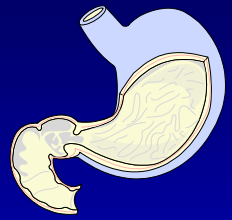
Why do need Cox-2 inhibitors ?

Conventional AINS are toxic ...

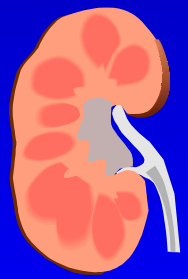
Adverse Effects of common NSAIDs

Upper - GI



- Dyspepsia
- Erosions
- Anaemia - GI bleeding
- Ulcers - bleeds/perforations

Renal

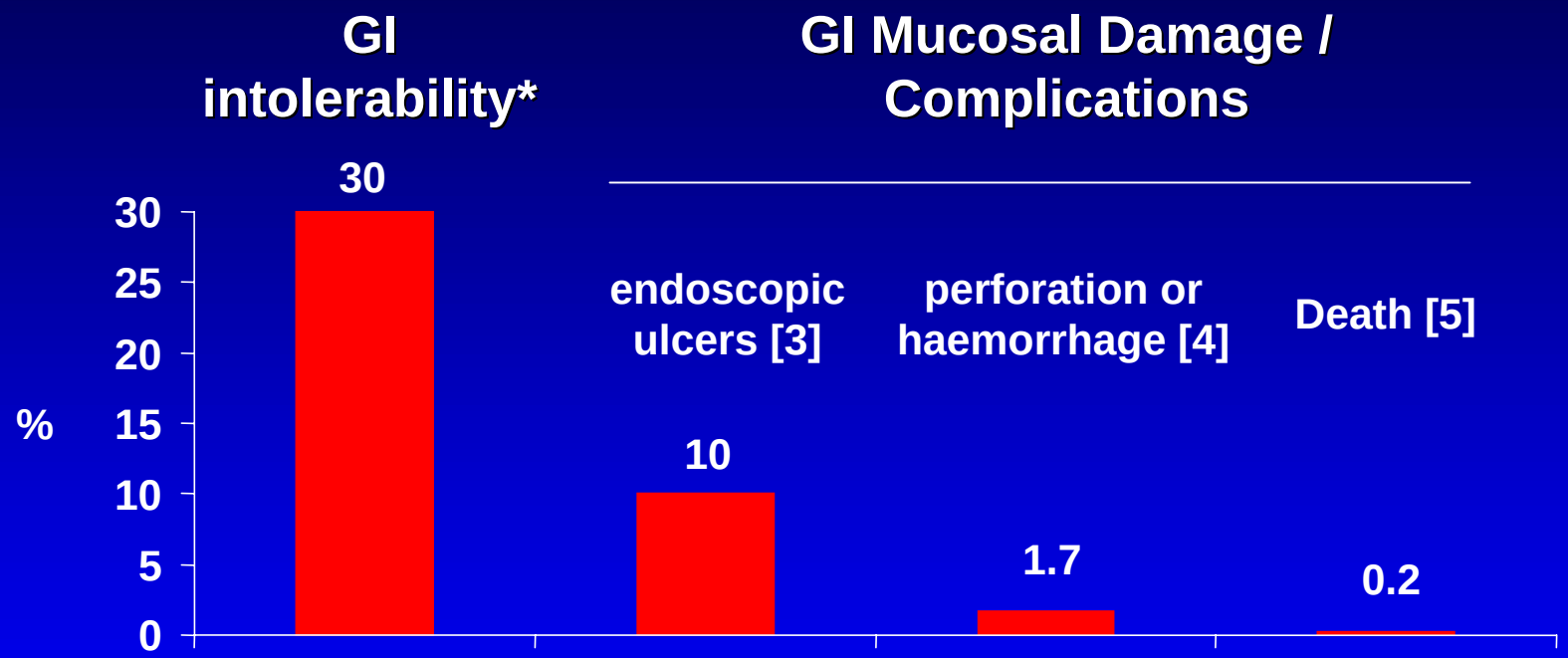


- Renal dysfunction
- Renal failure - acute/chronic
- Blood pressure
- Heart failure

Anti-platelet effects

- Contributes to blood loss

NSAIDs toxicity



* Range 20-50% based on
- withdrawals for GI symptoms[1]
- community surveys for GI symptoms[2]

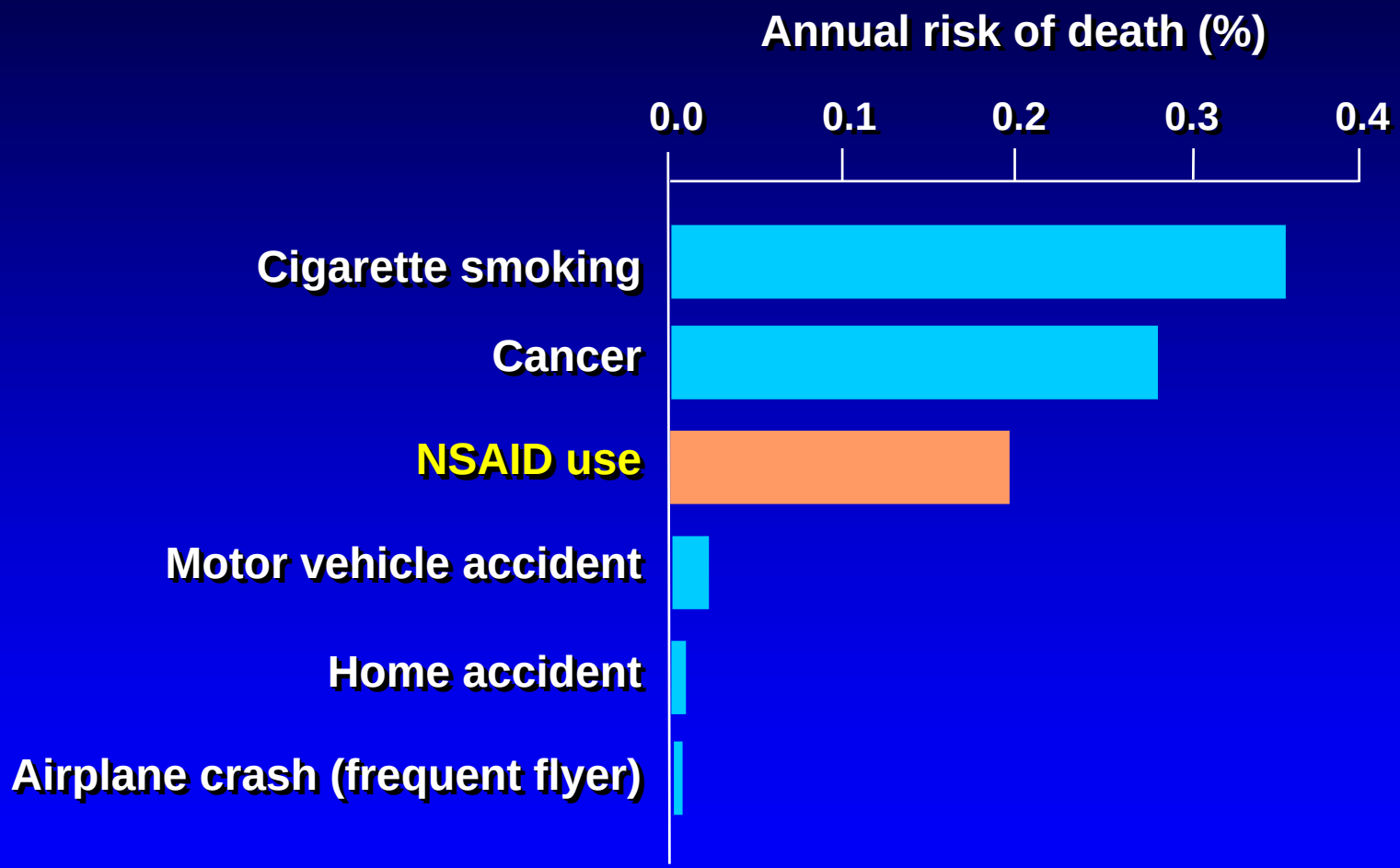
1. Kiff et al, Eur J Rheumatol, 1994; 2. Hardo et al, BJCP, 1993; 3. Graham DY et al, Am J Gastroenterol 1988;
4. Silverstein et al, Ann Int Med, 1995; 5. Blower et al, Aliment Pharmacol, 1997

NSAID Ulcers and Ulcer Complications

- **Endoscopic ulcer point prevalence: 10-30%**
- **Ulcer complications: 2-4% per year**
- **Most (>80%) hospitalizations for GI bleed occur without previous symptoms**
- **Inhibition of prostaglandin synthesis is principal mechanism for GI damage**
- **Use of antacids or H2 antagonists do not prevent NSAID induced gastric ulcers**

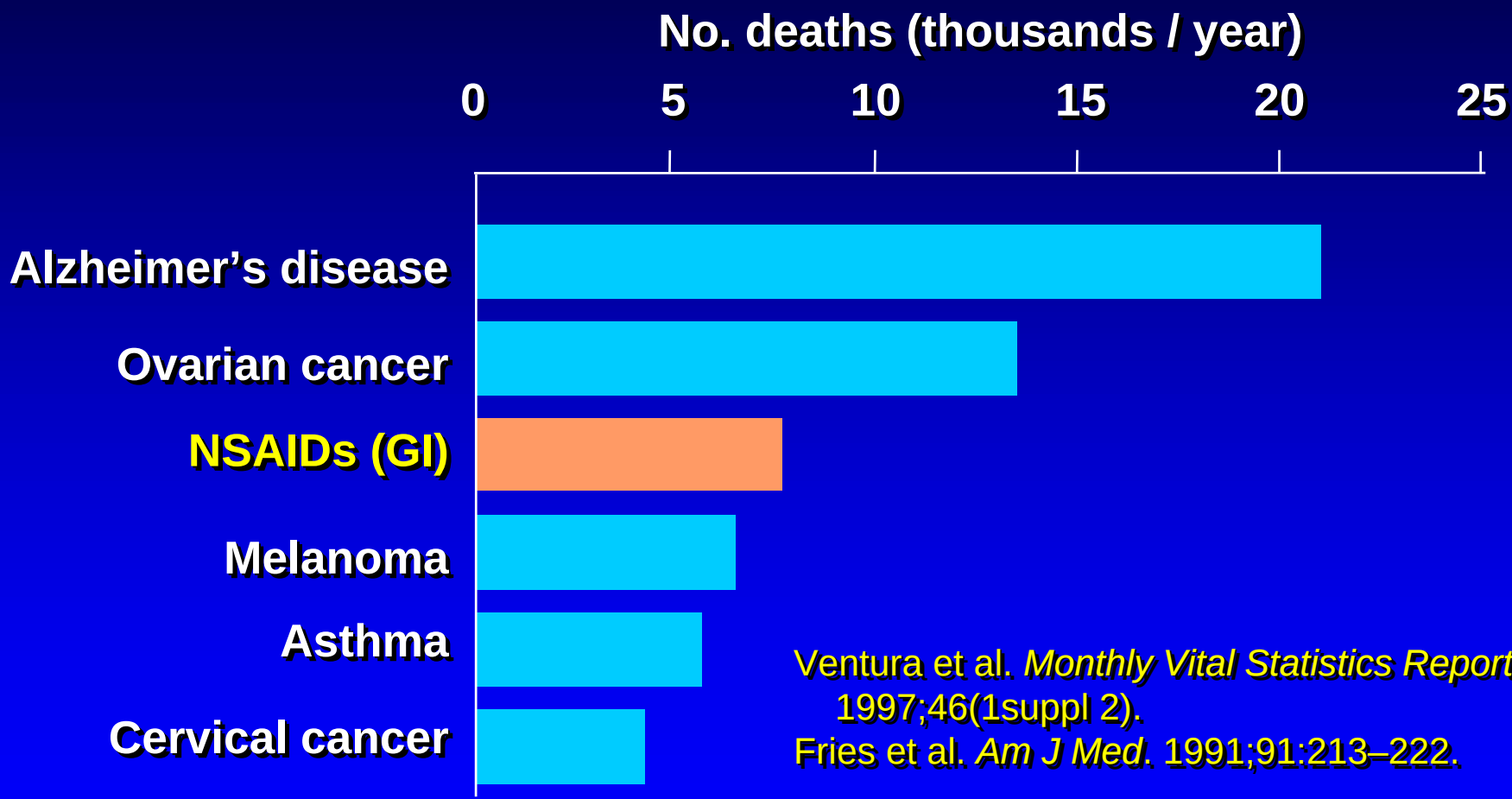
Singh G et al. *Am J Med* 1998;105(1B):31S-8S.
Geis GS et al. *J Rheumatol* 1991;18:11-14.

GI mortality associated with typical NSAIDs vs other causes in US (1of 2)



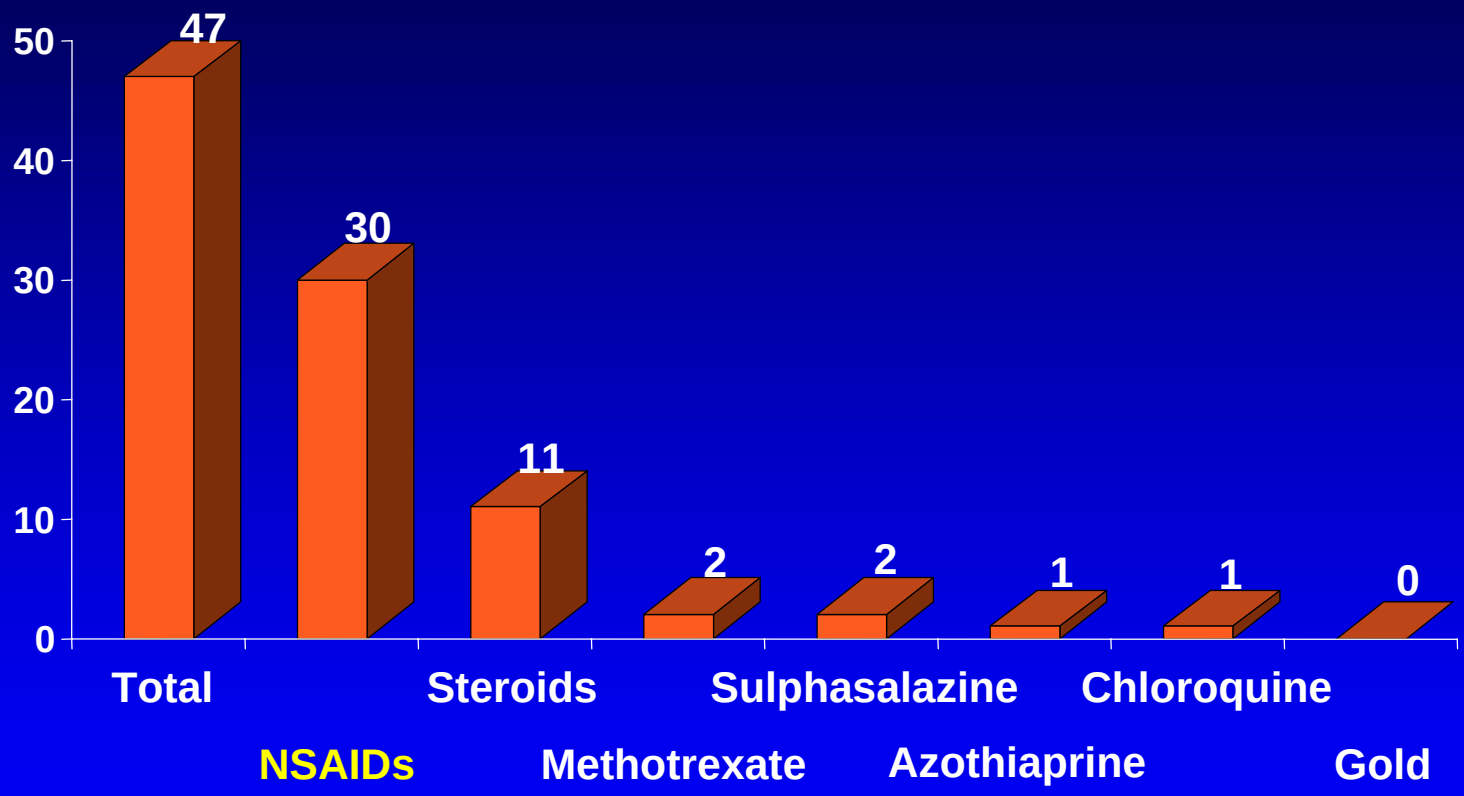
Fries et al. *Am J Med*. 1991;91:213–222;
Wilson, Crouch. *Science*. 1987;236:267–270.

GI mortality associated with typical NSAIDs vs other causes in US (2 of 2)



Ventura et al. *Monthly Vital Statistics Report*. 1997;46(1suppl 2).
Fries et al. *Am J Med*. 1991;91:213–222.

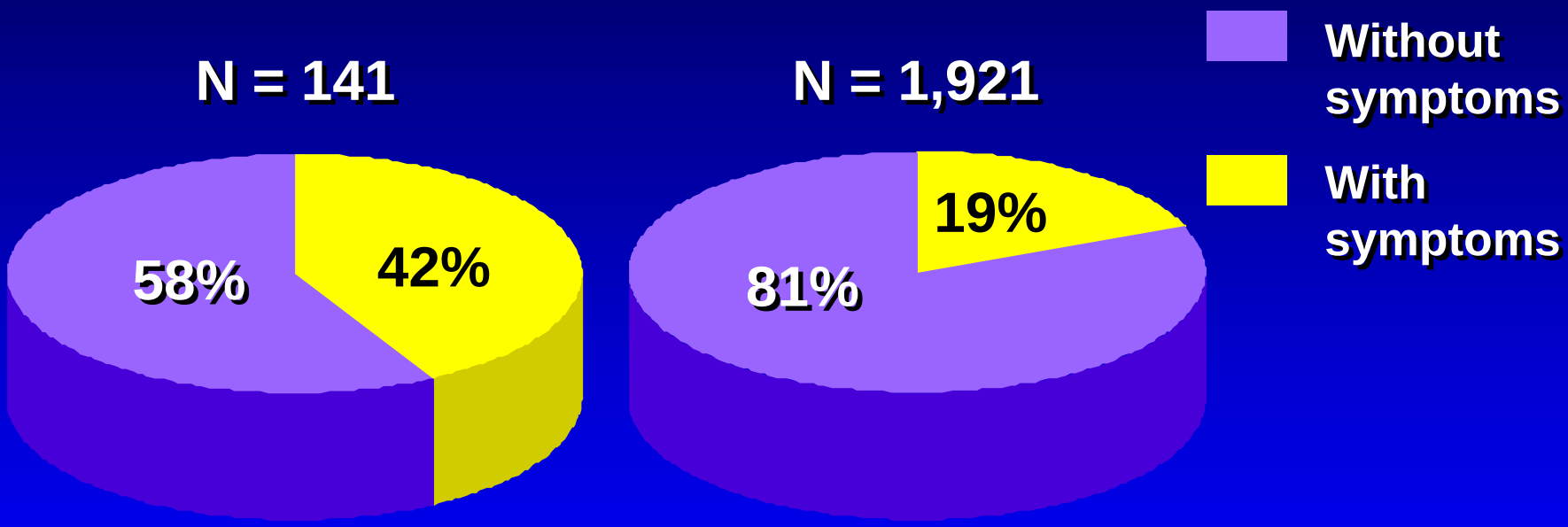
Deaths attributed to anti-rheumatic medication (series of 1666 patients with RA)



Myllykangas-Luosujarvi, J Rheum, 1995, 22, 2214-7

Most patients are asymptomatic prior to a serious NSAID-associated GI event ...

Bleeding, perforation, and gastric outlet obstruction



Armstrong &Blower. *Gut*. 1987;28:527–532.

Singh et al. *Arch Intern Med*. 1996;156:1530-1536.

*NSAIDs - Relative Risk of GI Complications

Drug	Relative Risk (95% C.I.)
None	**1**
Ibuprofen	**2.1** (0.6 - 7.1)
Diclofenac	**2.7** (1.5 - 4.8)
Other NSAID (n=16)	**2.9** (1.4 - 6.3)
Ketoprofen	**3.2** (0.9 - 11.9)
Naproxen	**4.3** (1.6 - 11.2)
Tenoxicam	**4.3** (1.9 - 9.7)
Nimesulide	**4.4** (2.5 - 7.7)
Indomethacin	**5.5** (1.6 - 18.9)
Piroxicam	**9.5** (6.5 - 13.8)
Ketorolac	*24.7* *(9.6 - 63.5)*

* Rodriguez et al, Arch Intern Med, 1998, 158, 33-39

Upper GI complications in Europe

- **1000 people are hospitalised <u>every day</u> for upper GI bleeds in Europe (~400 million population)**
- **In 400 of these 1000 patients the bleed (or perforation) will be directly attributable to NSAIDs**
- **100 (10%) of these 1000 will die from their complications**

Calculated from :
Blower AL et al, Aliment Pharmacol Ther, 1997, 11, 283-291
MacDonald T et al, BMJ, 1997, 315, 1333-1337

This is why ...

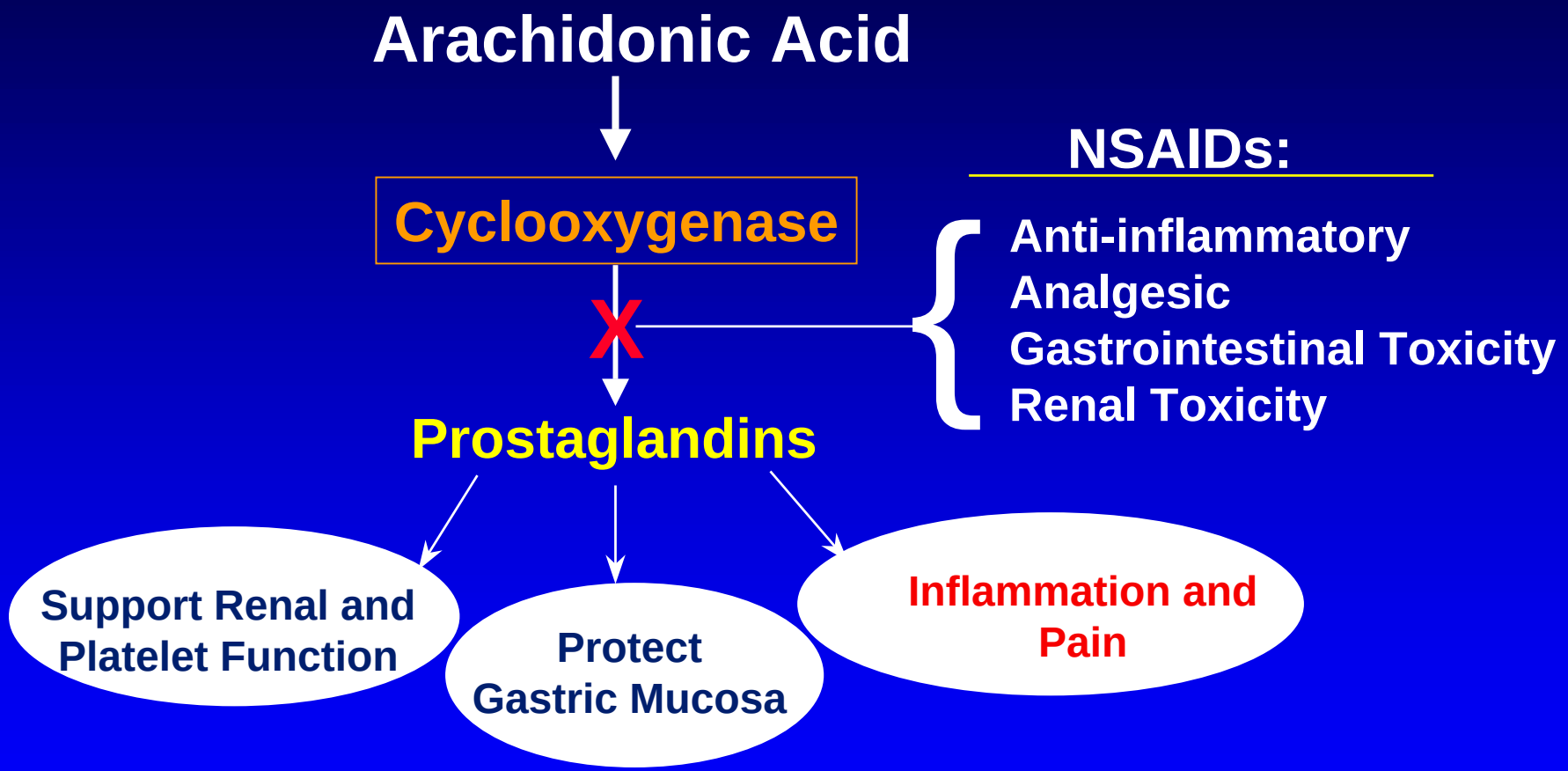
"Toxicity is the major reason for not recommending the use of NSAIDs as first-line therapy for patients with OA of the hip ….."

Osteo-arthritis hip, Management Guidelines
Hochberg et al, 1995, Arthritis & Rheumatism

Towards new medications ...

Discovery of cyclooxygenase-2 and
of cyclooxygenase-2 specific inhibitors

Role of cyclooxygenase

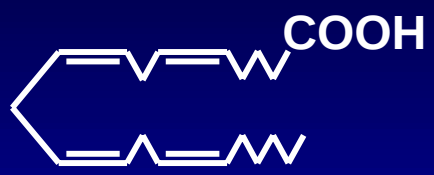


Shorrock CJ et al. *Am J Med* 1988;84 (Suppl):25-34.

The Discovery of the role of cyclooxygenase

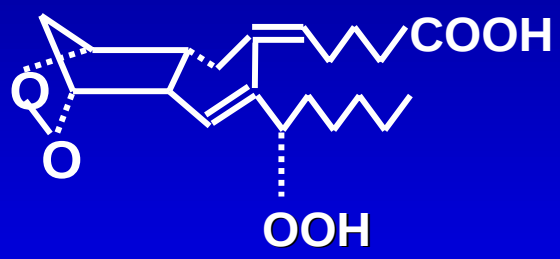
- **1898 … aspirin introduced**
- **1950s … corticosteroids introduced**
  - » **anti-inflammatory**
  - » **significant side effects**
- **1960s … NSAIDs introduced**
- **1971 … mode of action of NSAIDs explained on basis of COX inhibition (Vane)**
  - » **platelet activity induced by COX**
  - » **inhibited by aspirin and other NSAIDs**

Conversion of arachidonic acid to prostaglandins



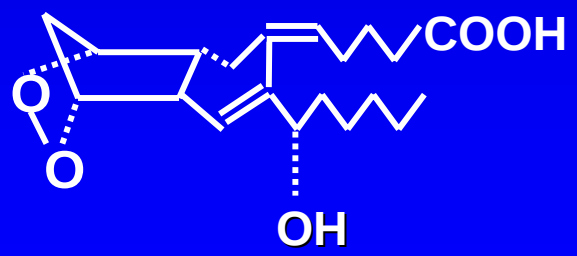
Arachidonic Acid

$2\ O_2$ → **Cyclooxygenase**



PGG_2

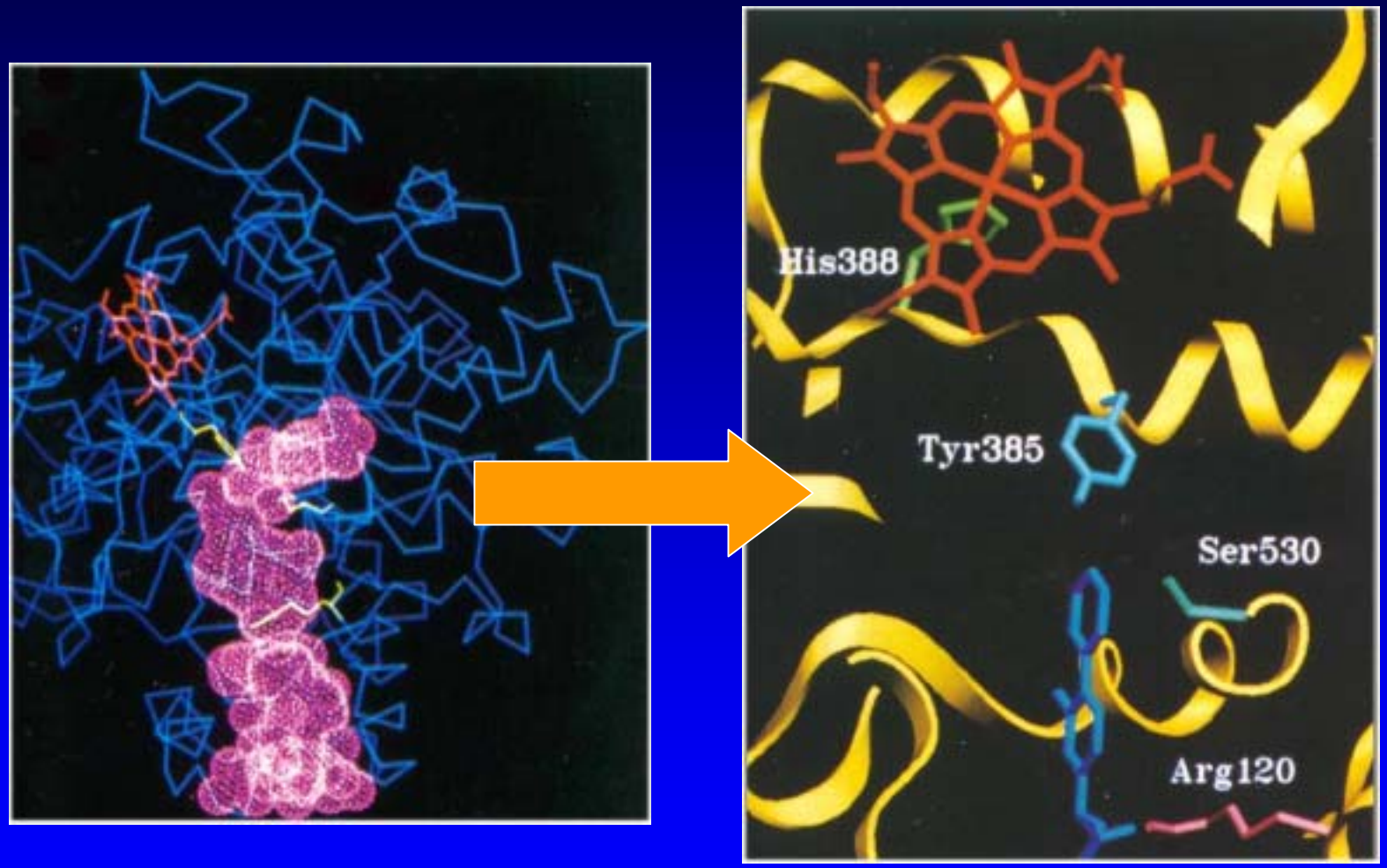
$2\ e^-$ → **Hydroperoxidase**



PGH_2 → **prostanoids**

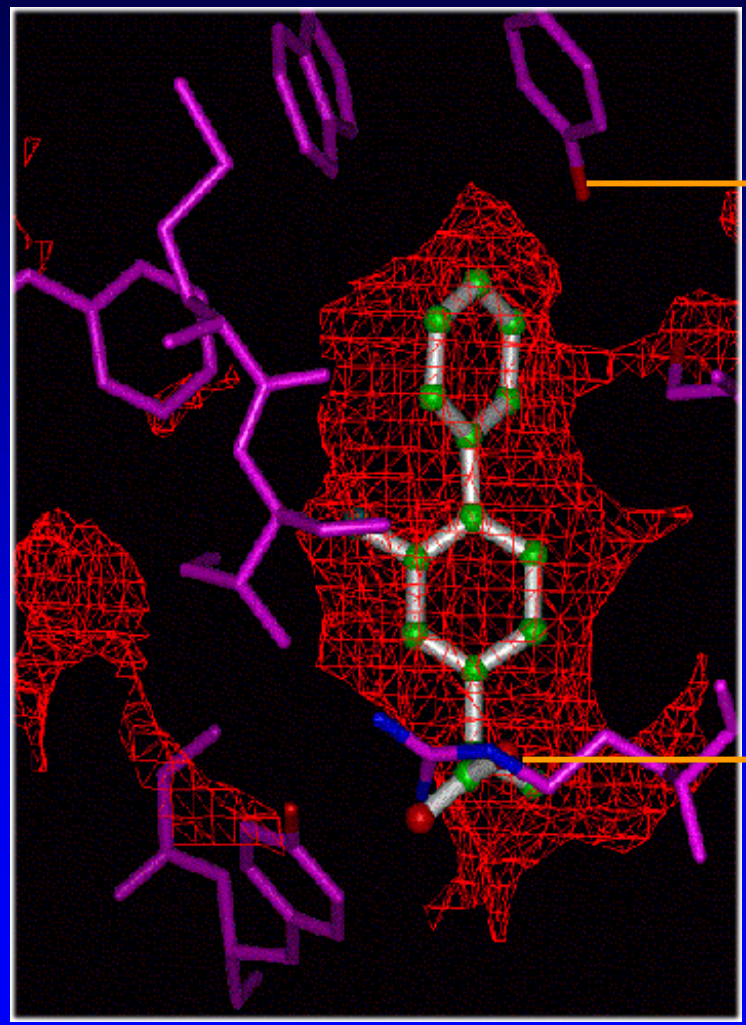
- **prostaglandins**
- **thromboxans**

Mapping of the cyclooxygenase active site



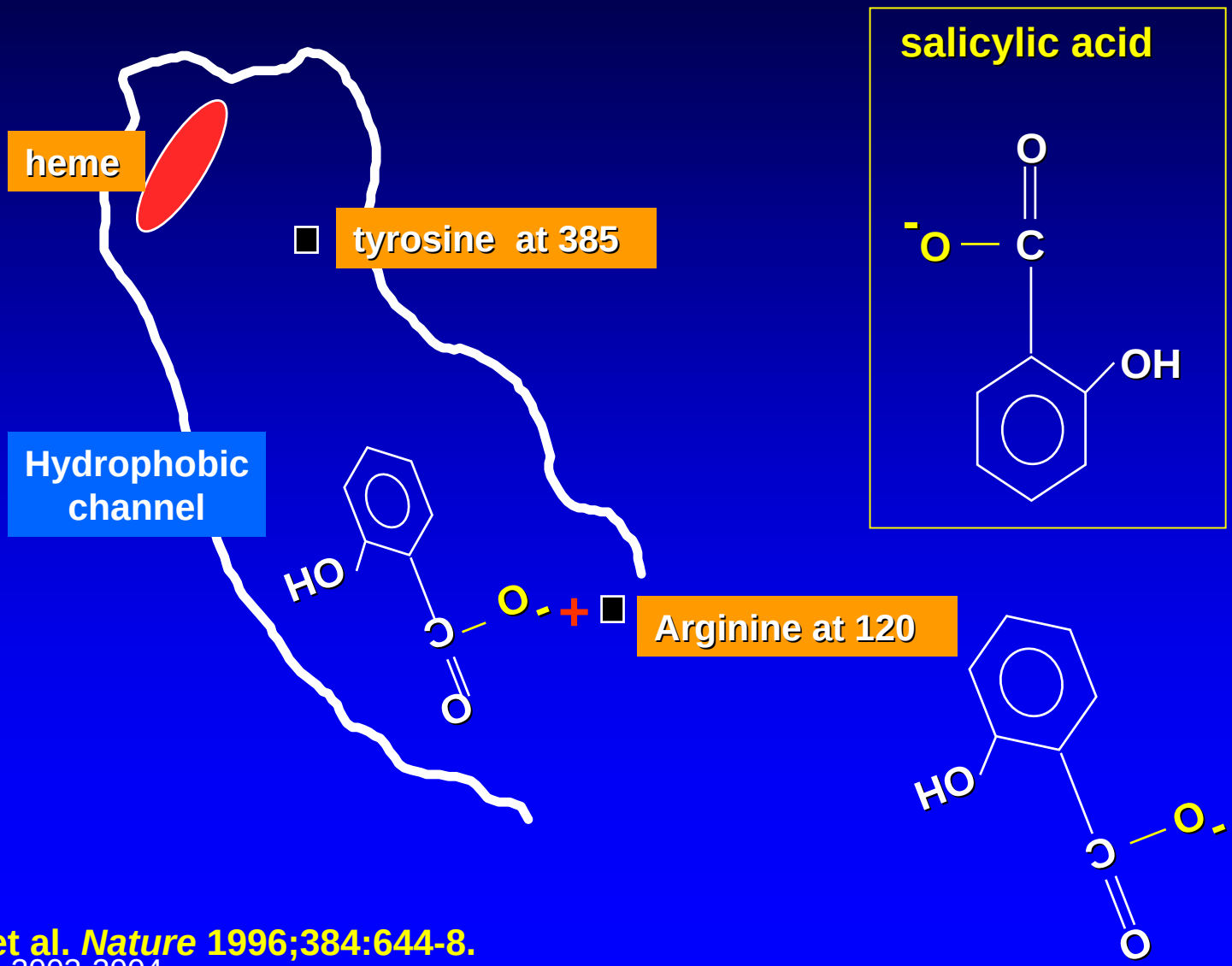
Mapping of the cyclooxygenase active site

COX-1 Active Site occupied by flurbiprofen



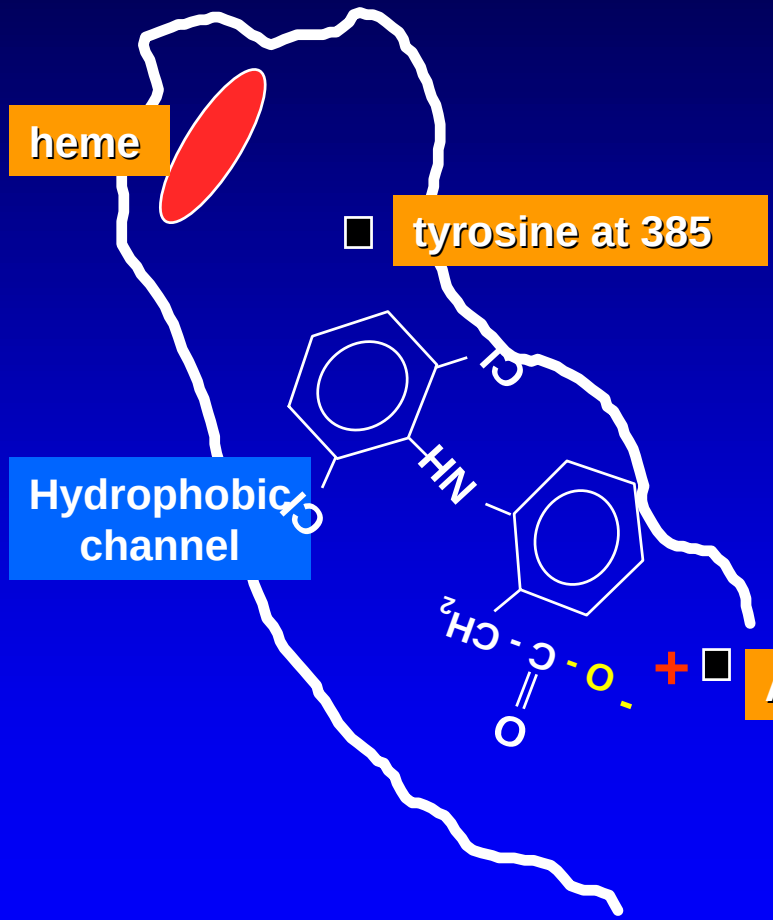
Picot, Loll and Garavito: Nature 1994; 367:243.

All conventional NSAIDs have a similar mechanism of action ...

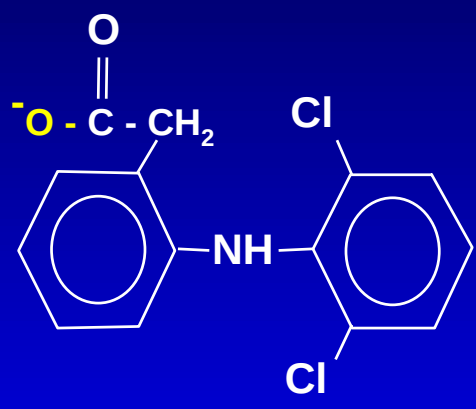


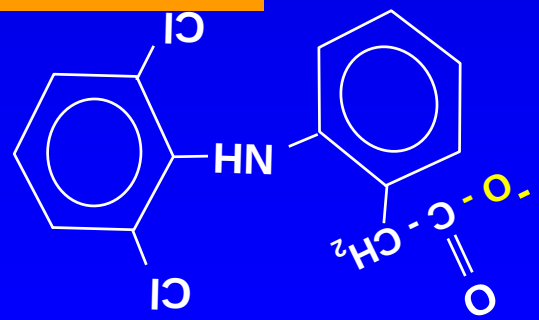
Kurumbail RG et al. *Nature* 1996;384:644-8.

All conventional NSAIDs have a similar mechanism of action ...



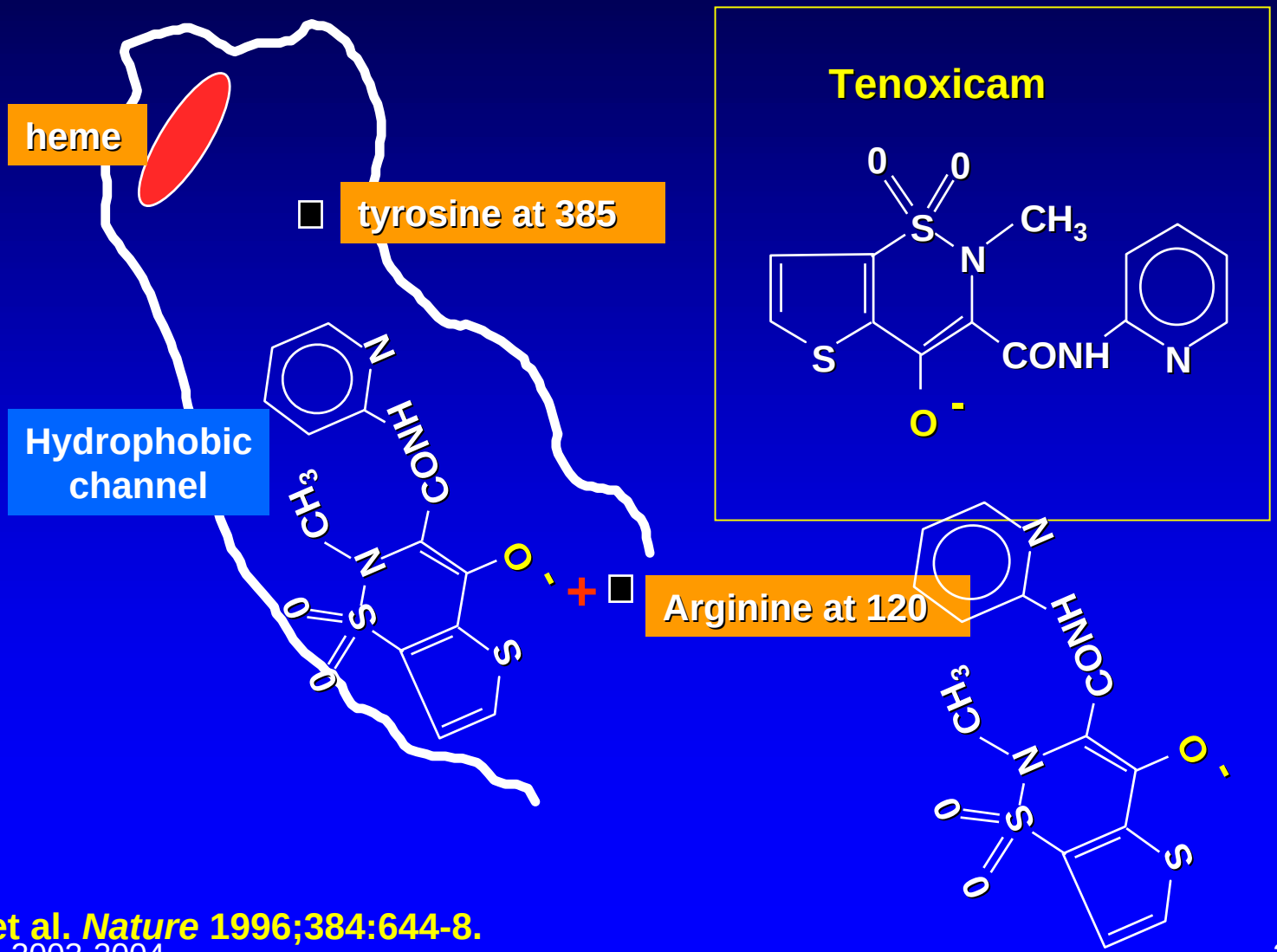
Diclofenac





Kurumbail RG et al. *Nature* 1996;384:644-8.

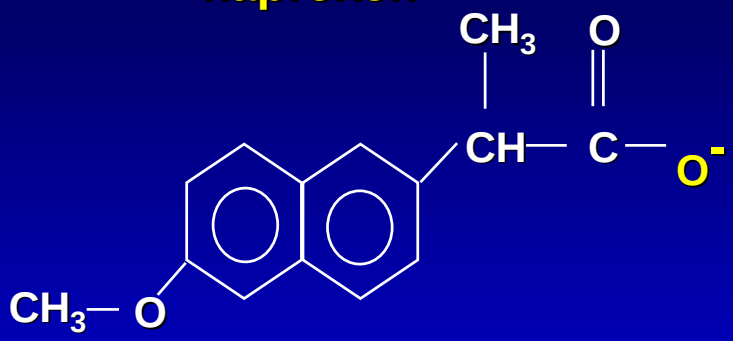
All conventional NSAIDs have a similar mechanism of action ...



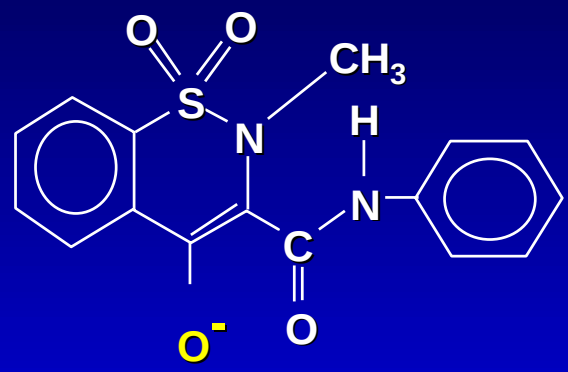
Kurumbail RG et al. *Nature* 1996;384:644-8.

Similarities of structures ...

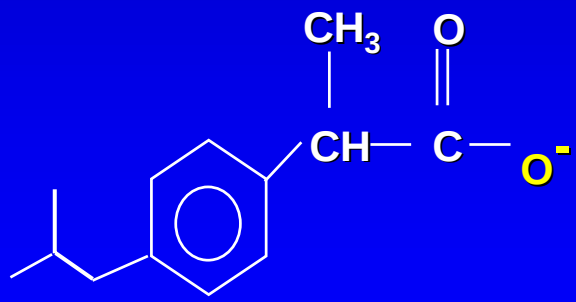
naproxen



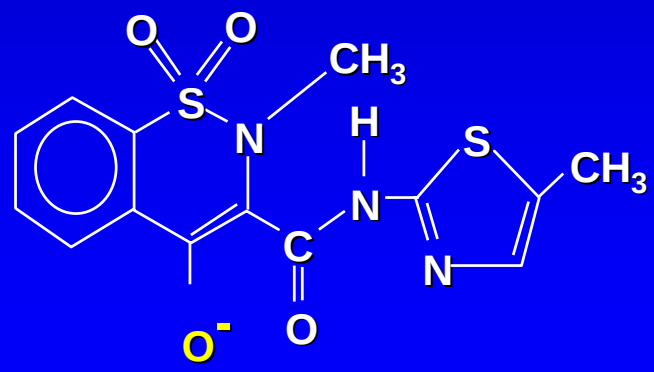
piroxicam



ibuprofen



meloxicam

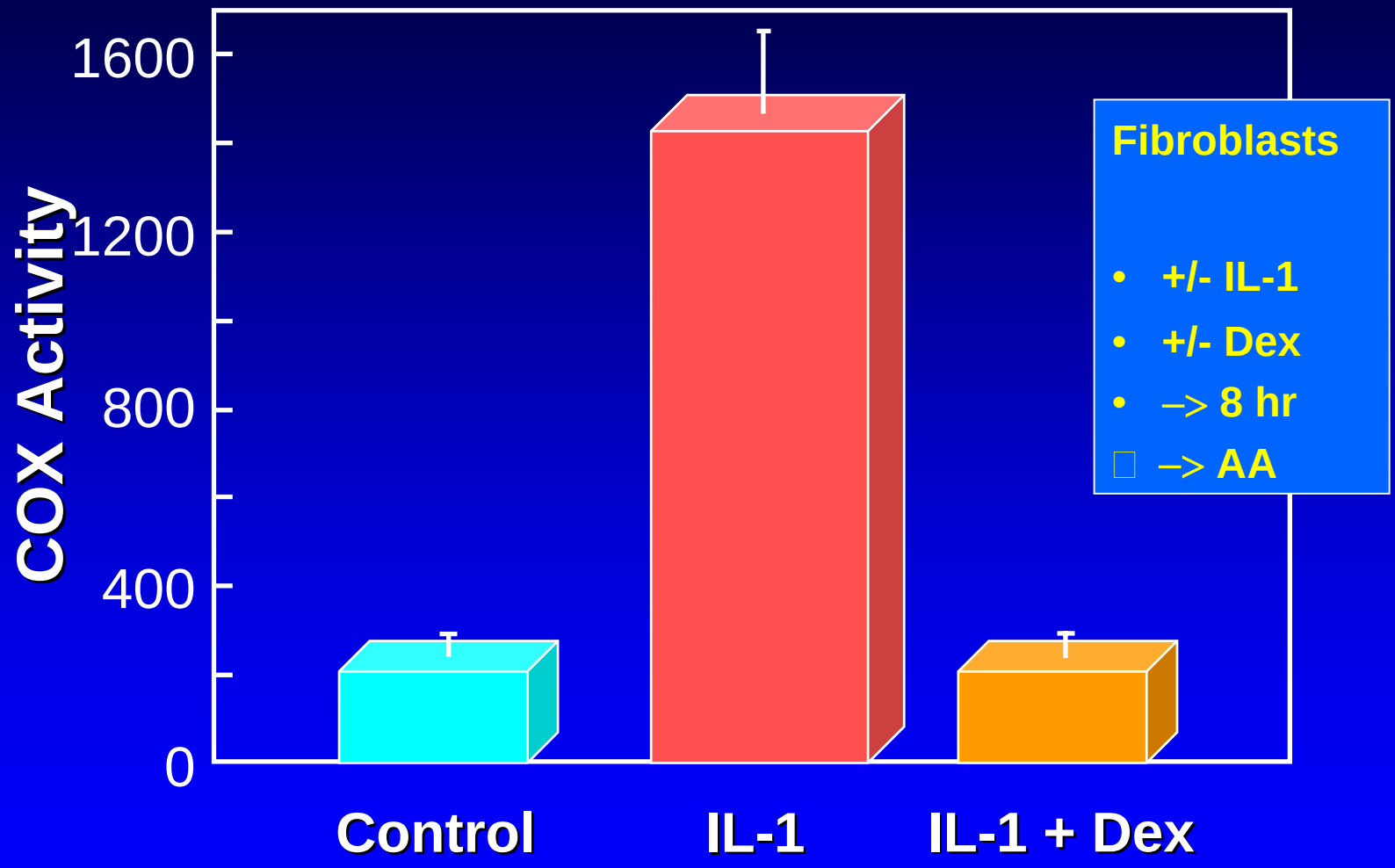


Discovery of two forms of cyclooxygenase

- **1989 ... IL-1 induces COX activity in fibroblasts [1]**
- **1990 … the inducible COX activity is inhibited by steroids [2]**
  steroids had no effect on basal cyclooxygenase activity
- **1991 … the inducible cycloxygenase is cloned [3]**
  - **60% identical to COX-1**
  - **certain important amino acid differences**
  - **cytokine induced and regulated by glucocorticoids**

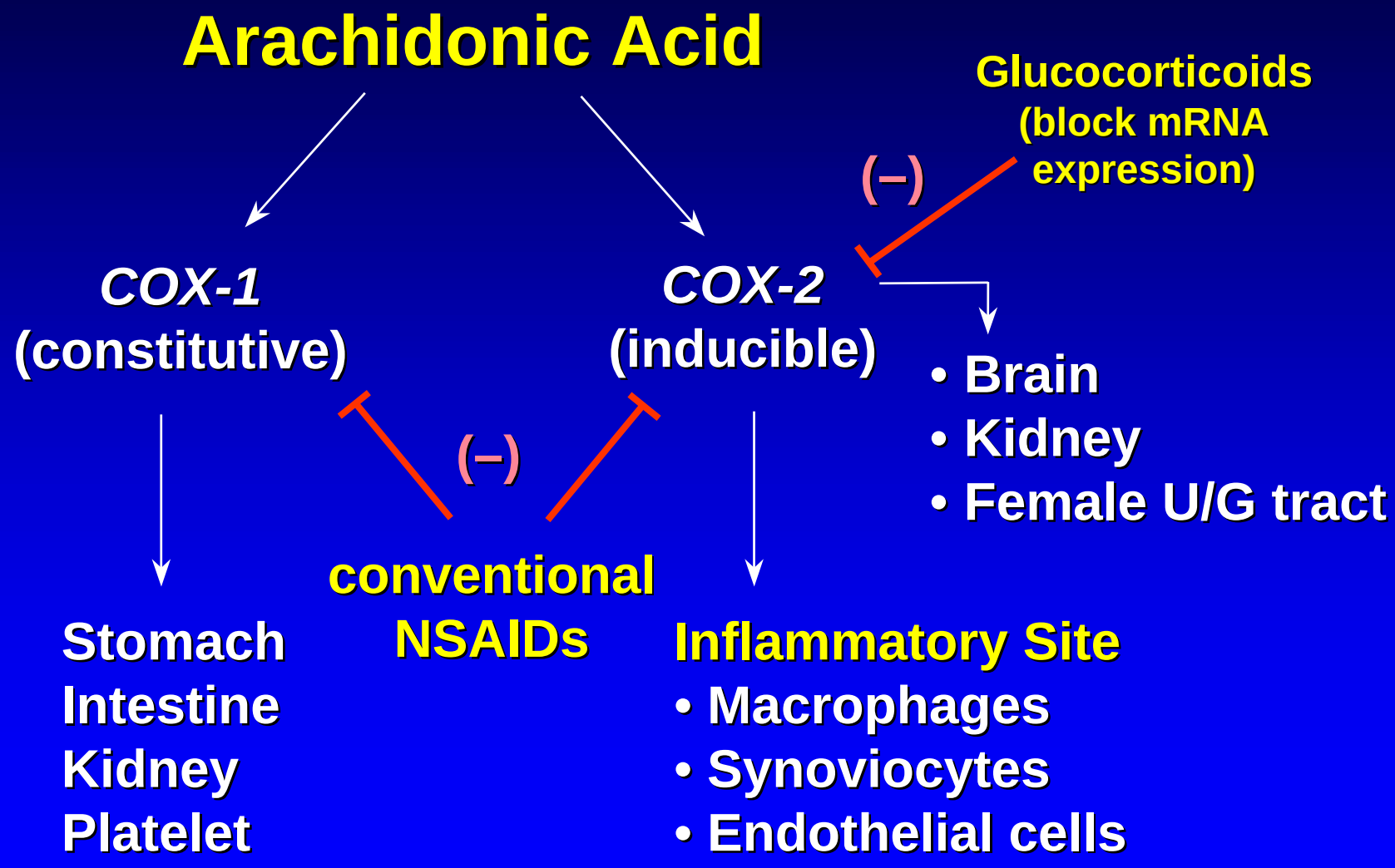
1 : Raz et al, PNAS, 1989, 86, 1657-1661
2 : Fu et al, J Biol Chem, 1990, 265. 16737-40
3 : Xie et al, 1991, PNAS, 88, 2692-6

Effect of IL-1 and dexamethasone on human fibroblast COX activity

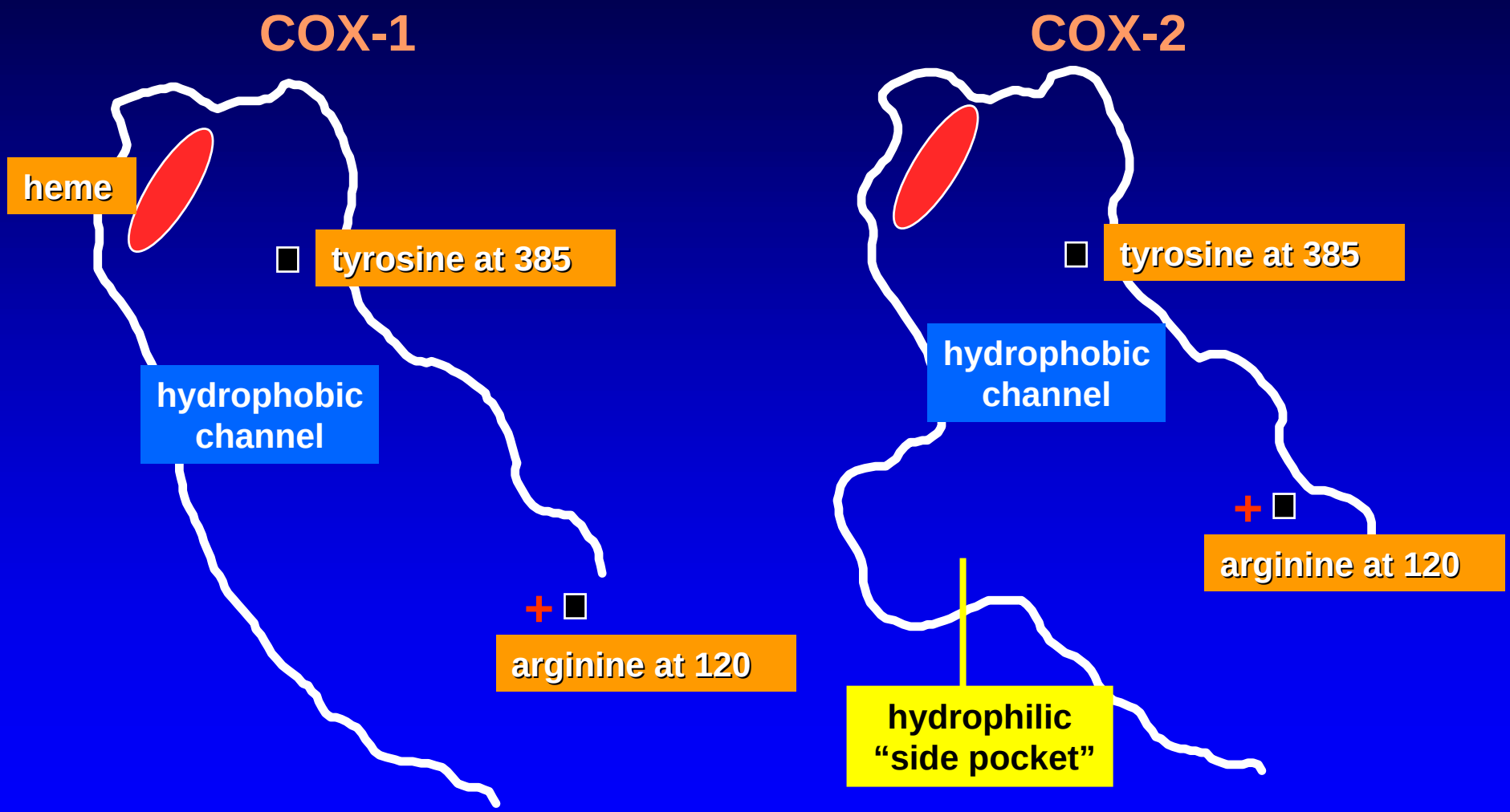


Raz et al, PNAS, 86,1657-1661

COX-2: a new anti-inflammatory drug target

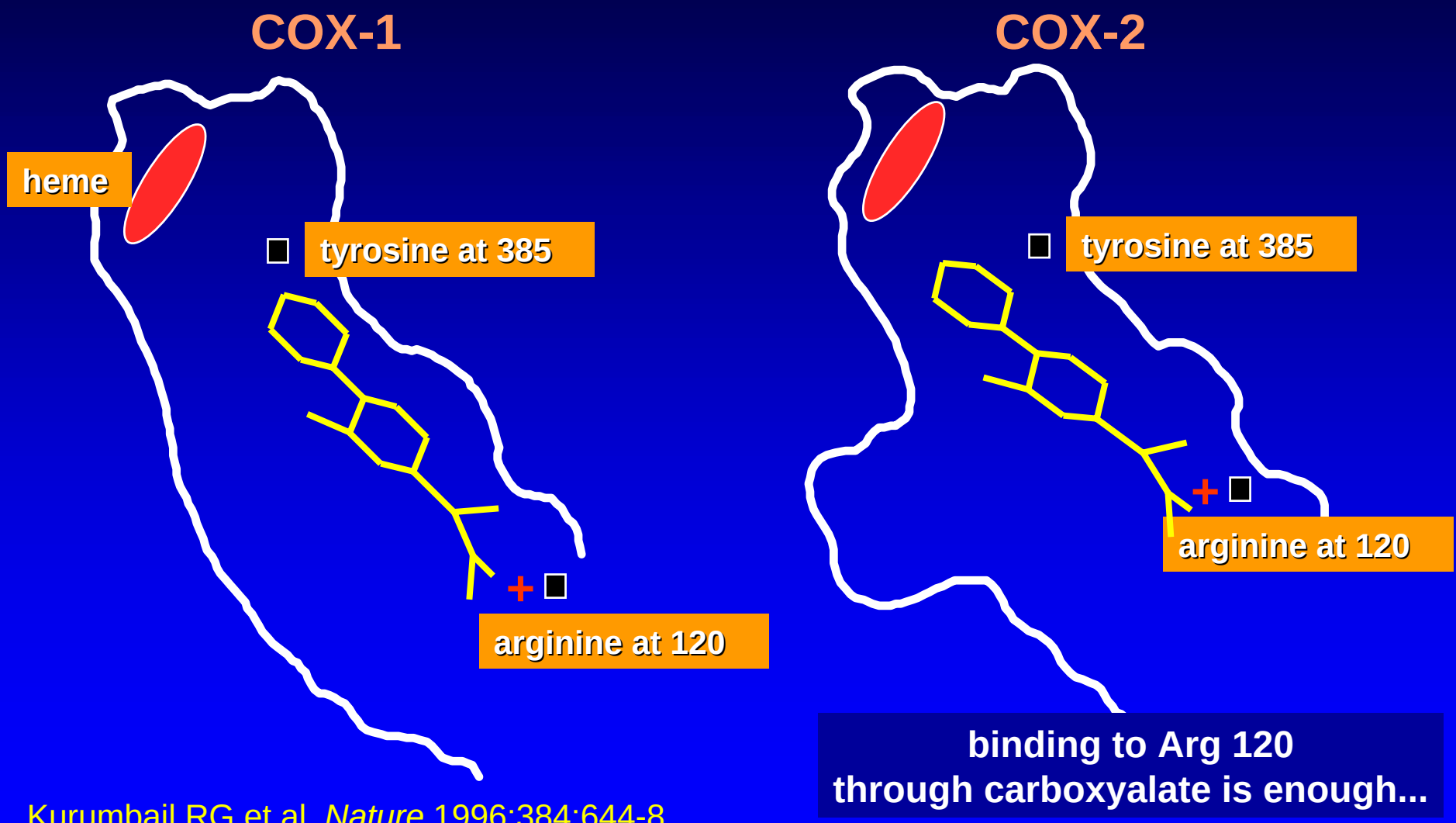


Structures of COX-1 and COX-2



Kurumbail RG et al. *Nature* 1996;384:644-8.

Conventional NSAIDs inhibit both COX-1 and COX-2

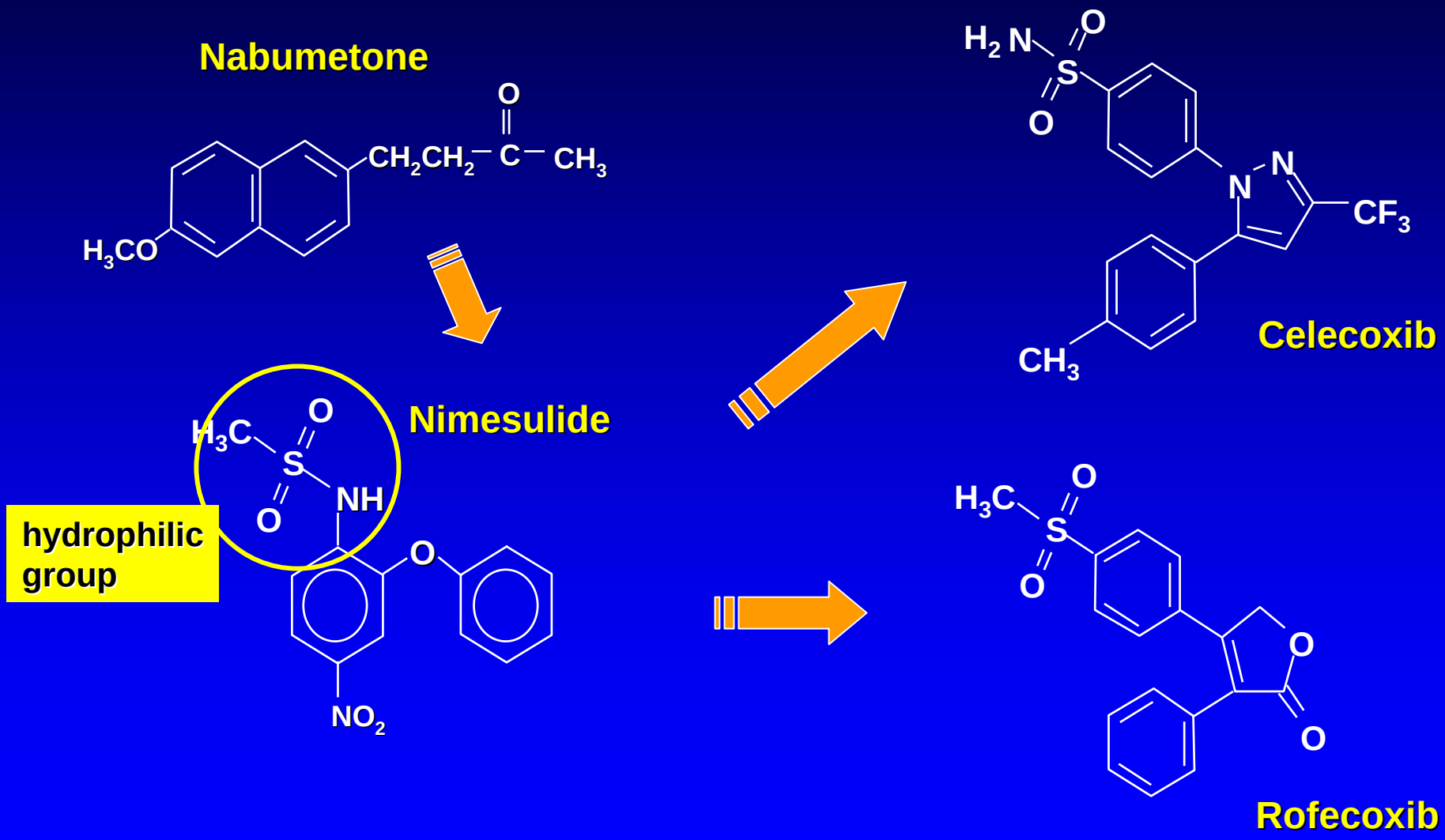


Kurumbail RG et al. *Nature* 1996;384:644-8.

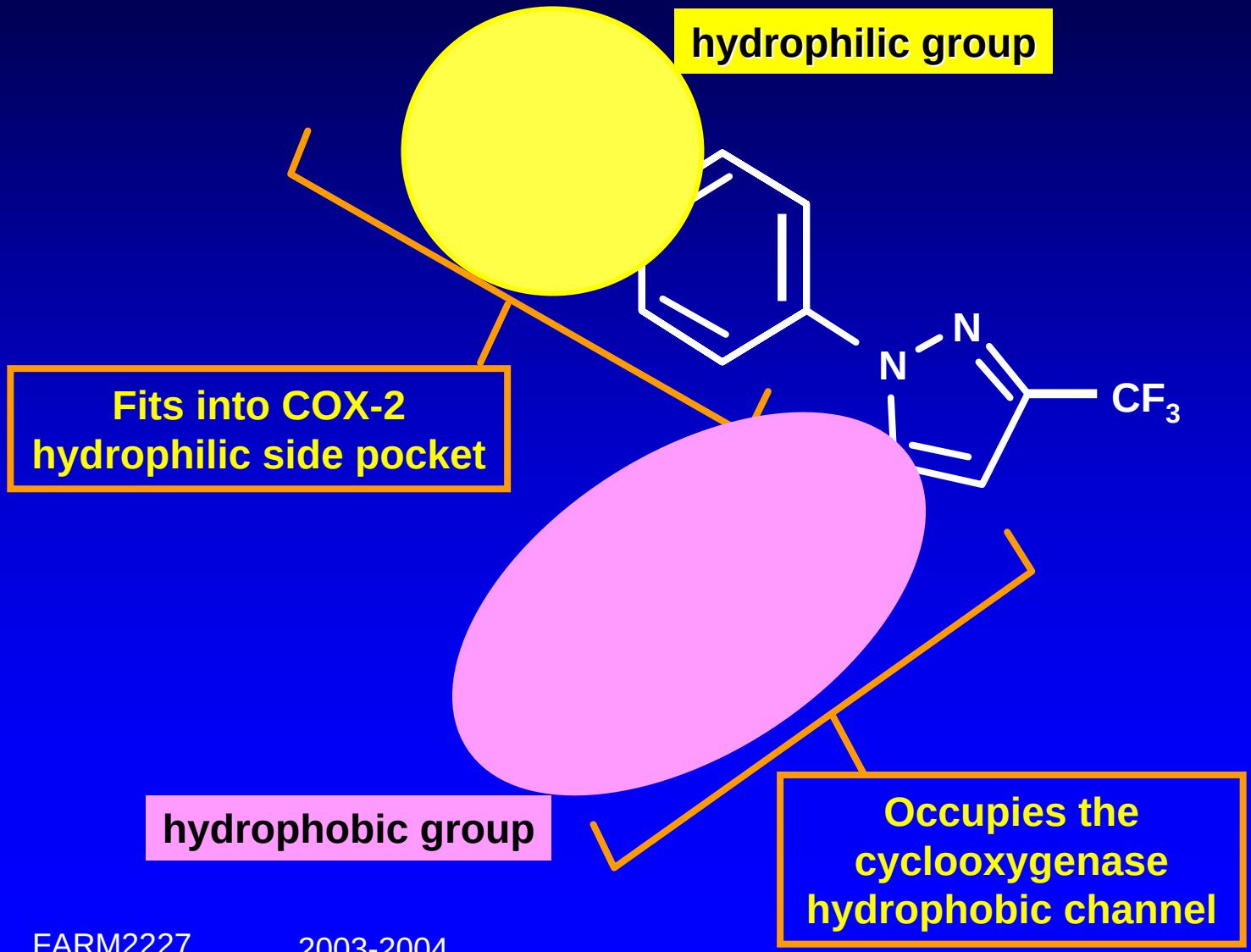
Chemistry and Activity

This is where all begins...

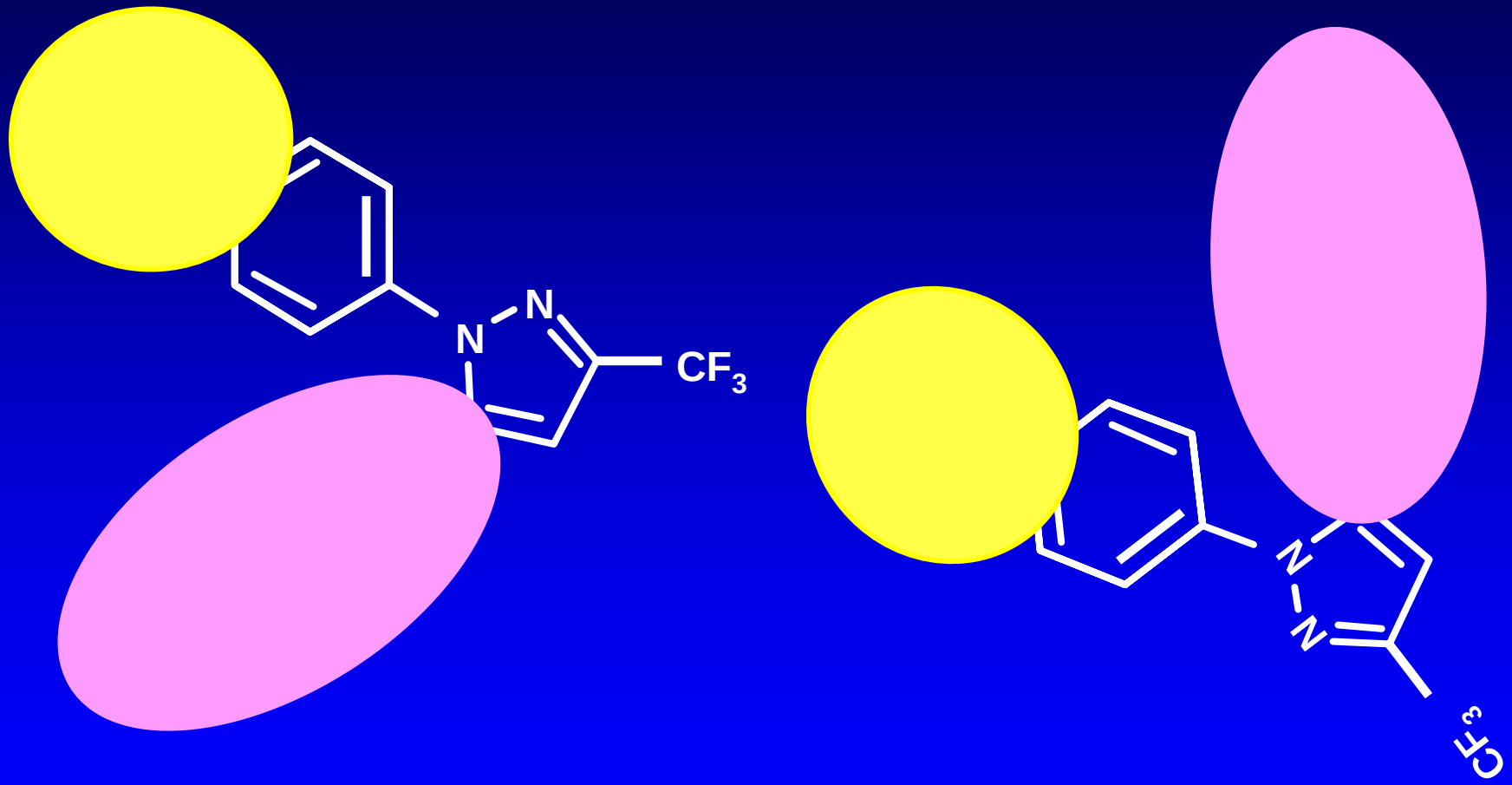
Pharmacochemistry of the COX-2 inhibitors



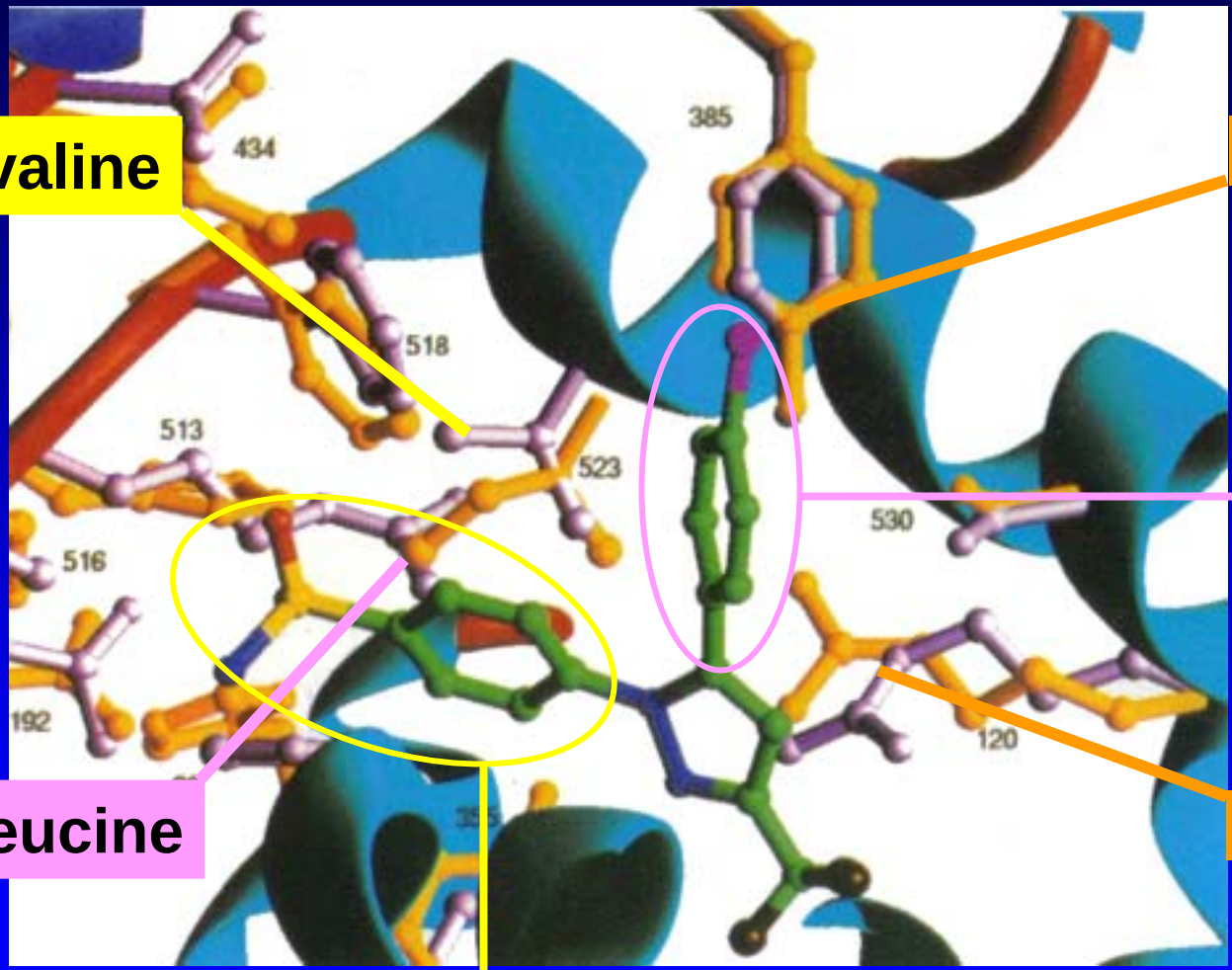
Pharmacochemical determinants in “coxibs”



Fitting “coxibs” in cyclooxygenases ...

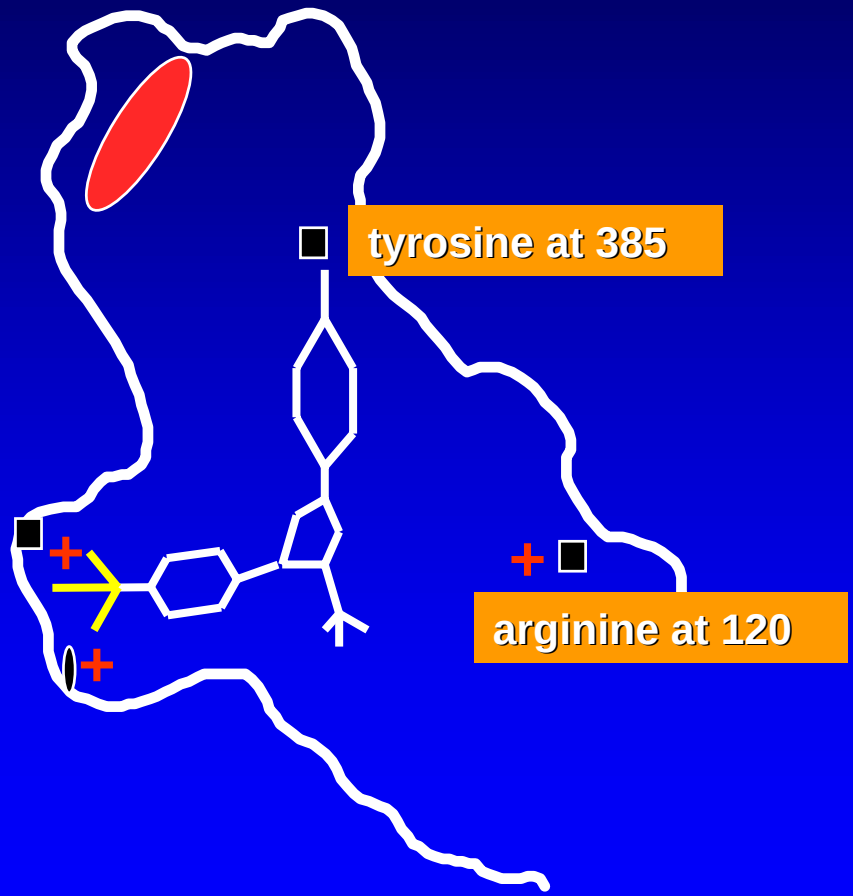


Structures of COX-1 and COX-2 with celecoxib



Why do “coxibs” bind so tightly to cycoloxygenase-2 ?

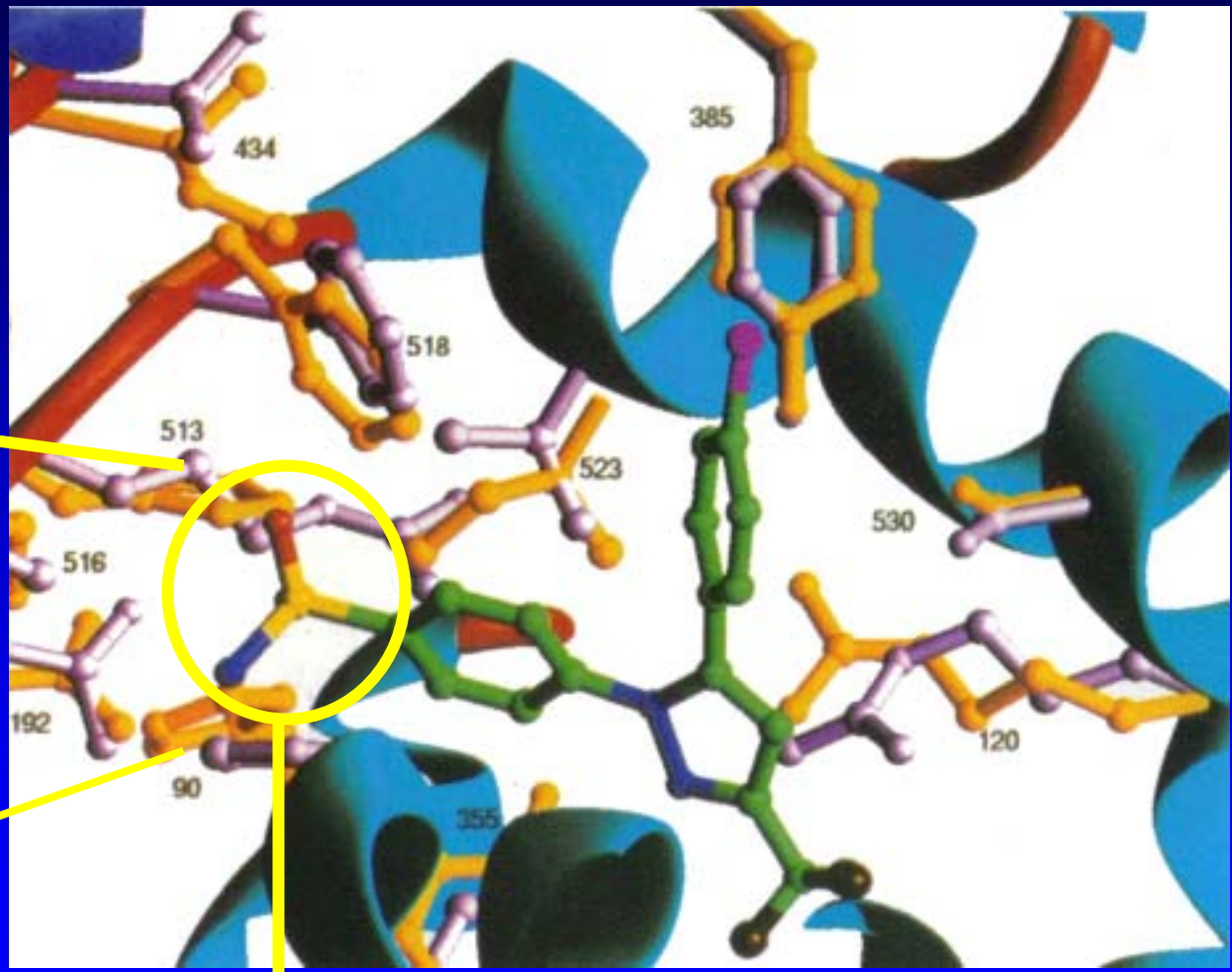
the polar sulphonamide side chain tightly bind to hydrophilic “side pocket”



Arg 513 and Hist 90 - forms hydrogen bonds with oxygen in sulphonamide side chain

Kurumbail RG et al. *Nature* 1996;384:644-8.

Binding of the slide chain to Arg 513 and His 90

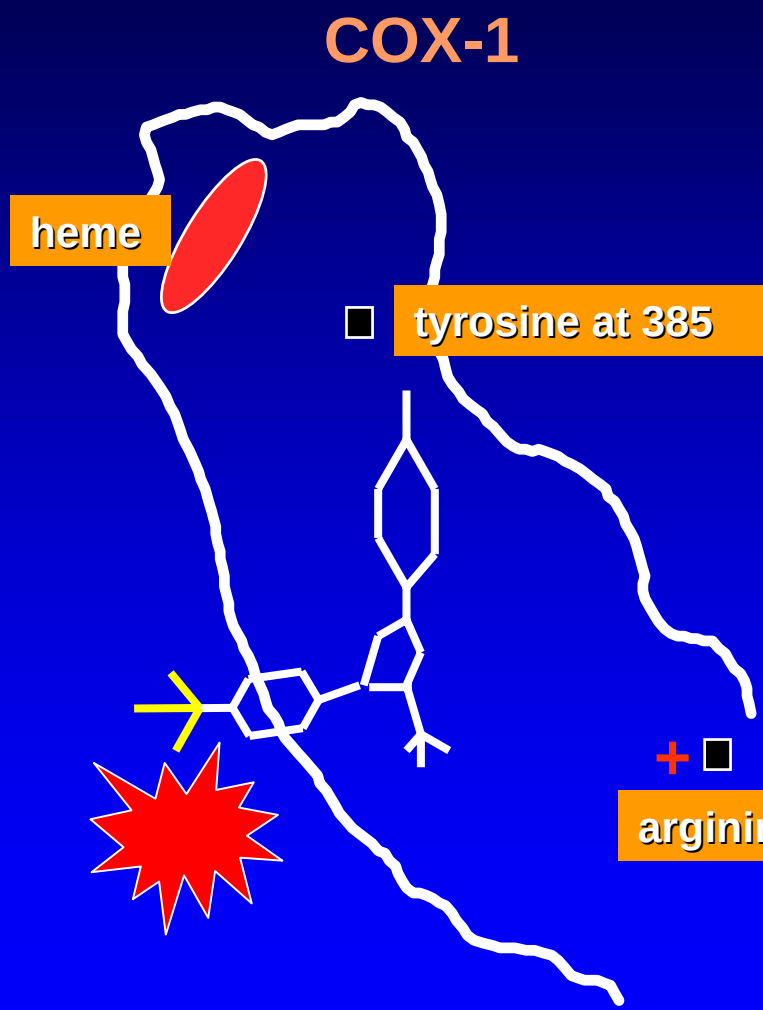


Arg 513

His 90

polar sulfonamide

Why do “coxibs” fail to inhibit cyclooxygenase-1 ?

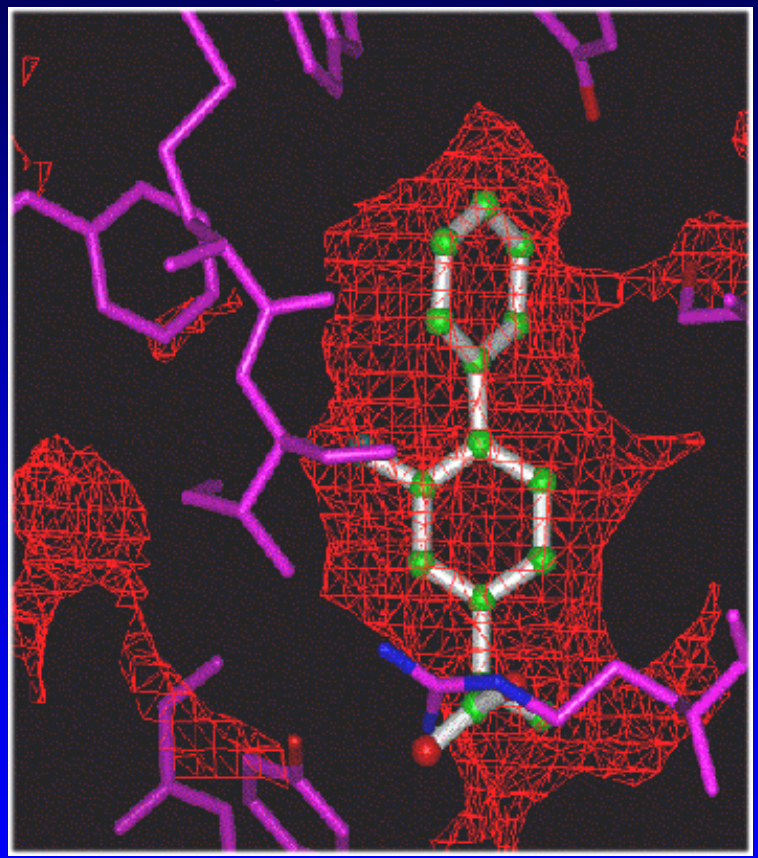


Can’t get in … and doesn’t bind very well

Kurumbail RG et al. *Nature* 1996;384:644-8.

Cox-1 vs Cox-2 ...

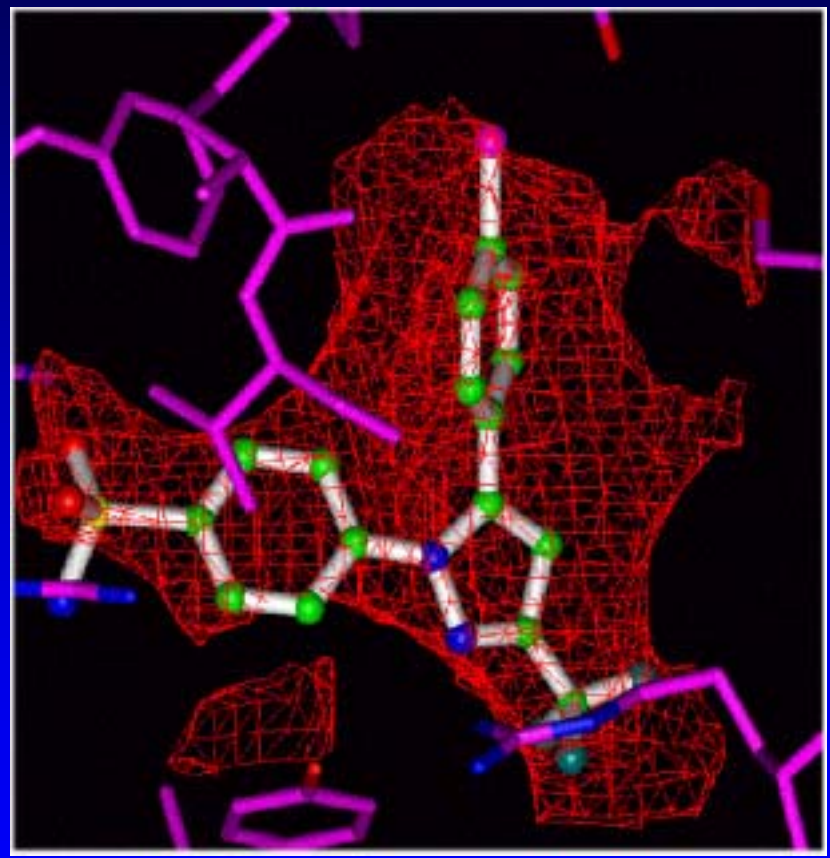
flurbiprofene in Cox-1



Picot, Loll and Garavito

Nature 1994; 367:243.

celecoxib in Cox-1



Kurumbail et al. Nature 1996;384:644-8.

Selectivity and specificity of Cox-inhibitors
(Lipsky et al, Editorial, J. Rheumatol, 1998, 25, 2298-2303)

Levels 1 & 2, Selectivity

1. **Enzymatic or biochemical**
   - **in vitro COX-1/COX- 2 ratio**
2. **Biological and pharmacologic**
   - **ex-vivo cell assays**

Level 3, Clinical specificity

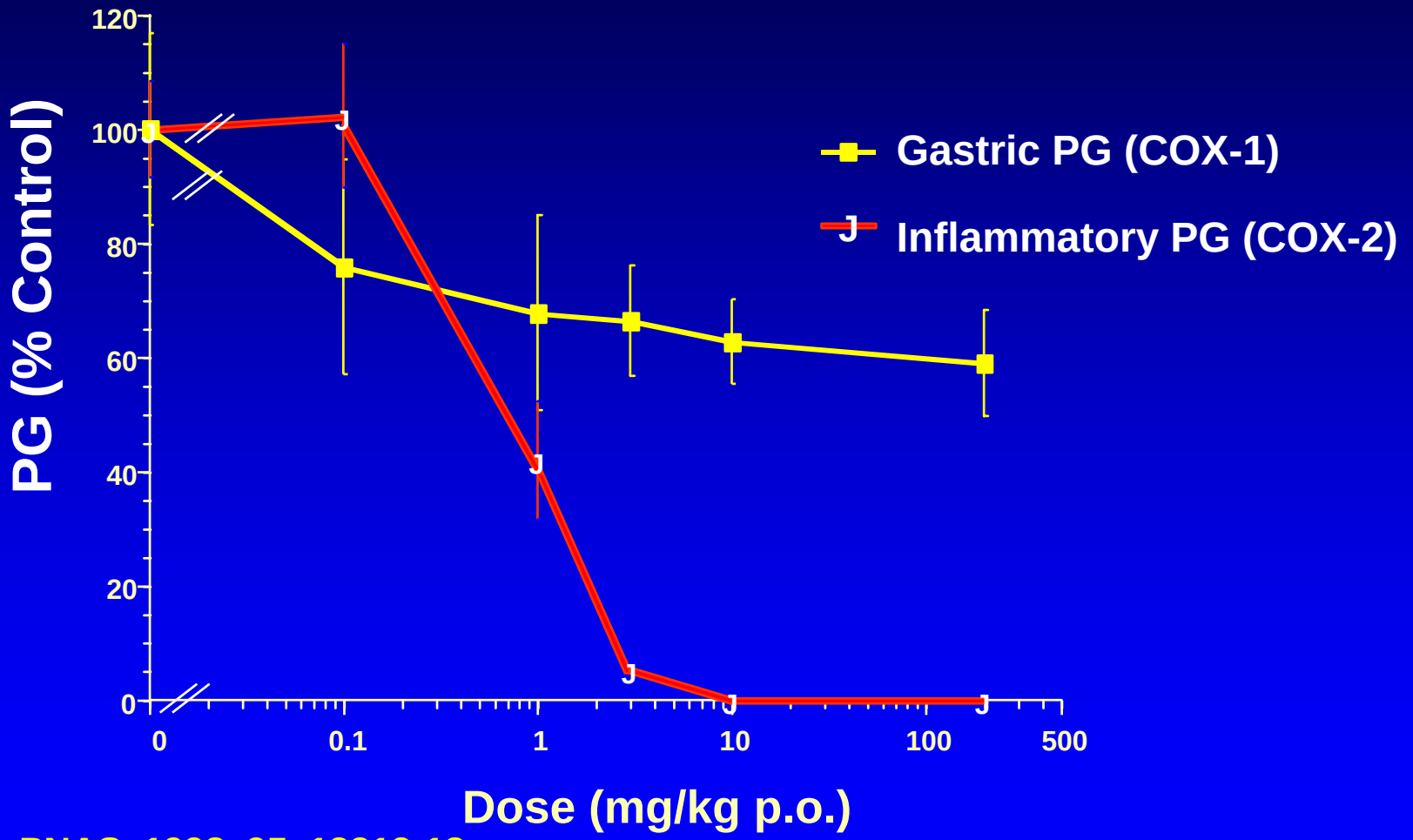
3. **At fully efficacious therapeutic concentration**
   - **No inhibition of COX-1 mediated platelet function**
   - **No clinically relevant COX-1 inhibitory effect on GI tract**

   = COX-2 SPECIFIC INHIBITION (CSI)

Categories of COX Inhibitors

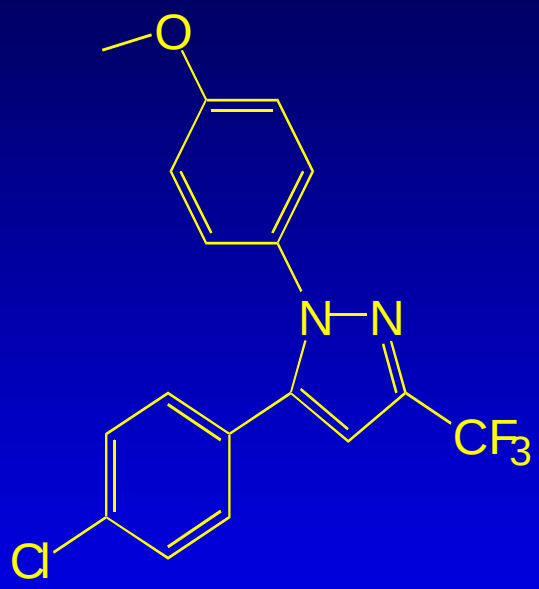
1. COX-1 specific	**Low dose aspirin**
2. COX non-specific	**All current NSAIDs**
3. COX-2 preferential*	**Agent with some anti-inflammatory or analgesic activities at a dose that inhibits COX-2 but causes no significant inhibition of COX-1**
4. COX-2 specific	**Agent which at maximal therapeutic dosing causes no clinically meaningful inhibition of COX-1**

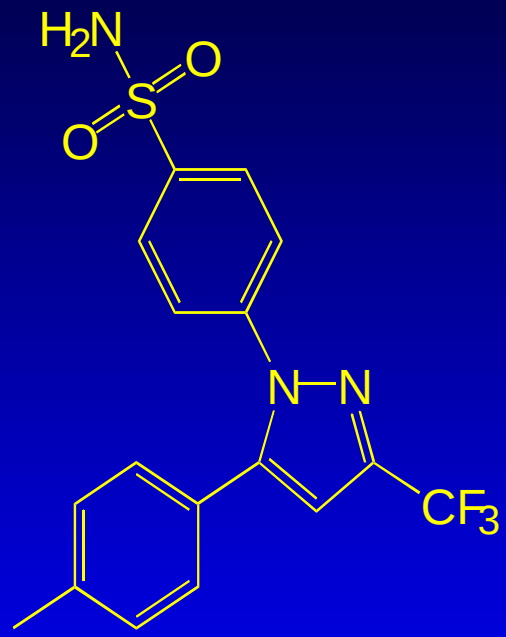
Specificity of Celecoxib *in vivo*



Smith CJ, PNAS, 1998, 95, 13313-18

Selective cyclooxygenase inhibitors



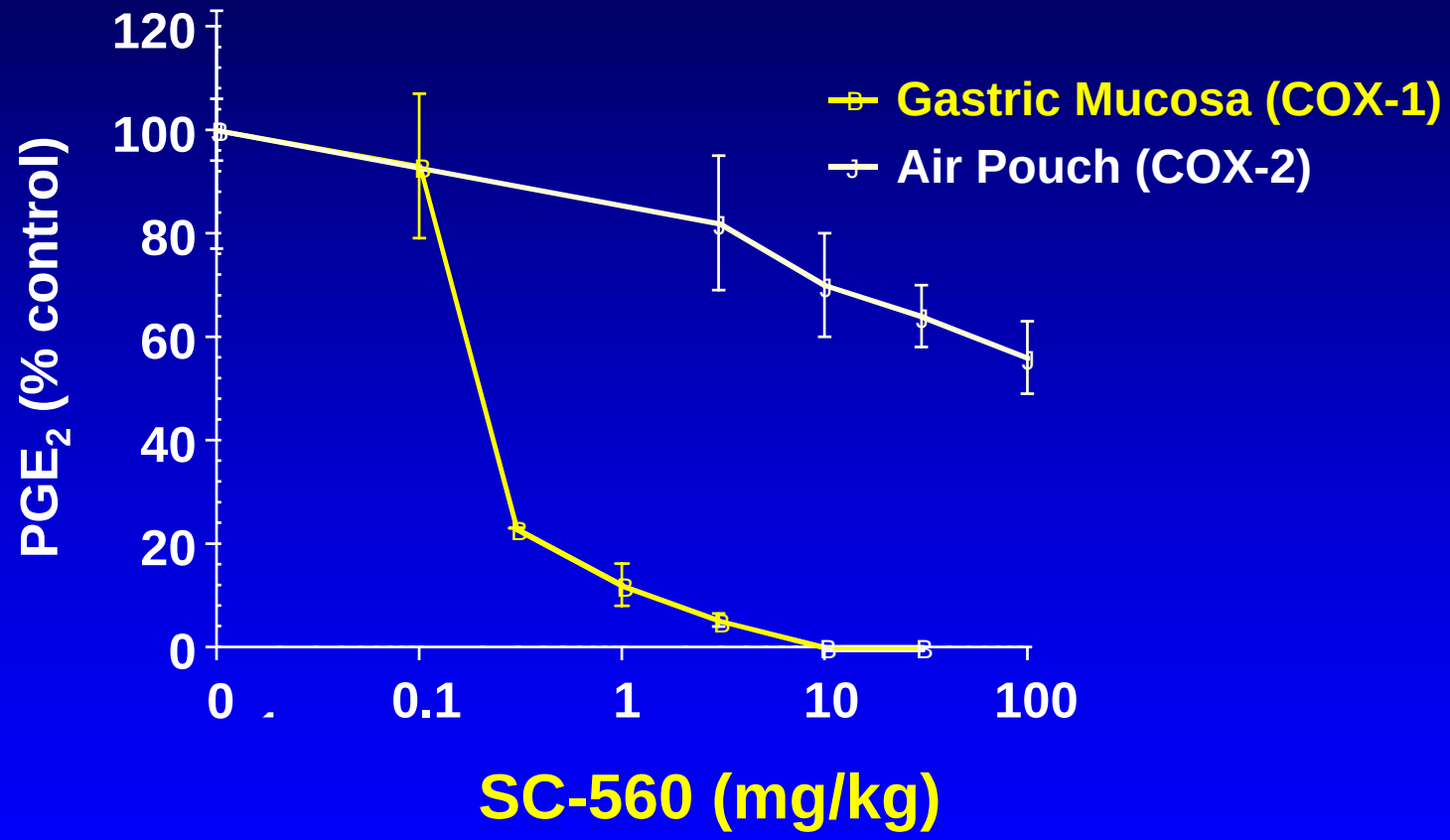


SC-560 **celecoxib**

IC_{50} (μM)	**COX-1**	**0.009**	**15**
	COX-2	**6.3**	**0.04**

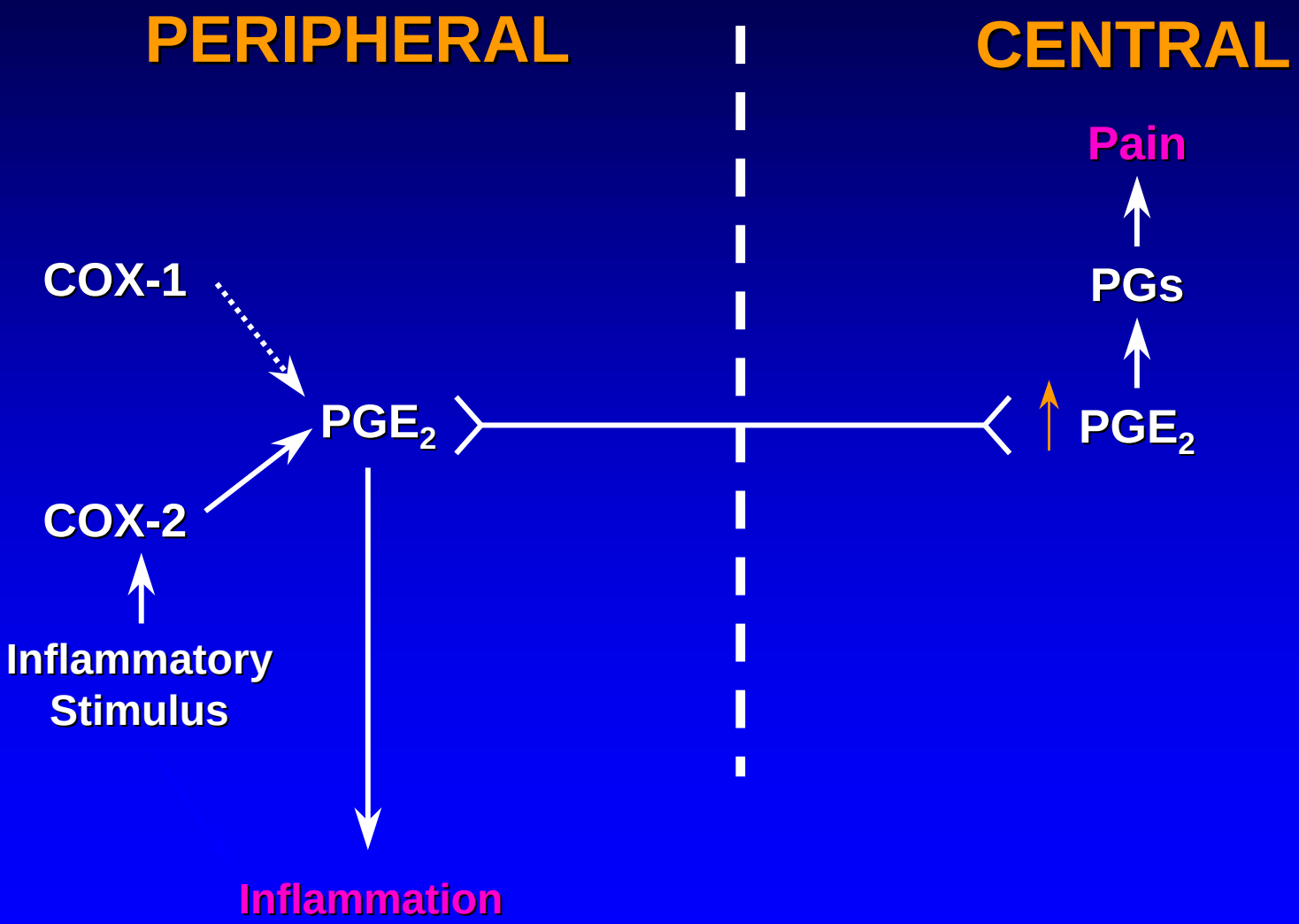
Smith CJ, PNAS, 1998, 95, 13313-18

In vivo Specificity of SC-560



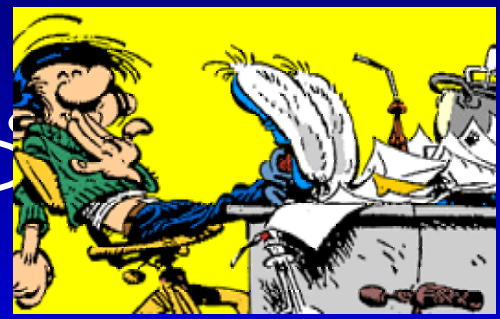
Smith CJ, PNAS, 1998, 95, 13313-18

Model for COX-1 and COX-2 derived prostaglandins in inflammation and pain



Smith CJ, PNAS, 1998, 95, 13313-18

Pharmacokinetics



This is where people start sleeping..

Pharmacokinetics of celecoxib

- **Absorption**
  - **75% bioavailable (versus oral solution)**
  - **food enhances bioavailability by 7-20%**
  - **antacids reduce bioavailability by ~25%**
- **Distribution**
  - **97% bound to plasma proteins**
  - **Protein binding is concentration independent**
  - **3% unbound with linear kinetic profile**

Potential drug interactions ...

- **Drugs that are Metabolized by the Cytochrome P450 2C9 Pathway**
  - S-Warfarin
  - tolbutamide
  - phenytoin
  - glyburide
- **Potential Protein Binding Displacement**
  - warfarin
  - phenytoin
  - glyburide
- **Drugs Eliminated by the Kidneys**
  - methotrexate
  - lithium
- **Drugs that are Metabolized by the Cytochrome P450 2D6 Pathway**
  - paroxetine
  - dextromethorphan

Actual results of drug interaction studies

Interactions observed :

- **lithium** (17% increase AUC and C_{max})
- **fluconazole** (2x increase celecoxib AUC and C_{max} by CYP $_{2C9}$ inhibition)
- **paroxetine** and **dextromethorphan** (moderate increases of PK values)

No interactions with :

- **methotrexate**
- **glyburide**
- **warfarin**
- **phenytoin**
- **tolbutamide**
- **ketoconazole**

Karim A et al. *Arthritis & Rheum* 1998;41(9) Suppl:1698A.
Data on File: Searle (Studies 017, 038, 039, 040, 050, 051,117)

Celecoxib platelet effects

- no alteration of aggregation or bleeding time [Lack of COX-1 inhibition] at 6 x the therapeutic dose
- Anaemia, ecchymoses were reduced on celecoxib vs NSAIDs (comparison with naproxen)

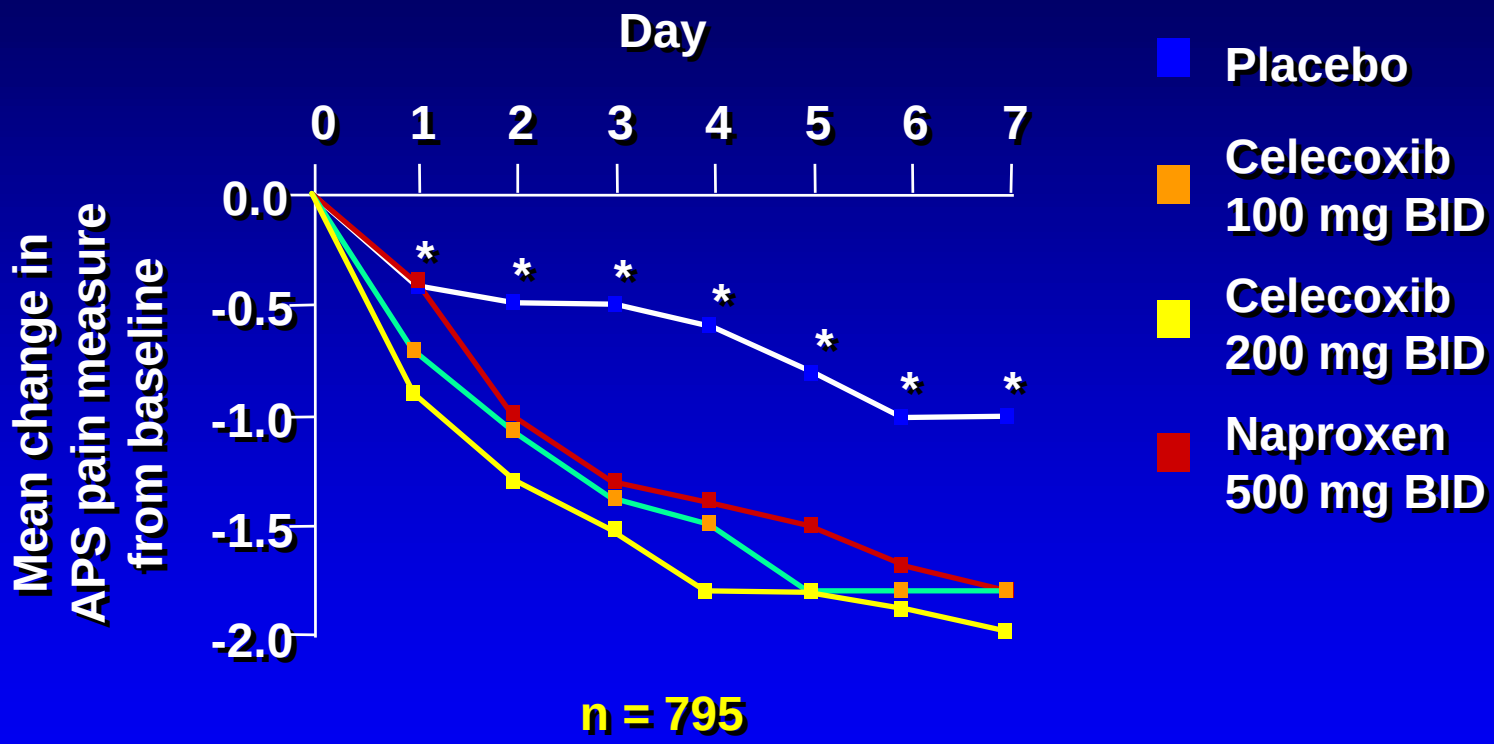
Clinical efficacy ?

Pain Measure Questionnaire
of the American Pain Society (APS)

1. **Have you experienced any pain in the last 24 h? (yes or no)**
2. **How much pain are you having right now? (0–10)**
3. **Indicate the worst pain you have had in the past 24 h. (0–10)**
4. **Indicate the average level of pain you have had in the past 24 h. (0–10)**
5. **Indicate how pain has interfered with you in: (7 daily activities; each scored 0–10)**

Patient's assessment of average arthritis pain in last 24h

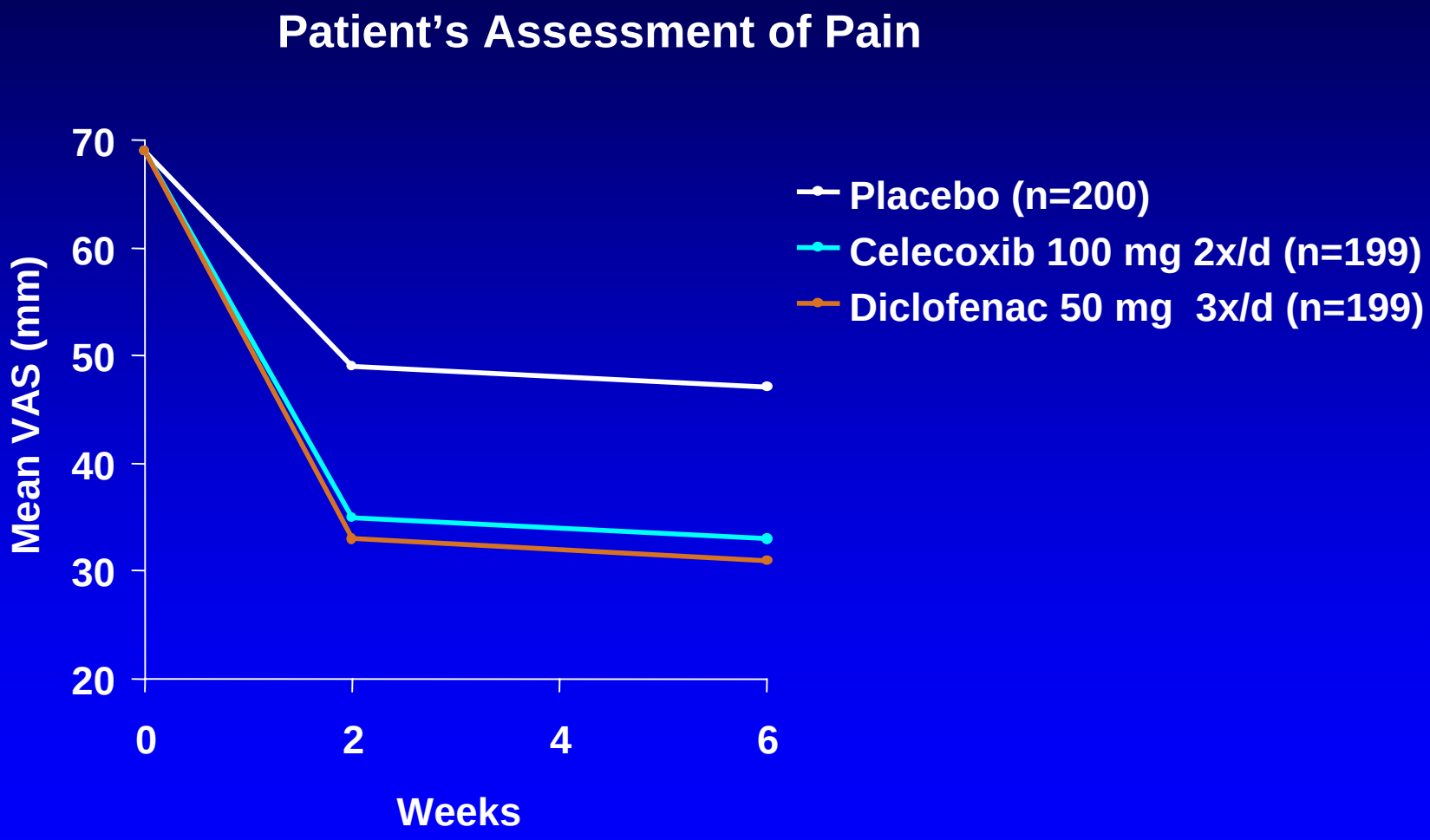
OA Knee Trial: Celecoxib vs Naproxen



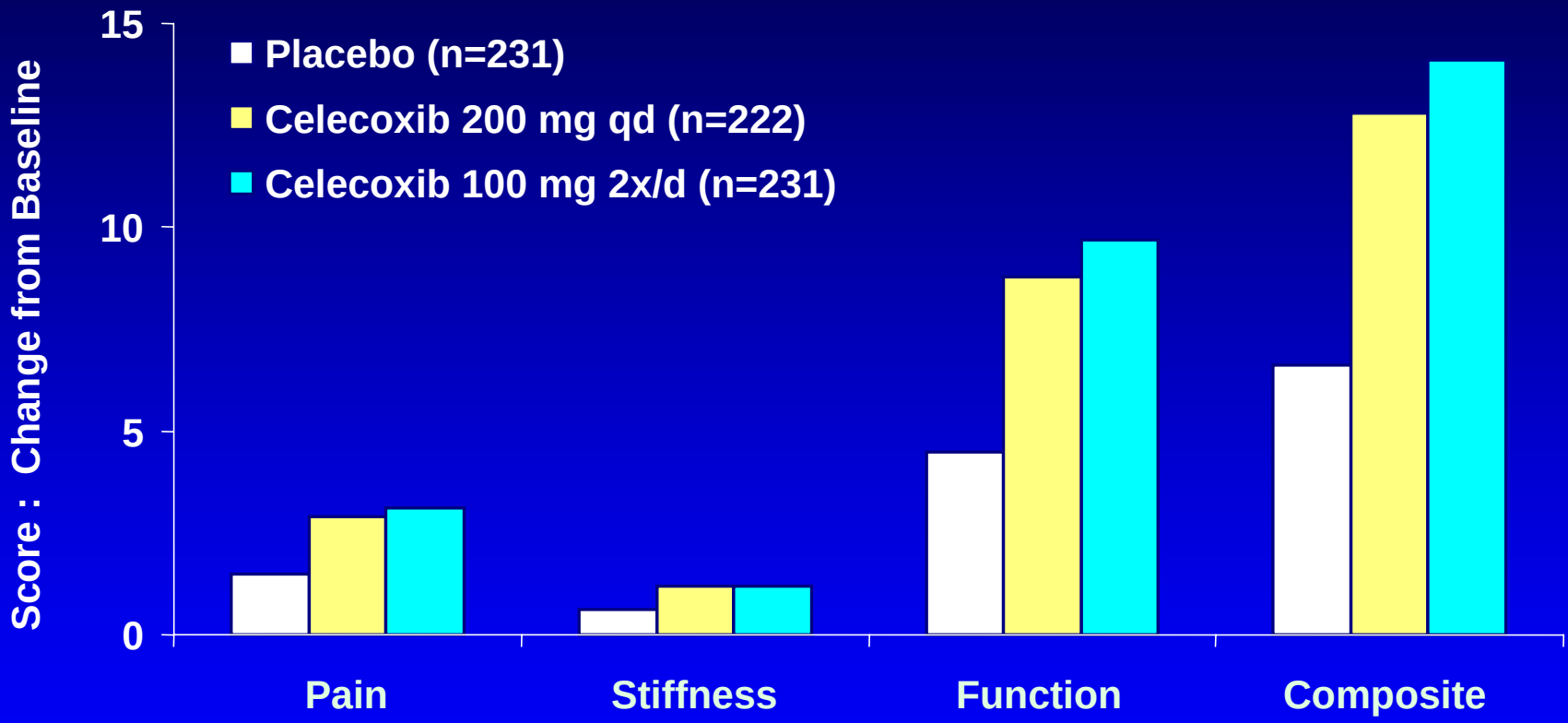
****P* < 0.05 vs all treatments (except naproxen at Day 1 and celecoxib 100 mg at Day 2)**

Data on file : Searle Study 020

Celecoxib vs Diclofenac in OA

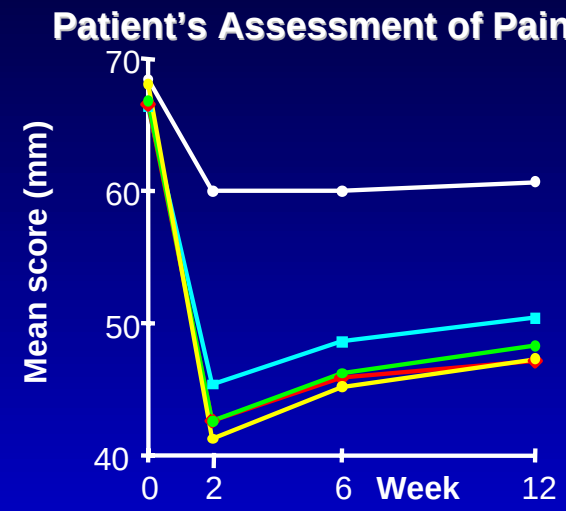


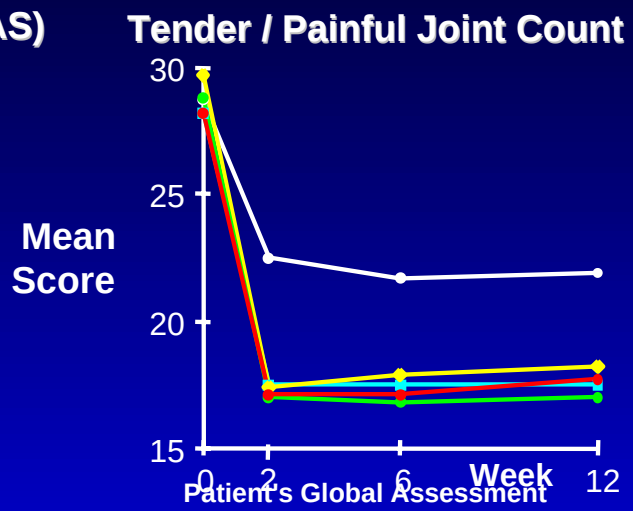
Efficacy of celecoxib 200 mg once a day (qd) in OA

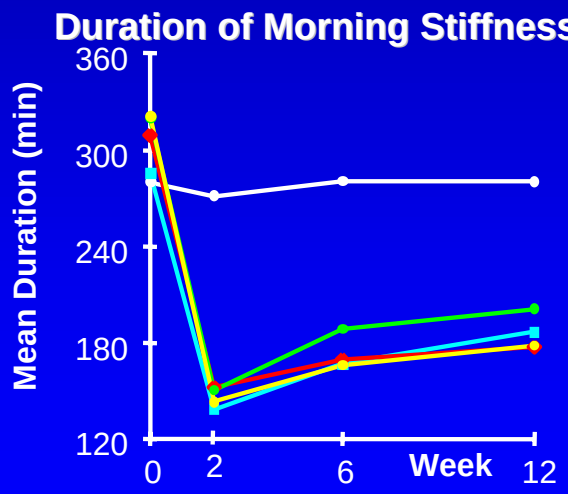


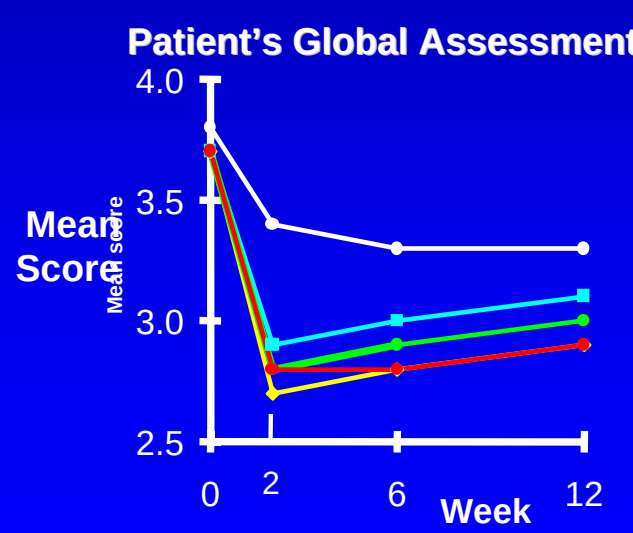
Searle Study 060

Celecoxib Efficacy in RA - Combined Results from 2 Studies (n = 400 per treatment group)









Placebo

Celecoxib

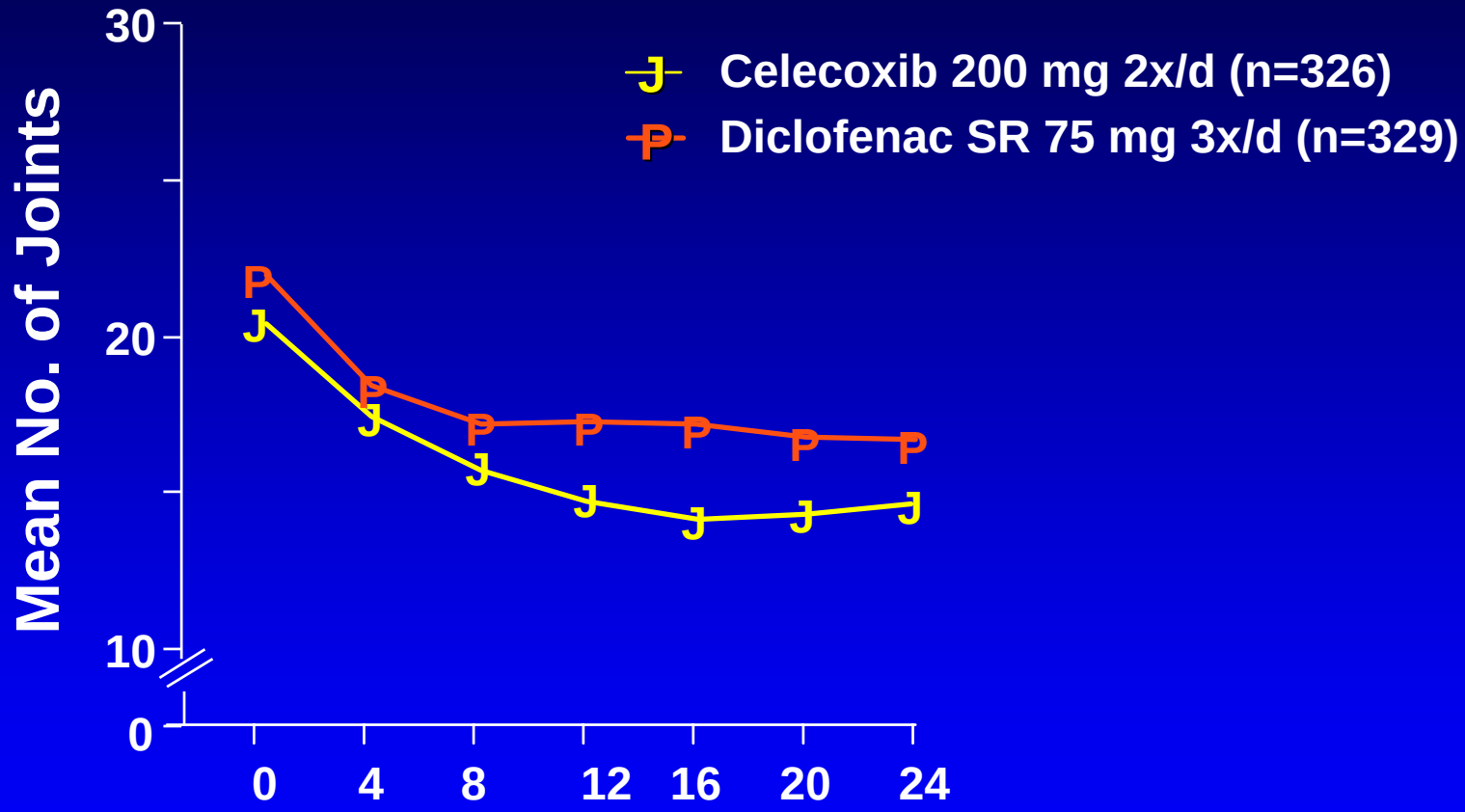
- 100 mg 2x/d
- 200 mg 2x/d
- 400 mg 2x/d

Naproxen

- 500 mg 2x/d

Data on file :
Searle Studies 022, 023

Number of tender / painful joints
6 Months International Study in RA



Data on File : Searle Study 041
Emery P et al, Lancet, 1999,2106-2111

Toxicity ??

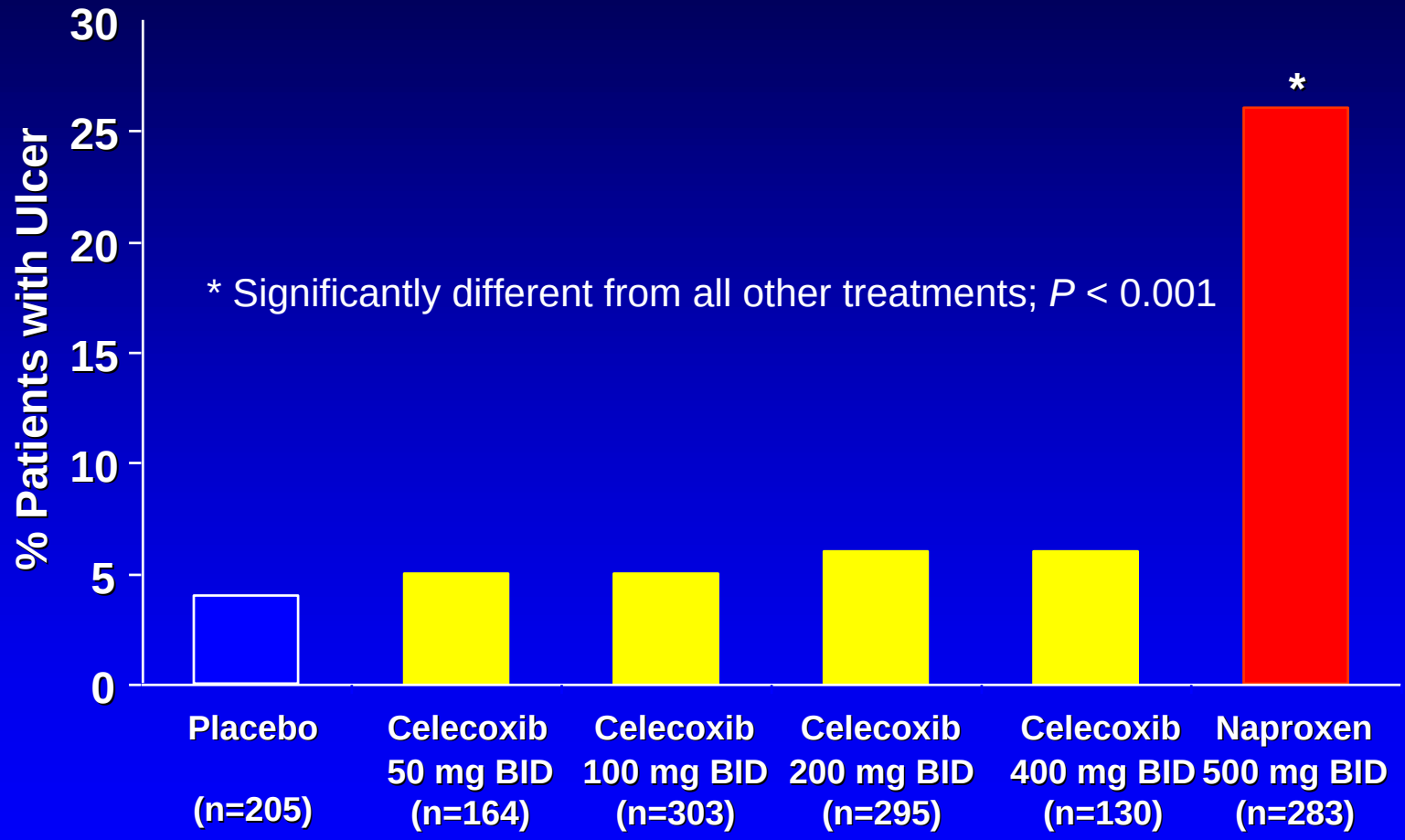
Gastrointestinal Safety and Tolerability Celecoxib vs NSAIDs

- **Gastroduodenal ulceration**
  - 6 endoscopy studies in >4000 individuals
- **Clinically significant upper GI events**
  - 4004 patient-years exposure data (All treatments)
- **Changes in haemoglobin**
- **GI Symptoms**

} **>11,000 patients with OA or RA in 14 Phase II / III**

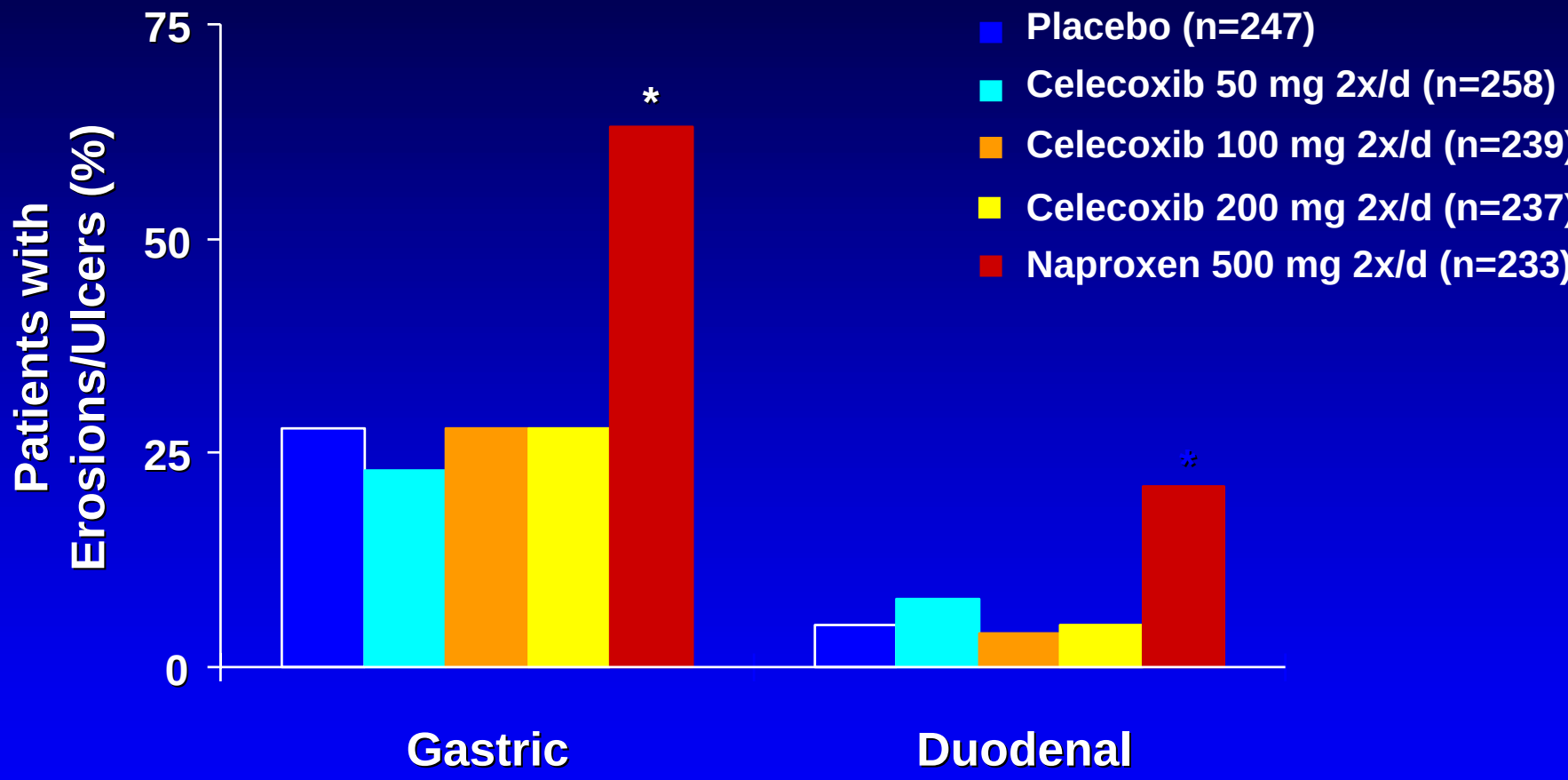
Incidence of gastroduodenal ulcers - week 12

Celecoxib - Phase III RA and OA UGI Safety Trials



Data on File: Searle (Studies 021 & 022)

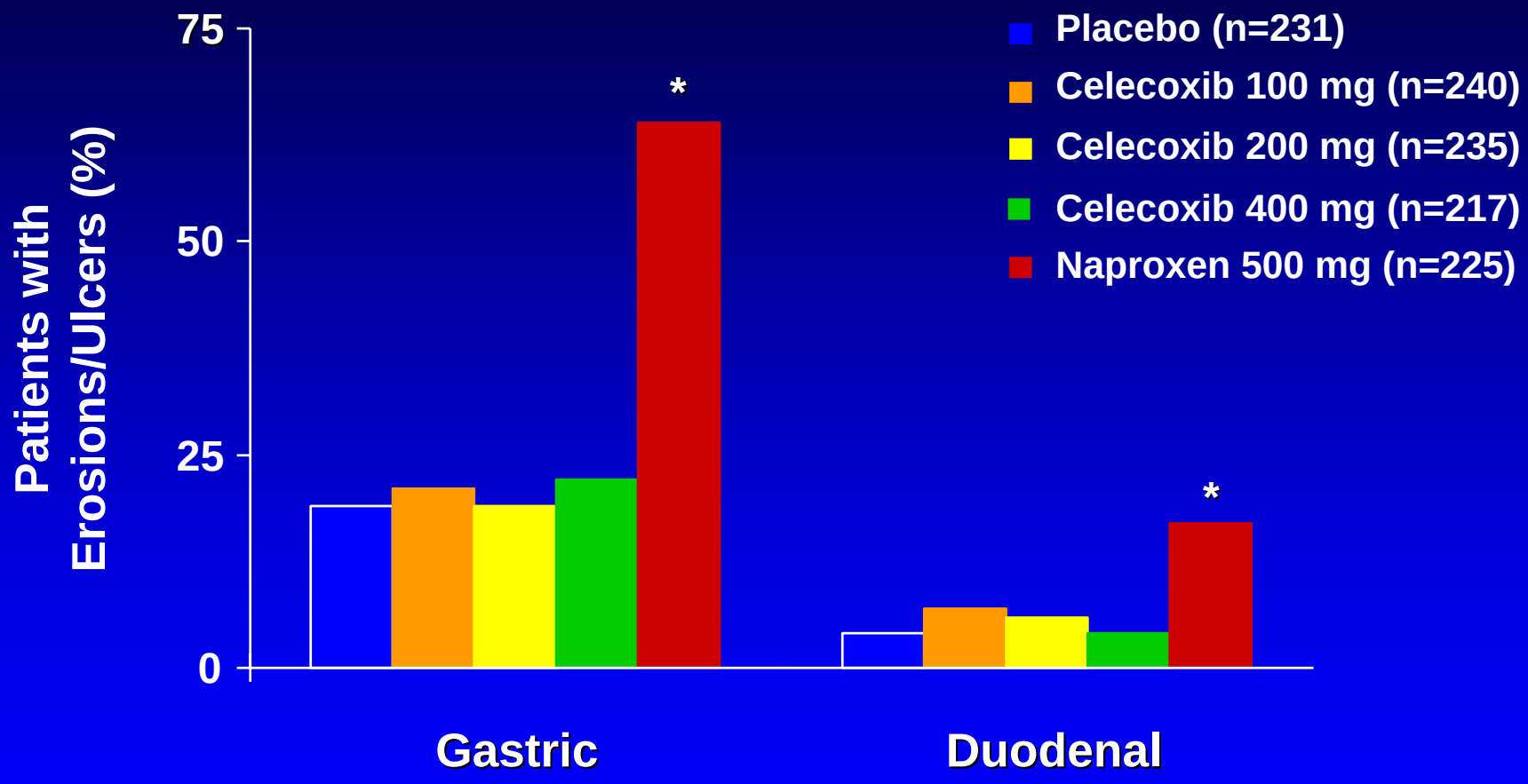
Incidence of erosions / ulcers in patients with OA



*** Significantly different from all other treatments; *P* < 0.001**

Data on file : Searle Study 021

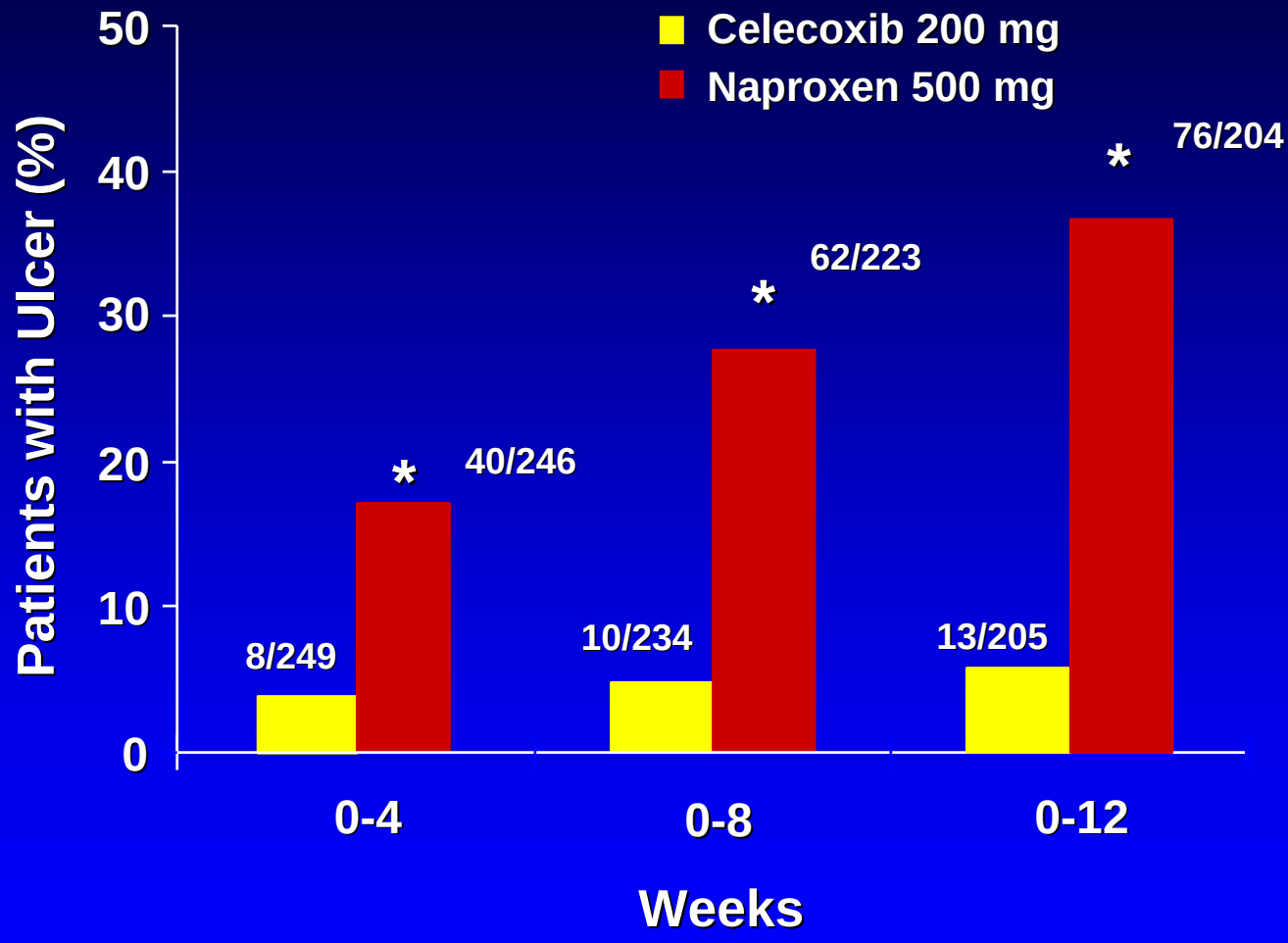
Incidence of Erosions / Ulcers in Patients with RA



*** Significantly different from all other treatments; *P* < 0.001**

Data on file : Searle Study 022

Cumulative Incidence of Gastric Ulcers



*** Significantly different from celecoxib; *P* < 0.001**

Data on File : Searle Study 062

Localization of COX-1 and COX-2 in the kidneys

+=COX-1 present +=COX-2 present	Dog	Rat	Monkey	Man
Renal Vasculature (Arteries, Arterioles, Veins)	+ ±	+	+ +	+ +
Glomerulus			+	+
Macula Densa	+ (+++)	+ (+++)	(-)	
Interstitium	+ +		+	+
Thick Ascending Loop	+ (+++)	+ (+++)		
Collecting Ducts	+ + +	+ + +	+ +	+ +

Khan KN et al. *Toxicol Pathol* 1998;26(1):137-42.