Most calcium channel blockers
  - Most benzodiazepines
  - Most HIV protease inhibitors
  - Most HMG-CoA-reductase inhibitors
  - Cyclosporine
  - Most non-sedating antihistamines
  - Cisapride
- Present in GI tract and liver



## CYP3A Inhibitors

- Ketoconazole
- Itraconazole
- Fluconazole
- Cimetidine
- Clarithromycin
- Erythromycin
- Troleandomycin
- Grapefruit juice

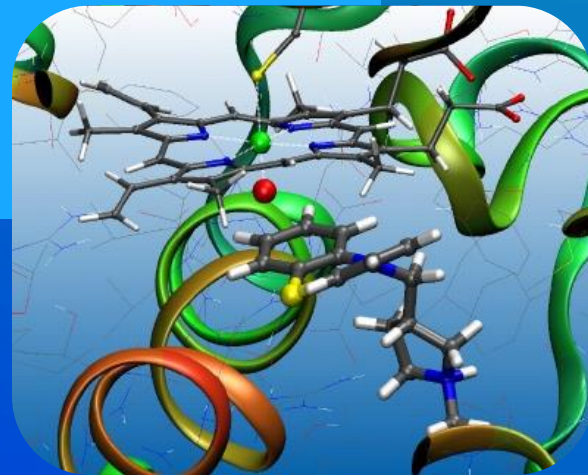
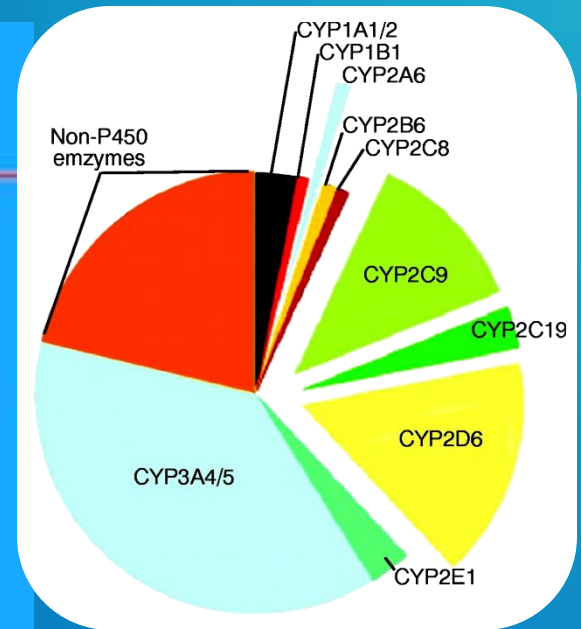


## CYP3A Inducers

- Carbamazepine
- Rifampin
- Rifabutin
- Ritonavir

# Cytochrome P450 2D6

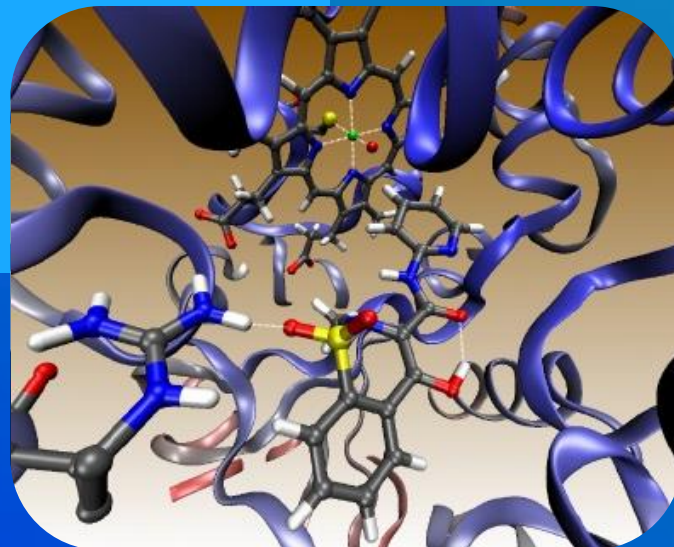
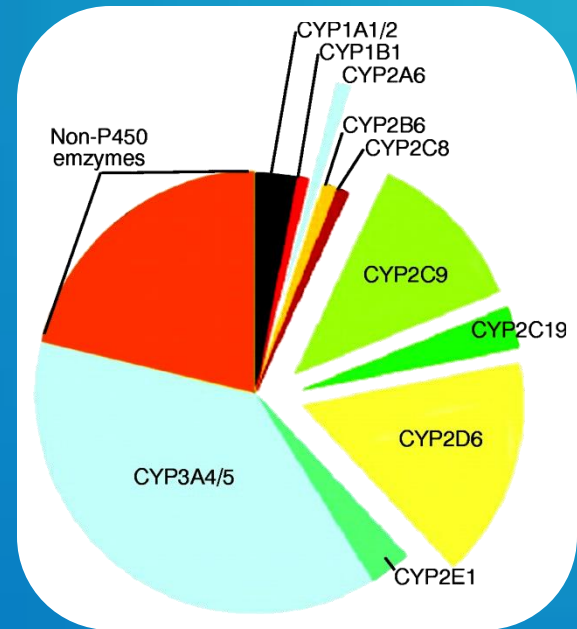
- Absent in 7% of Caucasians, 1–2% non-Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - Codeine
  - Many  $\beta$ -blockers
  - Many tricyclic antidepressants
- Inhibited by:
  - Fluoxetine
  - Haloperidol
  - Paroxetine
  - Quinidine





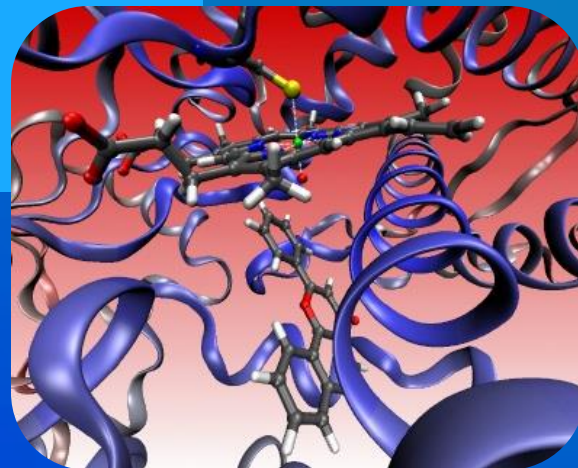
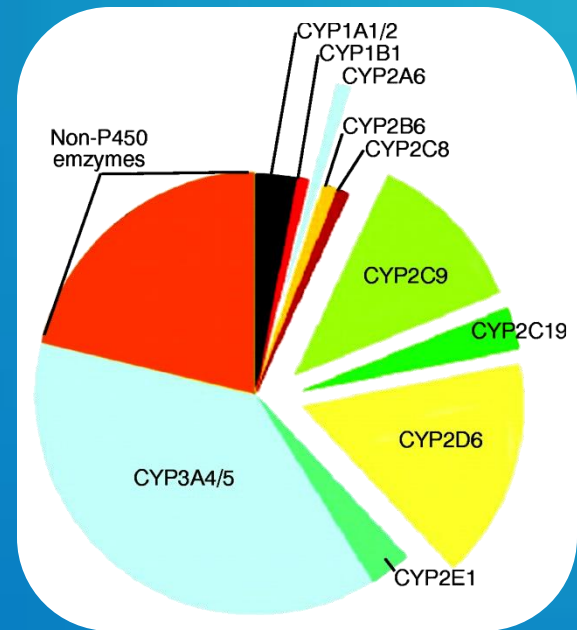
# Cytochrome P450 2C9

- Absent in 1% Caucasians and African-Americans
- Primary metabolism of:
  - Most NSAIDs (including COX-2)
  - S-warfarin (the active form)
  - Phenytoin
- Inhibited by:
  - Fluconazole



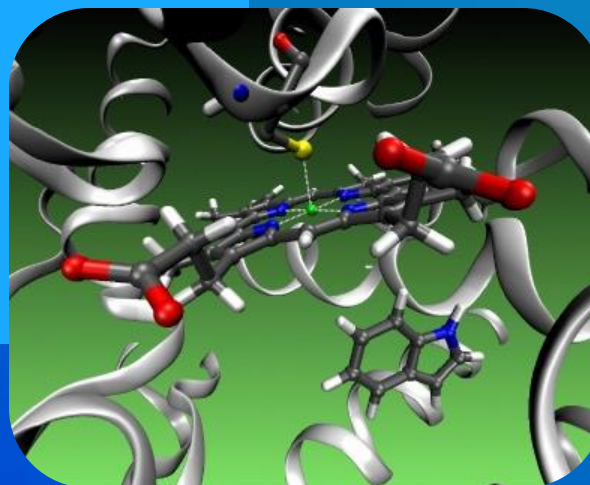
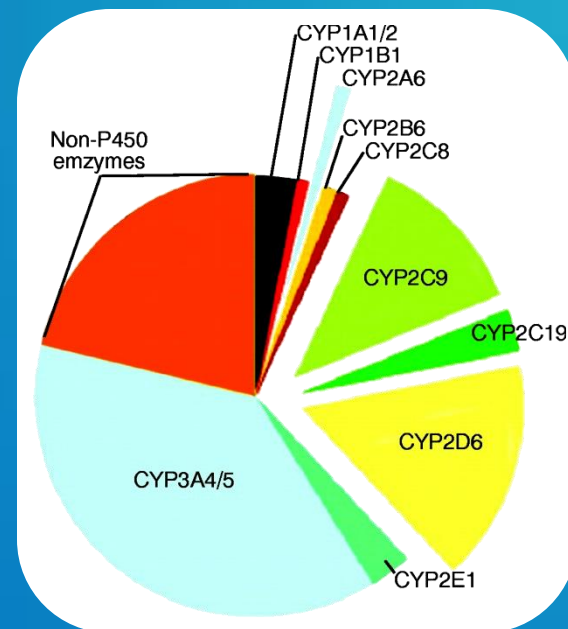
# Cytochrome P450 1A2

- Induced by smoking tobacco
- Catalyzes primary metabolism of:
  - Theophylline
  - Imipramine
  - Propranolol
  - Clozapine
- Inhibited by:
  - Many fluoroquinolone antibiotics
  - Fluvoxamine
  - Cimetidine



# Cytochrome P450 2C19

- Absent in 20–30% of Asians, 3–5% Caucasians
- Primary metabolism of:
  - Diazepam
  - Phenytoin
  - Omeprazole
- Inhibited by:
  - Omeprazole
  - Isoniazid
  - Ketoconazole



# CYT P450 3A4

Substrates	Inhibitors	Inducers
<p>Immunosuppressants <b>Cyclosporine</b></p> <p>Azole Antifungals <b>Fluconazole</b></p> <p>Antibiotics <b>Erythromycin, Clarithromycin</b></p> <p>Ca channel blockers <b>Amlodepine, Verapamil</b></p> <p>Statins; <b>Atorvastatin</b></p> <p><b>Amidarone</b></p> <p>Cancer Chemotherapy: <b>Cyclophosphamide, Tamoxifen</b></p> <p>Non-Sedating Antihistaminics <b>Astemizole</b></p> <p>Benzodiazepines <b>Midazolam, Clonazepam</b></p>	<p>→</p> <p>→</p> <p>→ <b>Protease Inhibitors</b> <b>Ritonavir</b></p> <p><b>Cimetidine</b></p> <p><b>Chloramphenicol</b></p> <p><b>Nefazadone</b></p> <p><b>Grape Fruits</b></p>	<p><b>Phenytoin</b></p> <p><b>Carbamazepine</b></p> <p><b>Barbiturates</b></p> <p><b>Rifampicin</b></p> <p><b>Dexamethazone</b></p> <p><b>Progestins</b></p>



*“A 50 years old, patient was treated for the last 3 years by the hypocholesterolemic agent; **atorvastatin**. Yesterday he began to complain of severe muscle pains, weakness and reddish discoloration of urine*

*He receives daily multivitamins and his lab results last week, proved that he has become diabetic, for which he was prescribed metformin. He was also started on a course of **fluconazole** for a concomitant fungal infection.*

*From drug history, the diagnosis of his current state was likely rhabdomyositis (severe musculoskeletal toxicity) and was verified by the lab finding of severe elevation in creatinine phosphokinase. “*

**Which one of the following drug-drug interaction on CYT 3A4 is the likely cause of his current state?**

Metformin + Atrovastatin

Atrovastatin + Fluconazole

Metformin + Fluconazole

Fluconazole+ Multivitamins



# Genetic Variation

Genetic polymorphisms in CYT P450 isoenzymes have been observed and are reasons behind the **ALTERED RESPONSE** to drug therapy

## CYP2D6

This isoenzyme has the most frequent polymorphisms in all CYT P450

When polymorphism occurs → ↓ metabolizing capacity of CYP2D6  
i.e those who exhibit the polymorphism become poor metabolizers:

1. Metabolism of some neuroleptics, tricyclic antidepressants, antianginals agent ( perihexiline), antiarrhythmics (propafenone & metoprolol) is suppressed → so side effects & toxicity develop. i.e.
  - Neuropathy after therapeutic doses of perihexiline
  - Bradycardias & arrhythmias on therapeutic dose of propafenone or metaprolol
2. The pro-drugs cannot be converted to their therapeutically active metabolite; e.g poor analgesia with codeine & tramadole because they are not transformed into active forms



# Genetic Variation

## CYP2C9.

Warfarin, phenytoin, & tolbutamide are examples of drugs with narrow therapeutic index that are metabolized by CYP2C9.

Clearance of these drugs is impaired in genetic variation of the enzyme

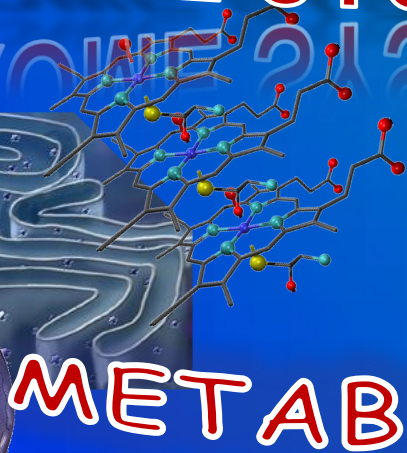
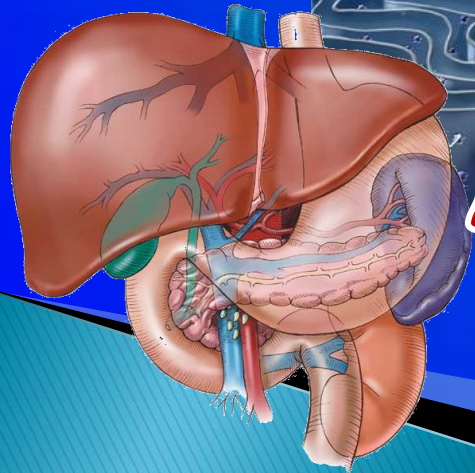
## CYP2C19

Polymorphism in CYP2C19 shows increased & prolonged action of its substrates such as omeprazole

This has been an advantage as in those variants → ↑ cure rates in peptic ulcer patient with *Helicobacter pylori*

Benefit

# CYTOCHROME SYSTEM



&

# DRUG METABOLISM

G

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