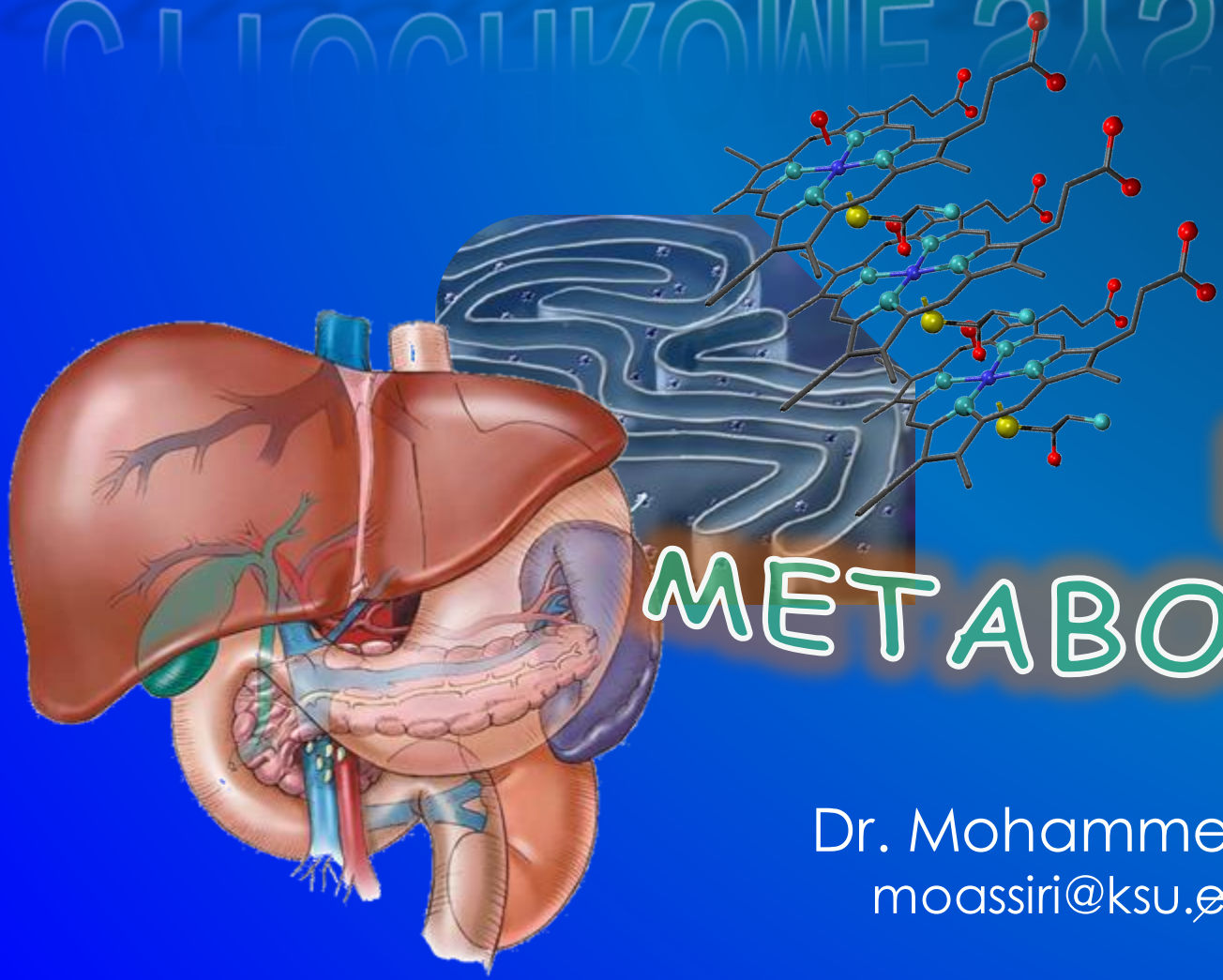
CYTOCHROME SYSTEM



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DRUG METABOLISM

Dr. Mohammed Assiri
moassiri@ksu.edu.sa

CYTOCHROME SYSTEM & DRUG METABOLISM

- Revise the aim & 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 in relevance to drug interactions
- Interpret molecular mechanism of interactions by CYTP450
- Classify its different isoforms, their substrates, inducers & inhibitors
- Delineate some of its genetic variations.

Where do drug biotransformations occur ?

RENAL Elimination

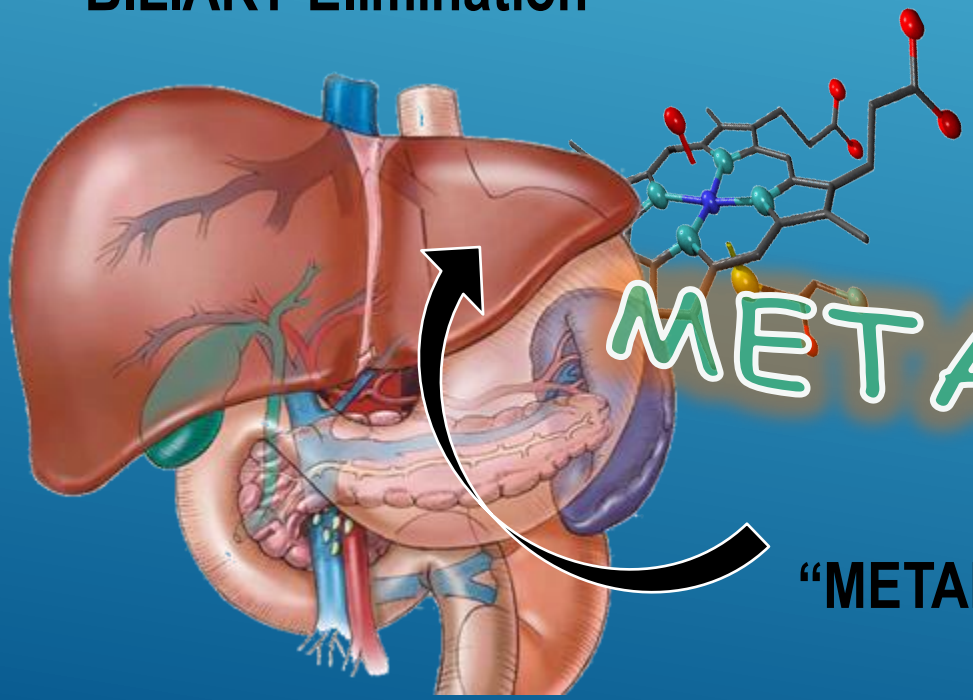
Polar product

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"

DRUG METABOLISM

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

Phase II
Conjugation

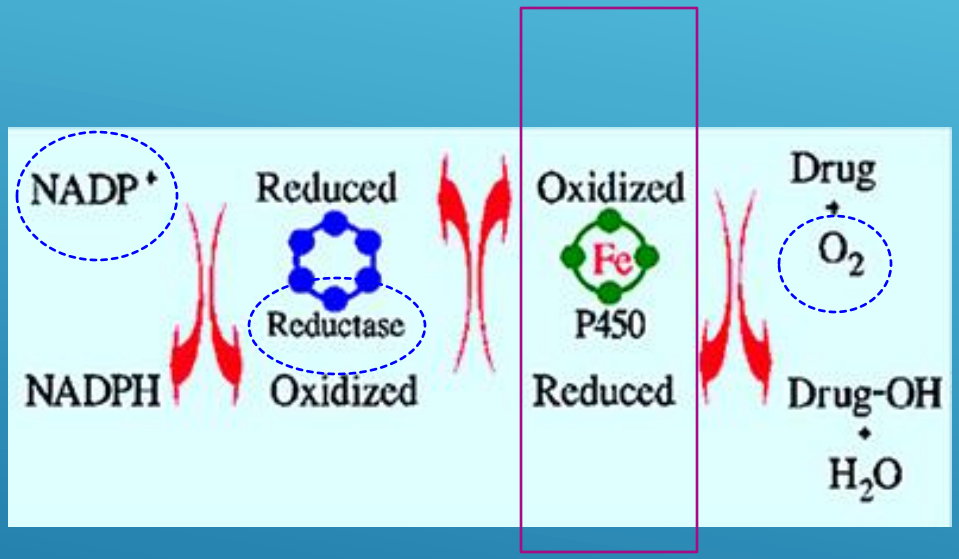
Create a conjugation site

Phase I
OXIDATION /Reduction/Hydrolysis

CYTOCHROME SYSTEM

" Cytochrome P450" " CYT 450"

Superfamily is the terminal rate limiting oxidase of this system



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

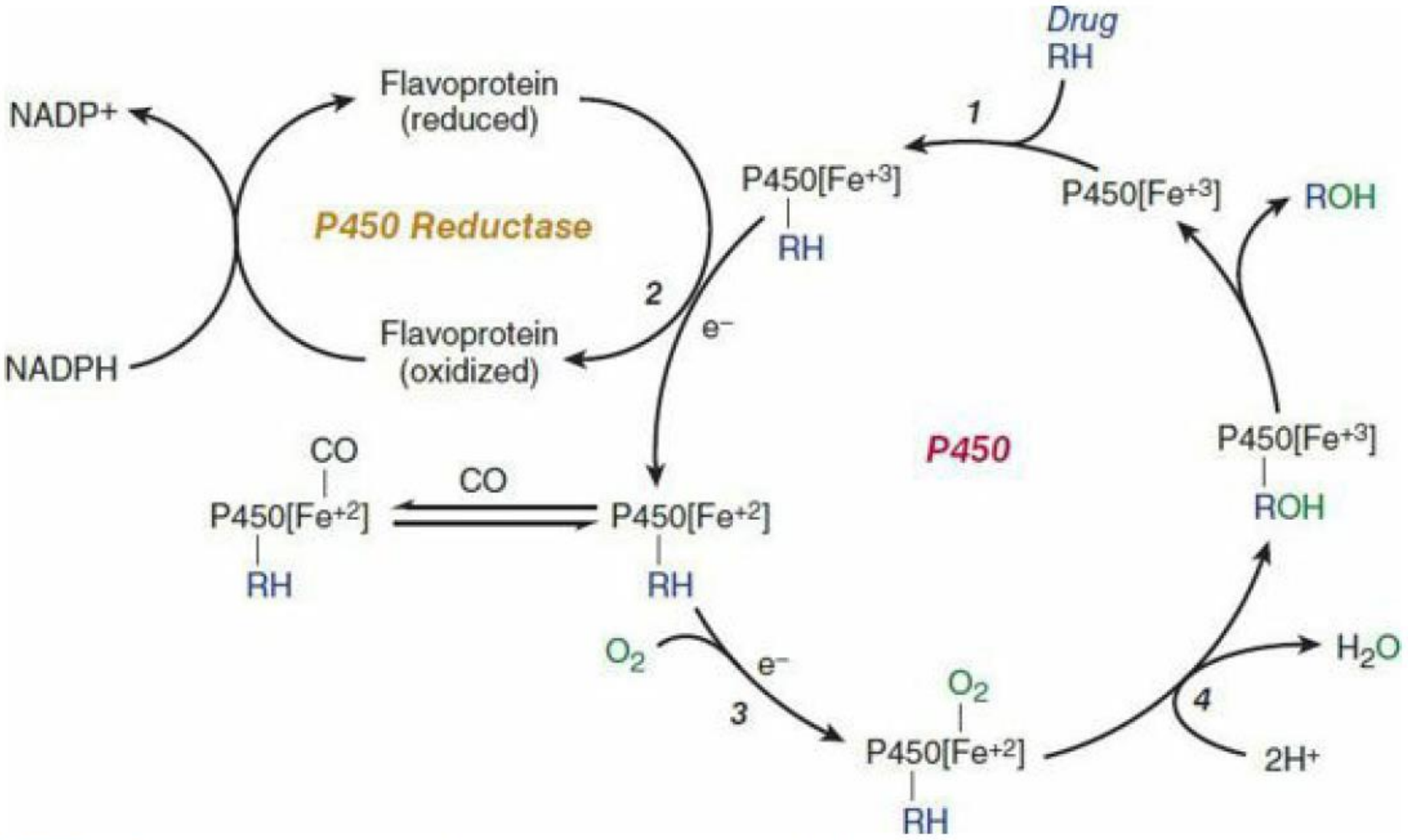


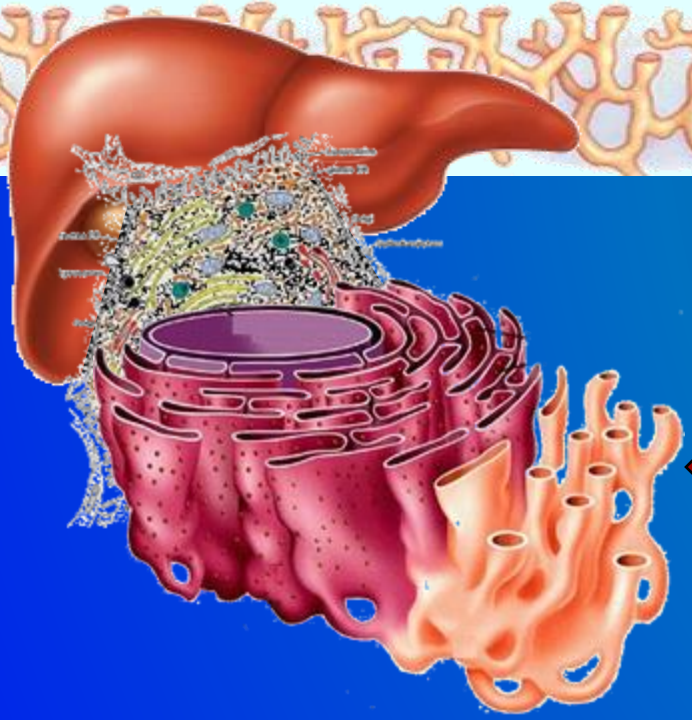
FIGURE 4–3 Cytochrome P450 cycle in drug oxidations. RH, parent drug; ROH, oxidized metabolite; e⁻, electron.

CYTOCHROME P450 CYCLE IN DRUG OXIDATIONS

- **Microsomal drug oxidations require P450, P450 reductase, NADPH, & molecular oxygen**
- **Briefly, oxidized (Fe3+) P450 combines with a drug substrate to form a binary complex (step 1). NADPH donates an electron to the flavoprotein P450 reductase, which in turn reduces the oxidized P450 drug complex (step 2).**

- **A second electron is introduced from NADPH via the same P450 reductase, which serves to reduce molecular oxygen & to form an activated oxygen – P450-substrate complex (step 3).**
- **This complex in turn transfers activated oxygen to the drug substrate to form the oxidized product (step 4).**

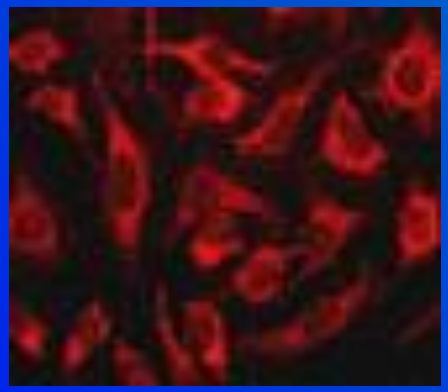
CYTOCHROME P450 FAMILY OF ENZYMES



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

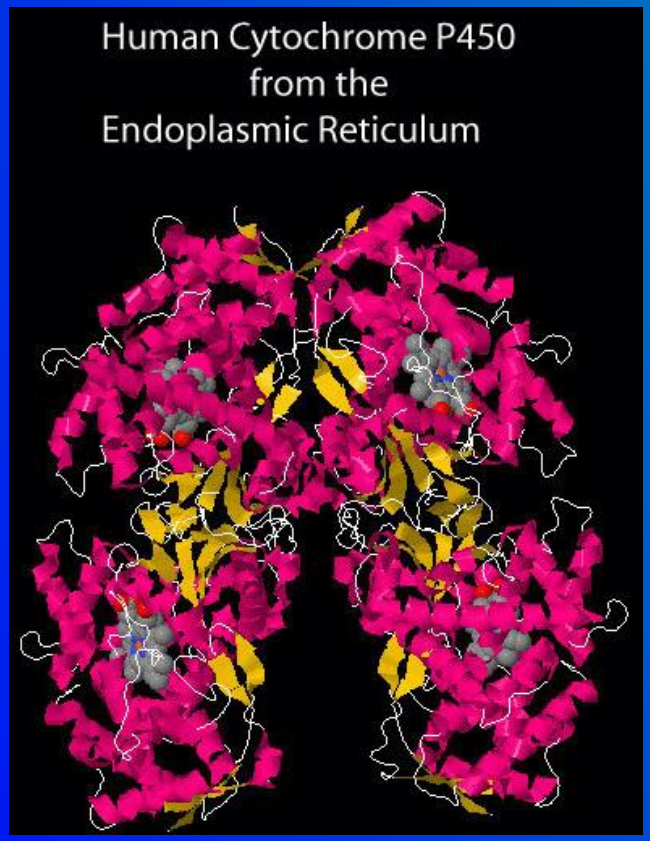


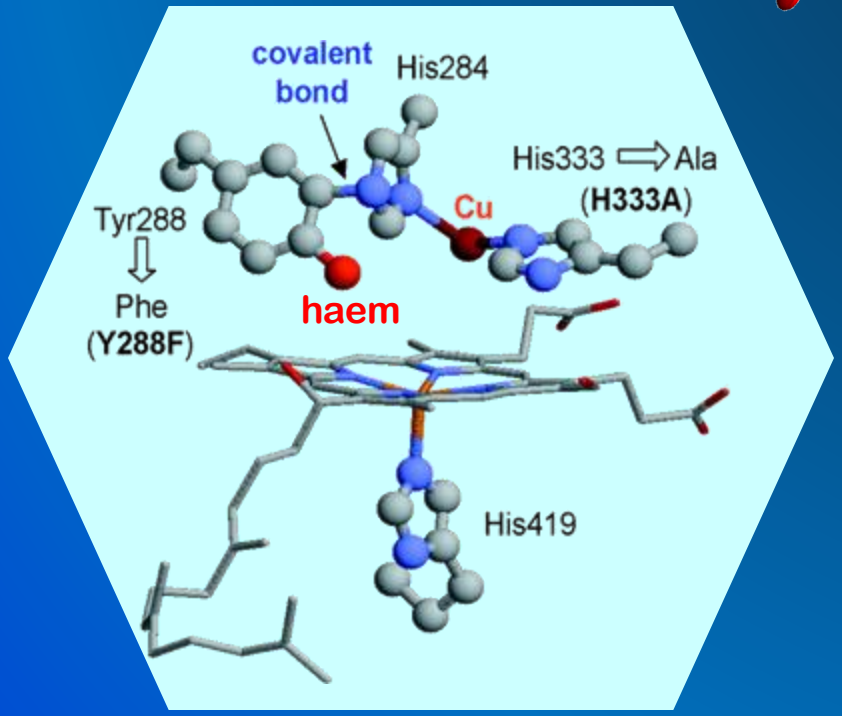
"Cytochrome" = colored cells They color the liver cells dark red as they contain iron

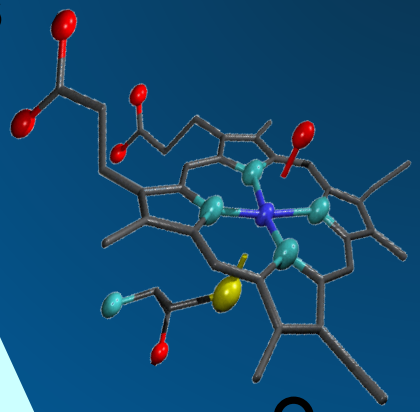
"P450" absorbs a very characteristic wavelength (450 nm) of UV light when it is exposed to carbon monoxide.

STRUCTURE

They are heme-containing isoenzymes







O_2
N_3
Cu
Fe

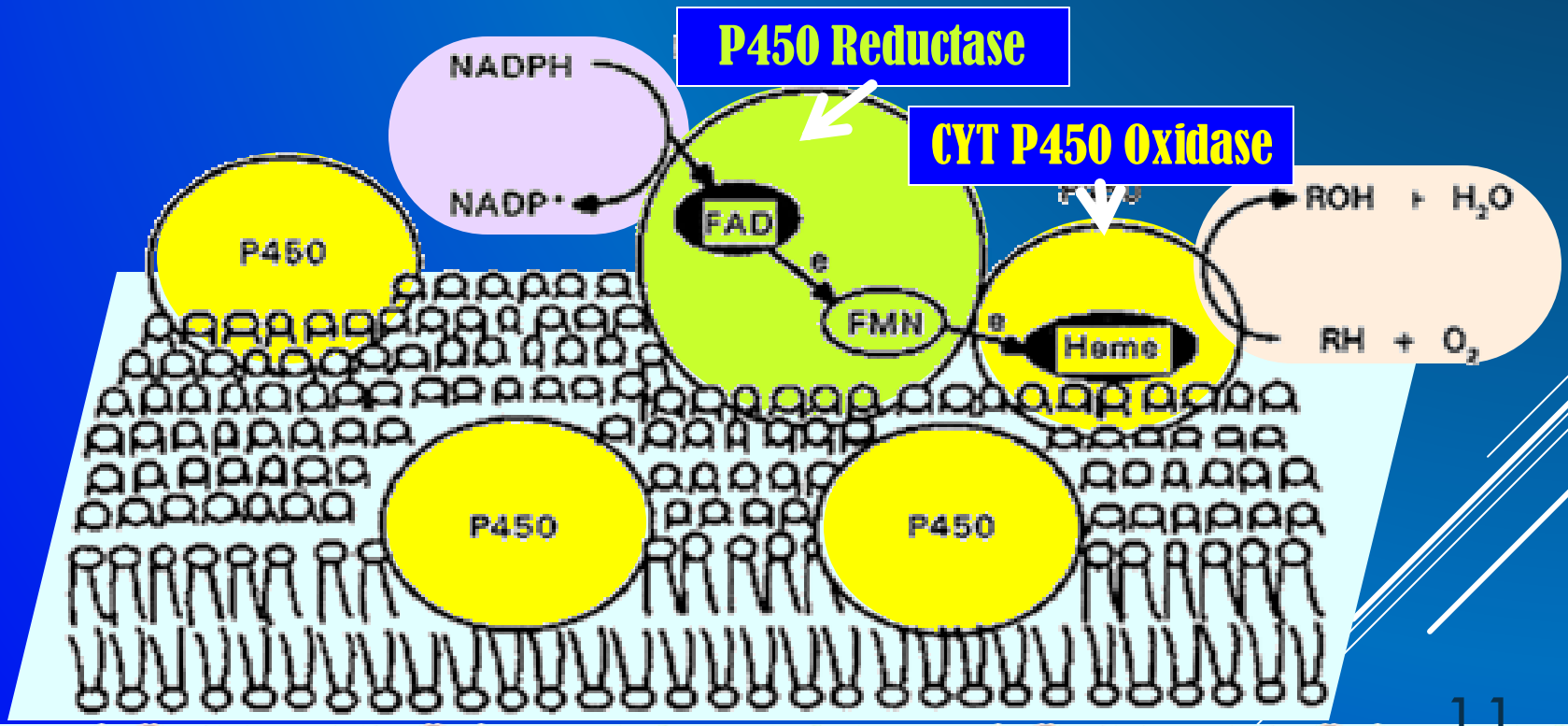
DISTRIBUTION

- 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.

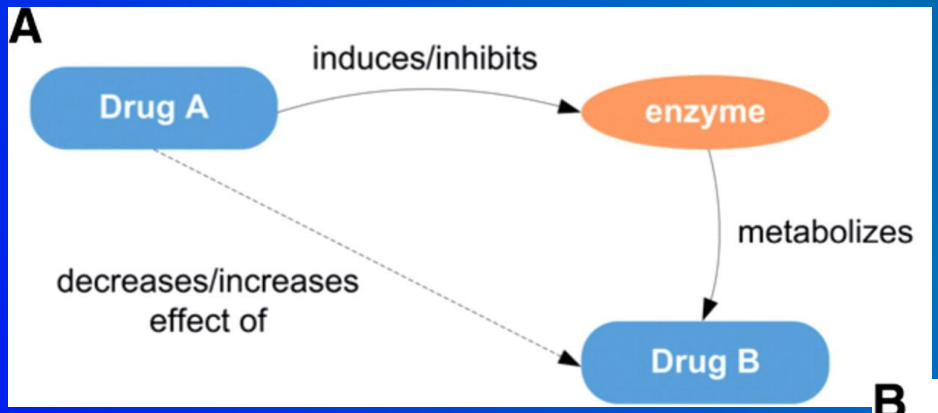
Substrates

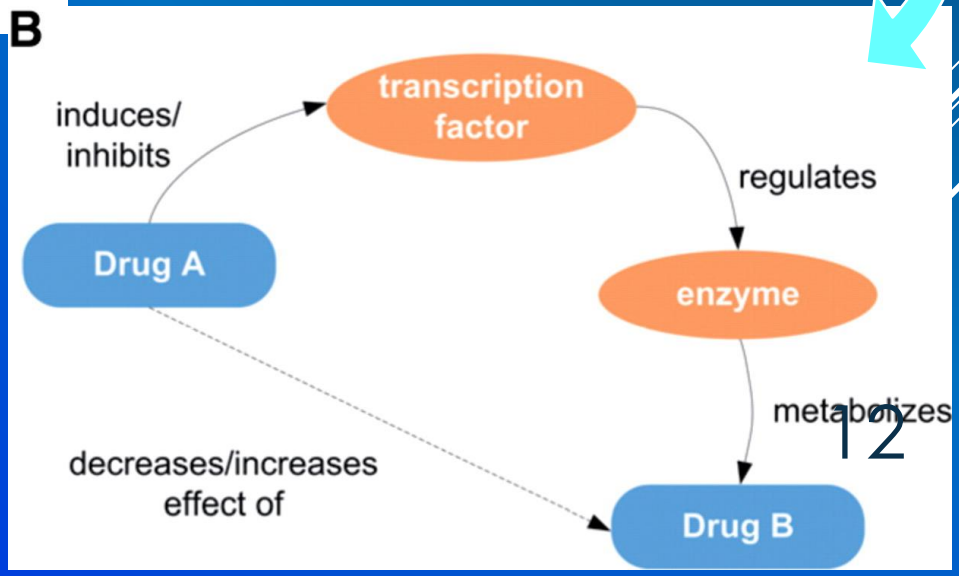


Regulation

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





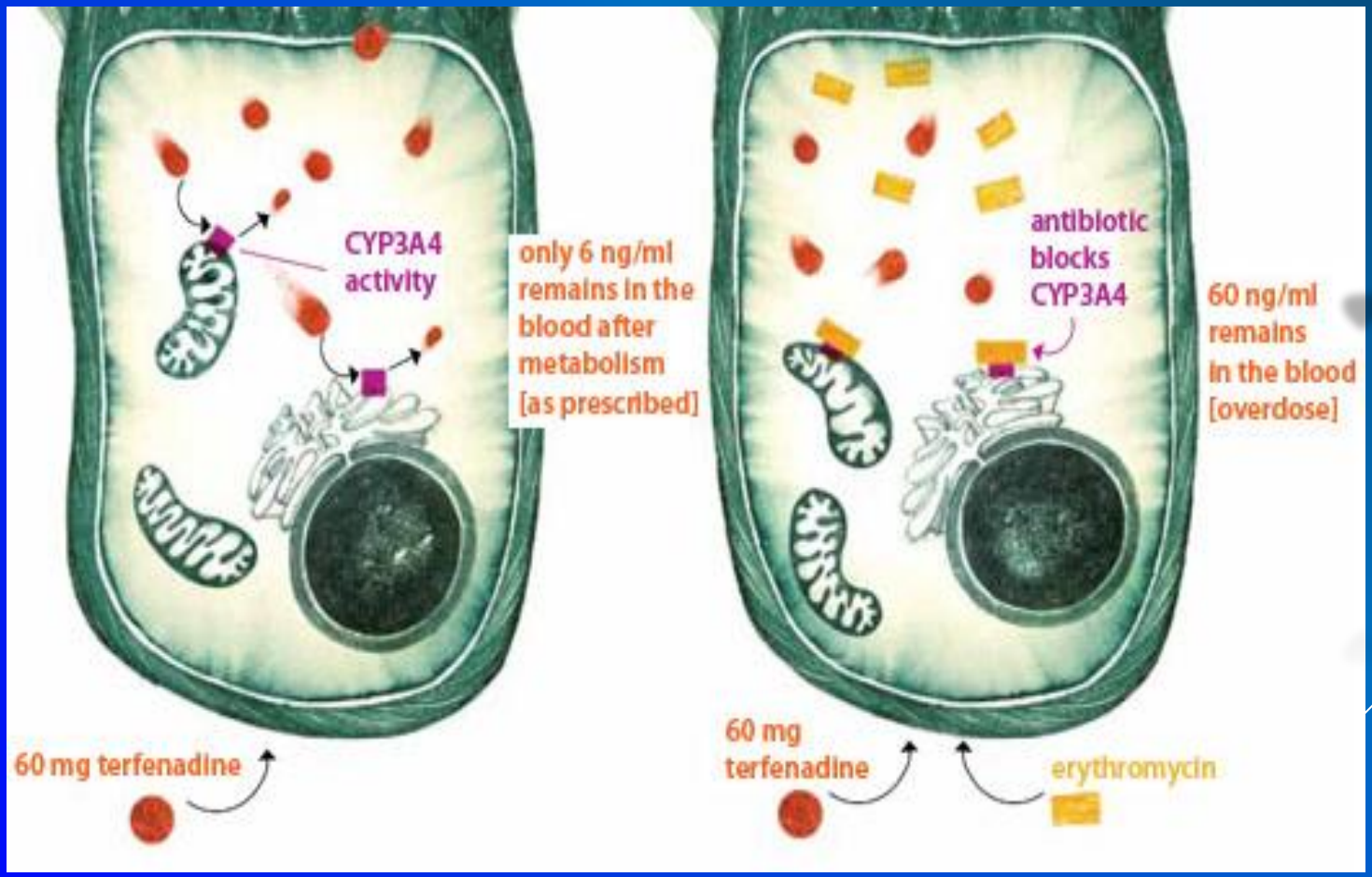
Activation or Inactivation can be processed by any food, intrinsic products or extrinsic xenobiotics as drugs (usually the lipophylic) that have to be metabolized.

Regulation

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

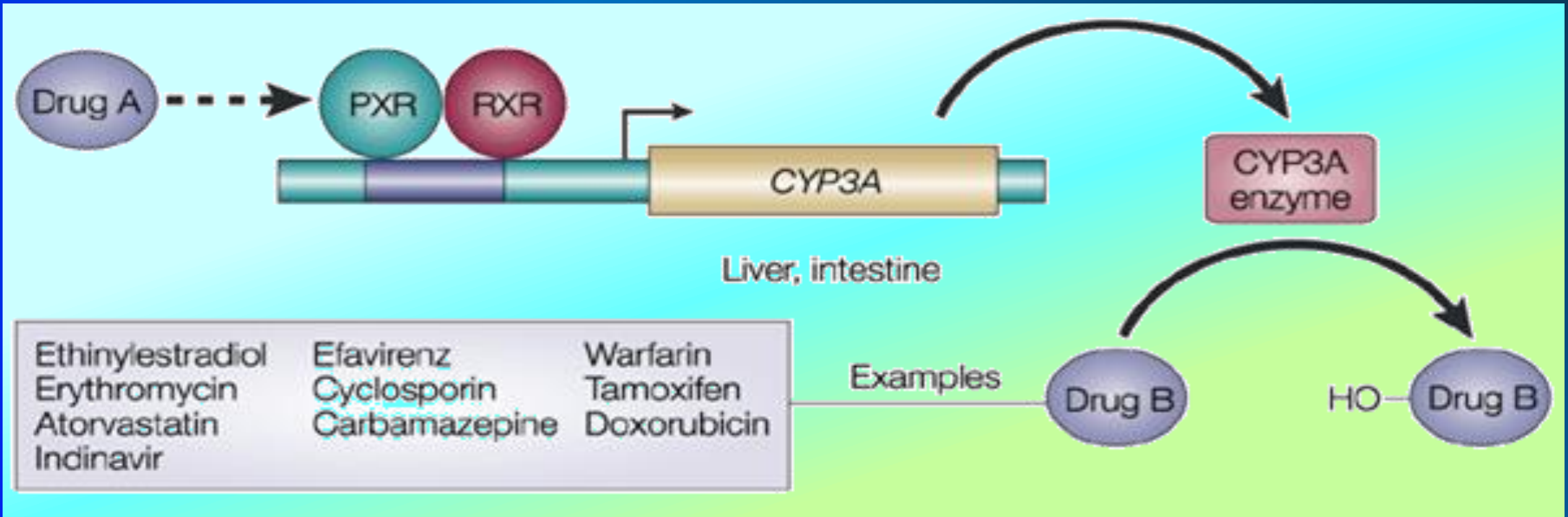
- Enzyme Inducers if Activate the enzyme
- Enzyme Inhibitors if Inactivate the enzyme

→ 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 into nucleus ➔ dimerize with RXR ➔ the heterodiamer 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 ➔ ↓ 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.

↑ TOXCICITY

Classification

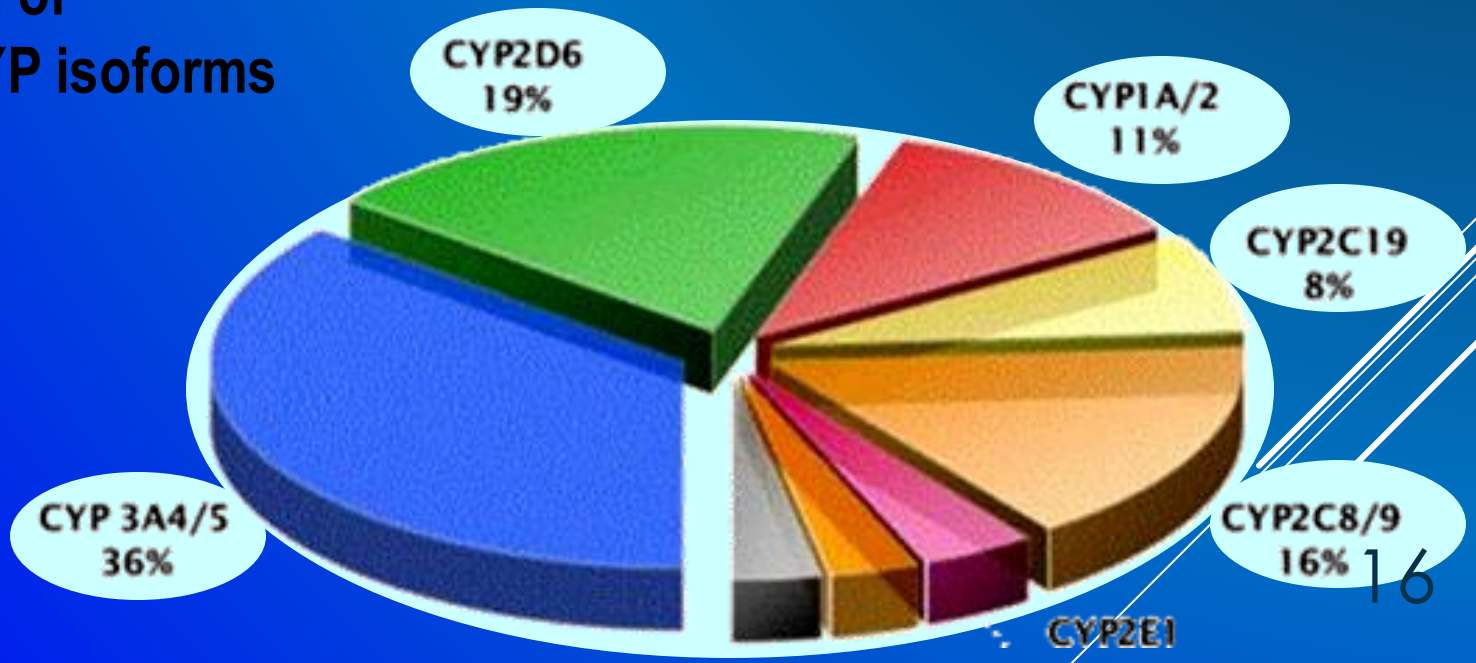
CYT P450 has been classified into

- Families designated by Numbers
- Sub families designated by Letters

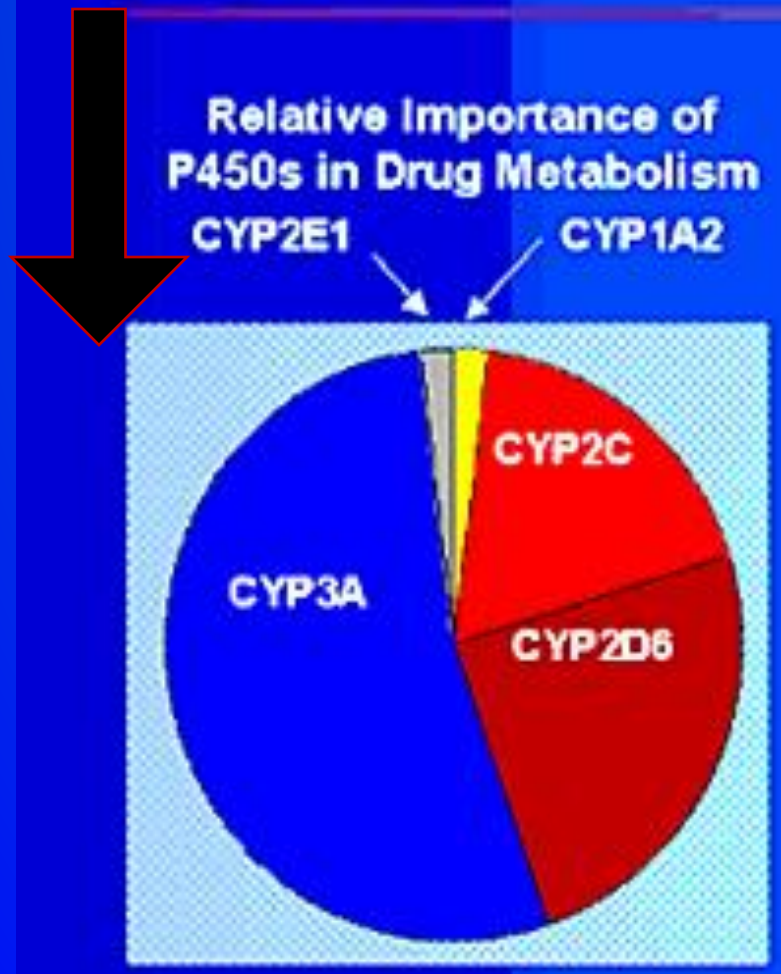
Cytochrome P450 Isoforms

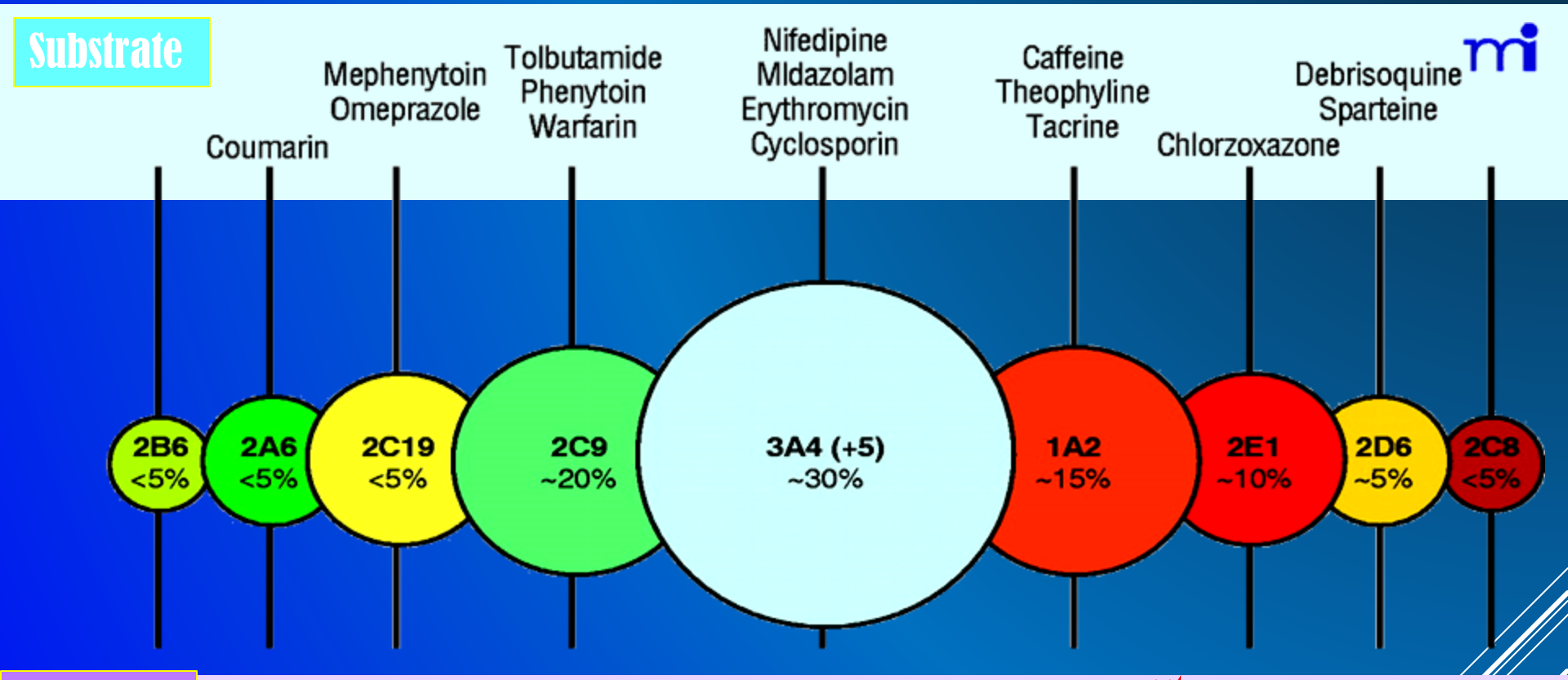
- CYP1A2
- CYP3A
- CYP2C9
- CYP2C19
- CYP2D6

Distribution of different CYP isoforms in the liver.



CYP450 → Major Contributor to Phase I Metabolism





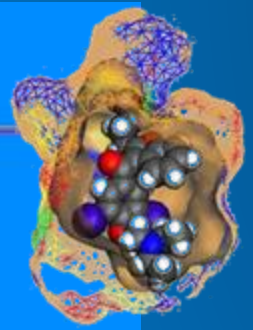
Inhibitors

Fluconazole
Methoxsalen
Sulfaphenazole
Ketoconzaole
Gestodene
Furafylline
Fluvoxamine
Disulfiram
Quinidine

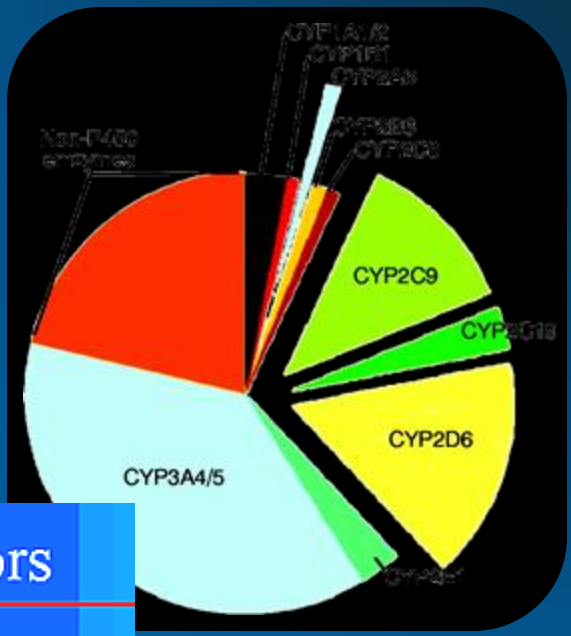
Inducers

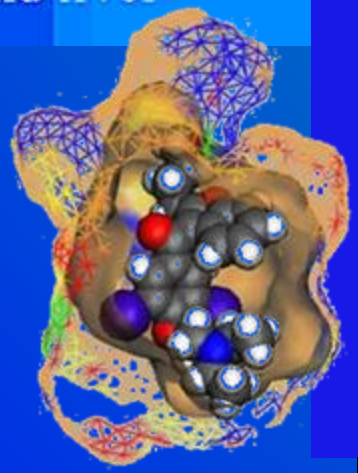
Barbiturates
Rifampicin
Barbiturates
Rifampicin
Barbiturates
Rifampicin
Dexamethasone
Carbamazepine
Omeprazole
Tobacco smoke
Ethanol
Isoniazid

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
- Ritonavir

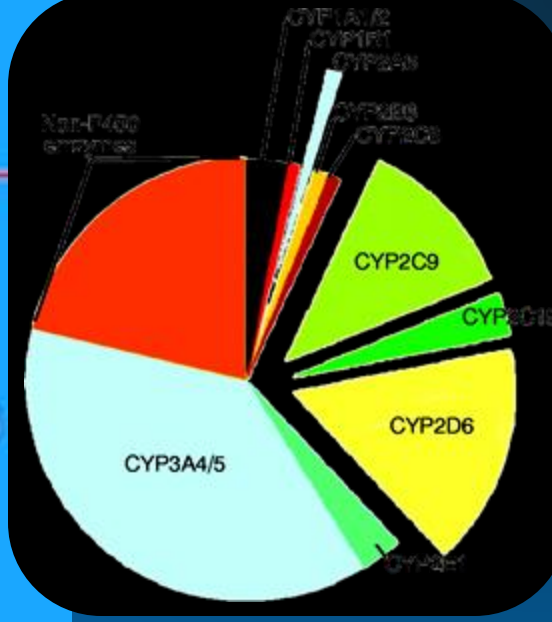
CYP3A Inducers

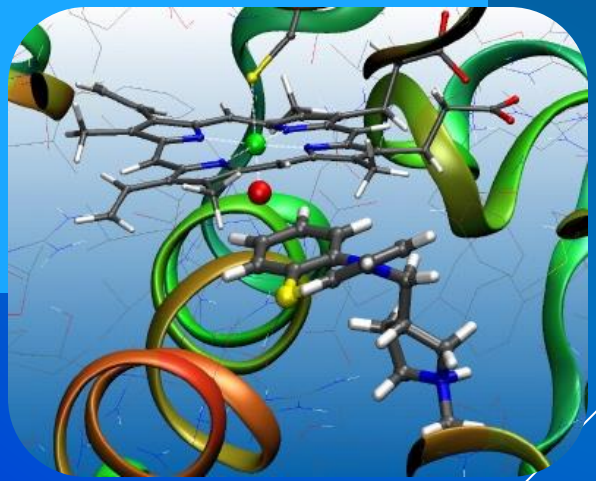
- Carbamazepine
- Rifampin
- Rifabutin

Cytochrome P450 3A4

Cytochrome P450 2D6

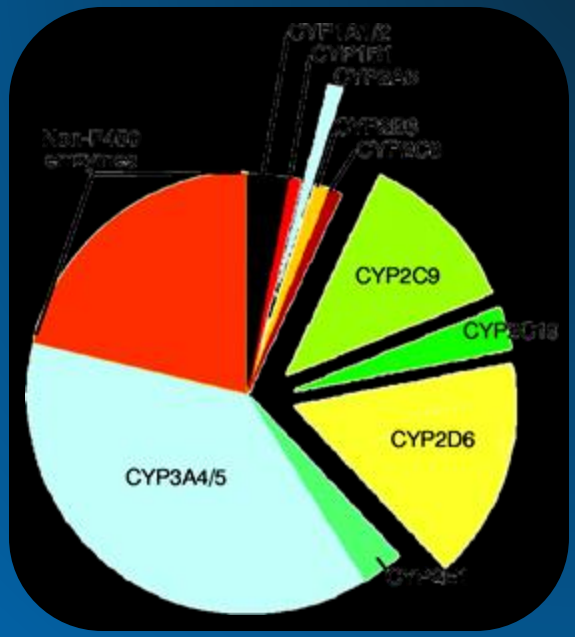
- Absent in 7% of Caucasians, 1–2% non-Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - Codeine
  - Many β-blockers
  - Many tricyclic antidepressants
- Inhibited by:
  - Fluoxetine
  - Haloperidol
  - Paroxetine
  - Quinidine

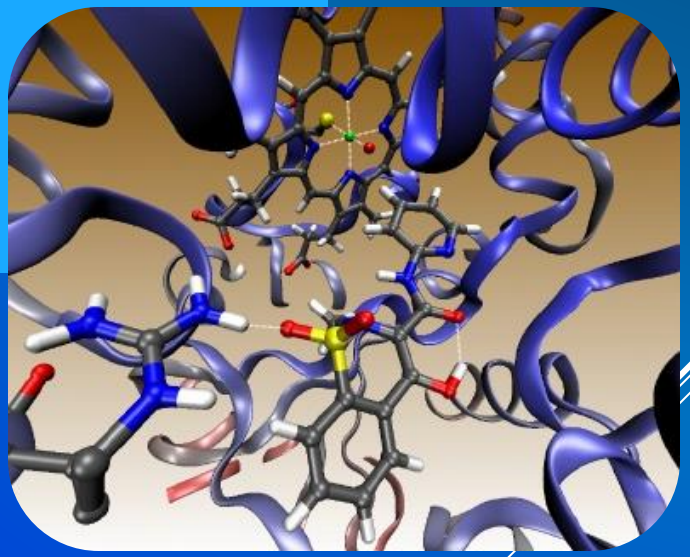




Cytochrome P450 2C9

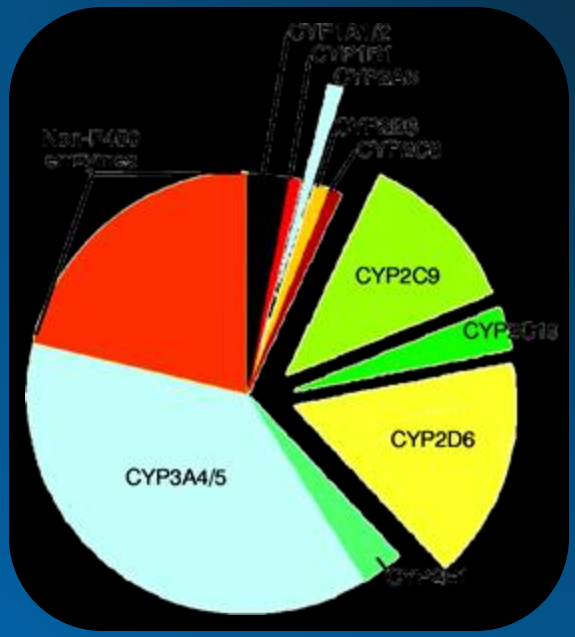
- Absent in 1% Caucasians and African-Americans
- Primary metabolism of:
  - Most NSAIDs (including COX-2)
  - S-warfarin (the active form)
  - Phenytoin
- Inhibited by:
  - Fluconazole

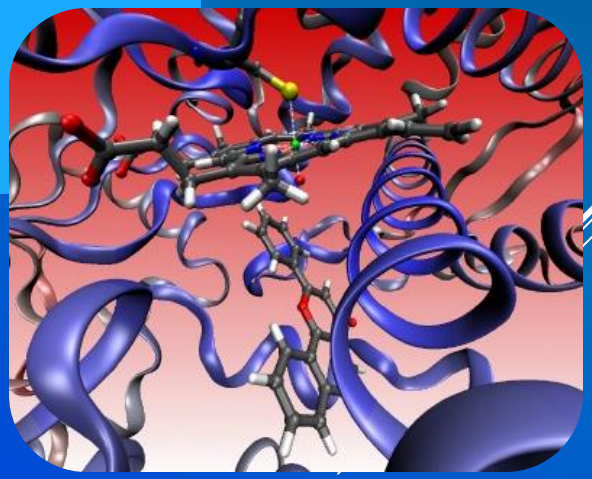




Cytochrome P450 1A2

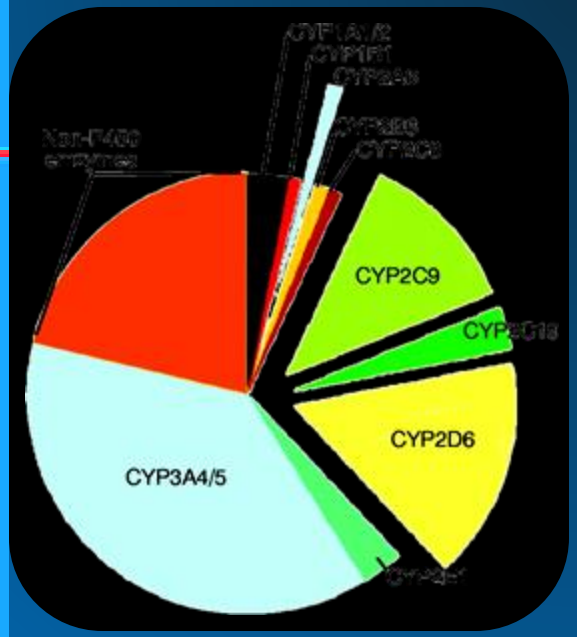
- Induced by smoking tobacco
- Catalyzes primary metabolism of:
  - Theophylline
  - Imipramine
  - Propranolol
  - Clozapine
- Inhibited by:
  - Many fluoroquinolone antibiotics
  - Fluvoxamine
  - Cimetidine

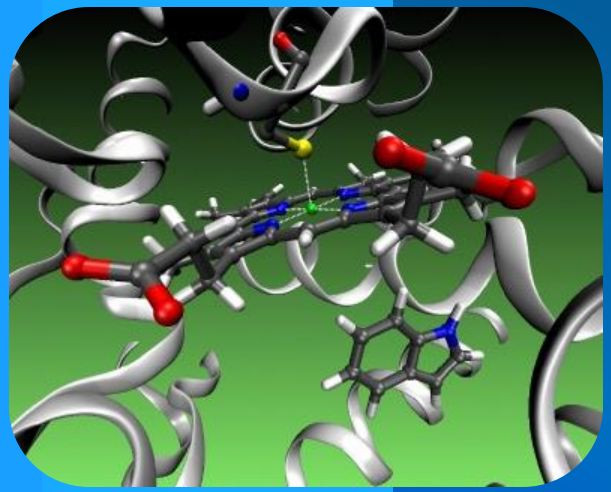




Cytochrome P450 2C19

- 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
• Immunosuppressants (Cyclosporine) • Azole Antifungals (Fluconazole) • Antibiotics (Erythromycin, Clarithromycin) • Ca channel blockers (Amlodepine, Verapamil) • Statins (Atorvastatin) • Cancer Chemotherapy (Cyclophosphamide, Tamoxifen) • Non-Sedating Antihistamines (Astemizole) • Benzodiazepines (Midazolam, Clonazepam).	Ritonavir Cimetidine Chlorampheni-col Nefazodone Grape Fruits	Phenytoin Carbamazepine Barbiturates Rifampicin Dexamethazone Progestins

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

He receives daily multivitamins & 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 rhabdo-myositis (severe musculoskeletal toxicity) & 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 + Atorvastatin

Atorvastatin + Fluconazole

Metformin + Fluconazole

Fluconazole+ Multivitamins

Genetic Variation

Genetic polymorphisms in CYT P450 isoenzymes have been observed & 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, antianginal agents (perhexiline), antiarrhythmics (propafenone & metoprolol) is suppressed ➔ so side effects & toxicity develop. i.e.
   - Neuropathy after therapeutic doses of perhexiline
   - Bradycardia & arrhythmias on therapeutic dose of propafenone or metoprolol
2. The pro-drugs cannot be converted to their therapeutically active metabolite; e.g poor analgesia with codeine & tramadol 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

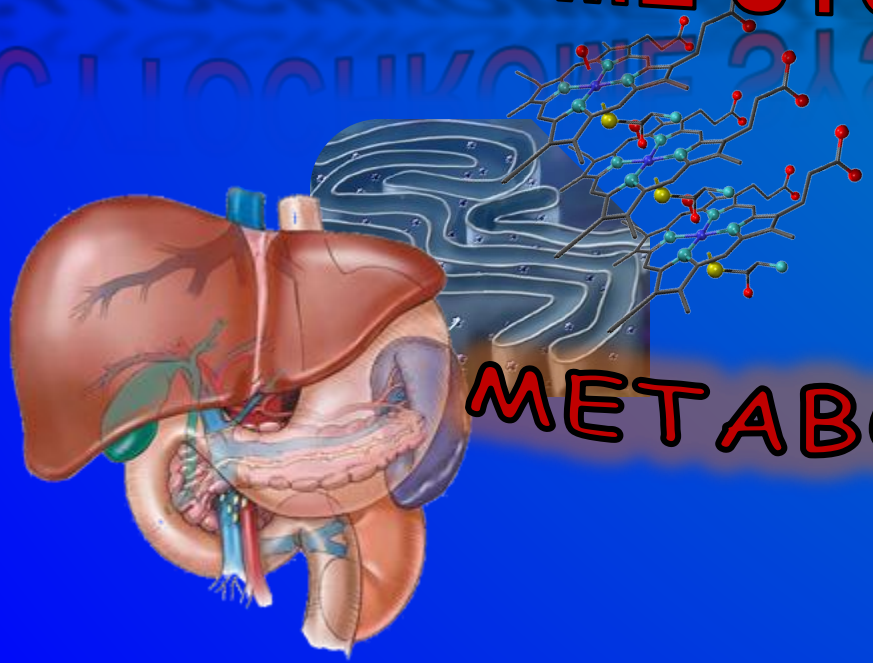
CYP2C19

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

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

Benefit

CYTOCHROME SYSTEM



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DRUG METABOLISM

GOODLUCK