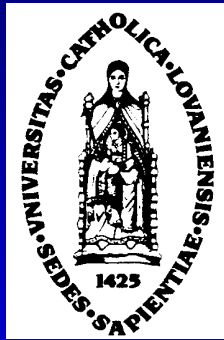


Cox-2 inhibitors: where are we ?

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Cox-2 inhibitors: where are we ?

Questions ...

- Are Cox-2 inhibitors effective ?
- What are (exactly) Cox-2 inhibitors and why and how were they made ?
- Are they safe ?

Overview of celecoxib clinical trials

- Studies : 56 randomised controlled trials
2 long-term open-label studies
- Sites : > 600 worldwide
- Patients / Subjects: ~ 14,000
- Endoscopy: > 4,700 patients
- Patient Years: ~ 3,000

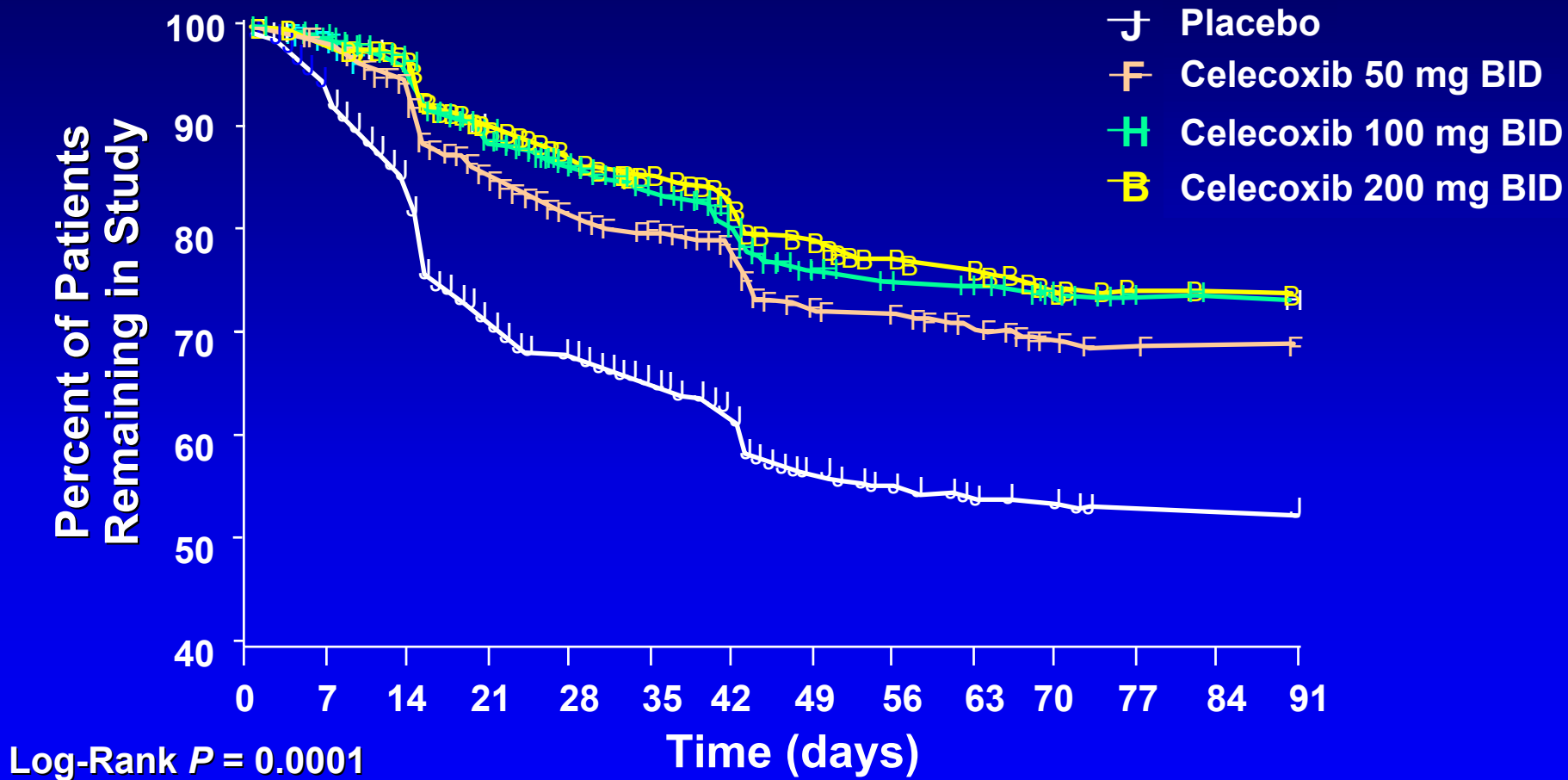
Phase III Pivotal OA Trials : Study Design

Randomised & double-blind	Placebo BID			
	Osteoarthritis Flare	Celecoxib 50 mg BID		
		Celecoxib 100 mg BID		
		Celecoxib 200 mg BID		
		Naproxen 500mg BID		
Hip or Knee				
		Week 2	Week 6	Week 12
Physical Examination	x			x
Arthritis Assessments	x	x	x	x
Laboratory Tests	x	x	x	x

Hubbard R et al. *Arthritis & Rheum* 1998;41(9) Suppl:982A.
 Data on file: Searle Studies 020, 021, 054

Phase III pivotal OA trials

time to withdrawal due to lack of efficacy



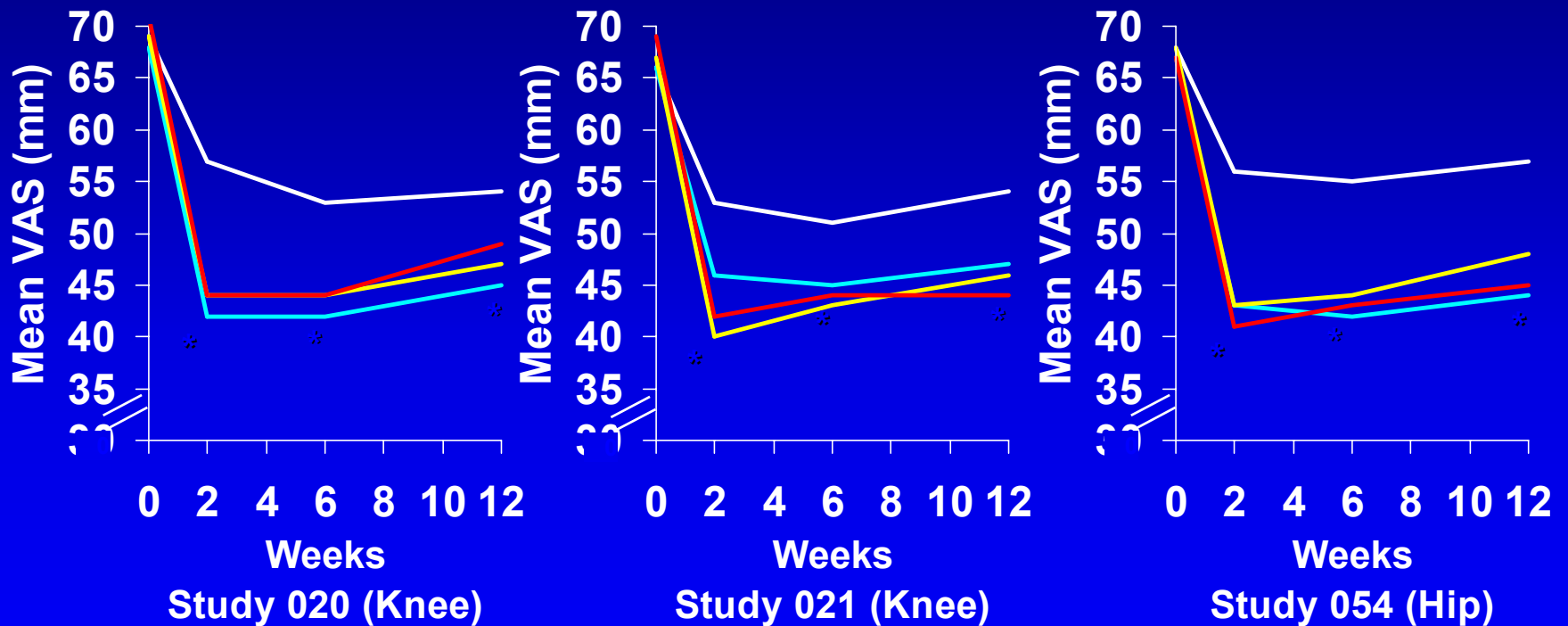
Hubbard R et al. *Arthritis & Rheum* 1998;41(9) Suppl:982A.
Data on File: Searle (Studies 020, 021 & 054)

Phase III Pivotal OA Trials

Patient's Assessment of Arthritis Pain

- Placebo
- Celecoxib 100 mg 2x/d
- Celecoxib 200 mg 2x/d
- Naproxen 500 mg 2x/d

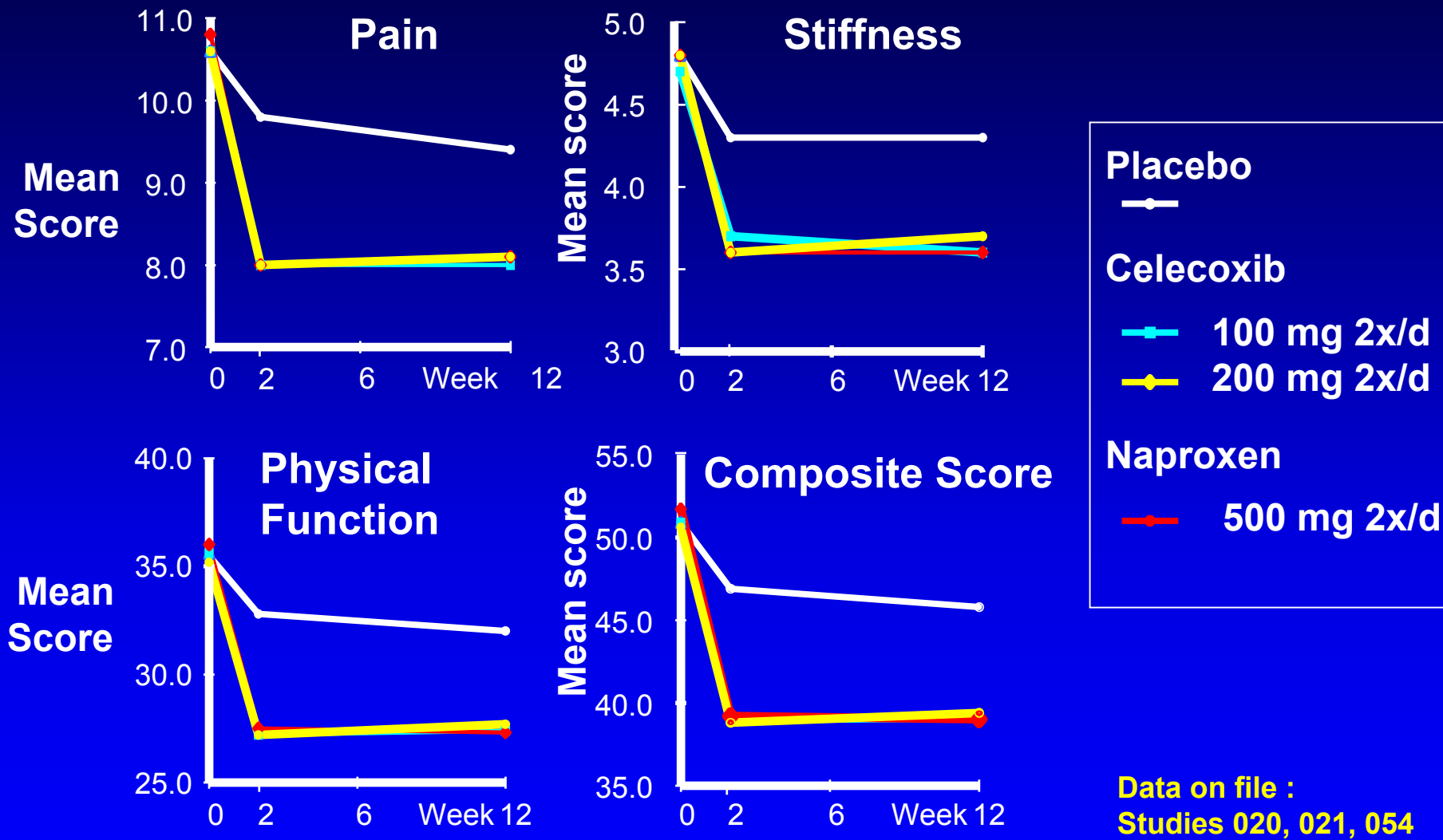
*p<0.05 vs placebo for all treatment groups
 ~200 per treatment arm in each study



Hubbard R et al. *Arthritis & Rheum* 1998;41(9) Suppl:982A. Data on File: Searle

Combined WOMAC outcomes from 3 OA Studies

n = ~600 per treatment group



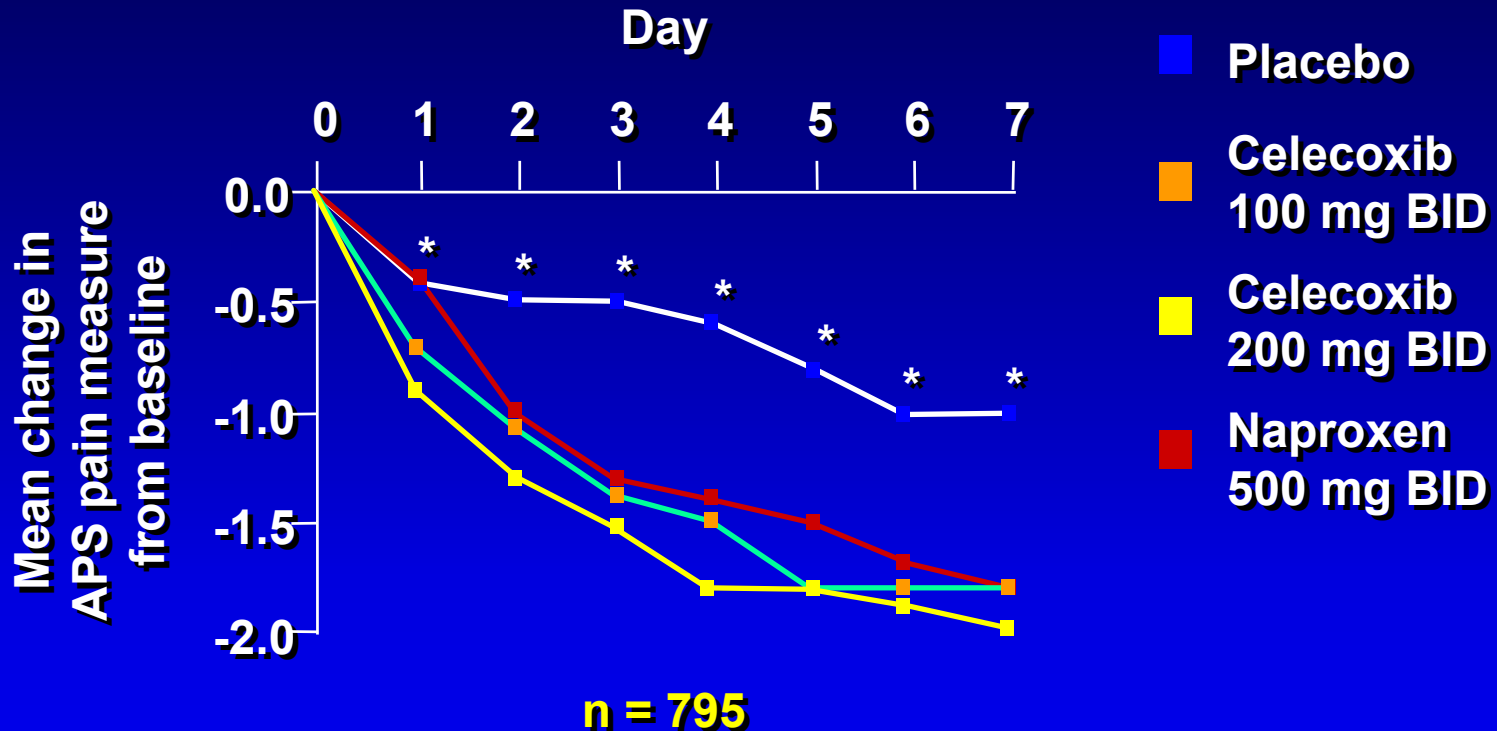
Data on file :
Studies 020, 021, 054

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

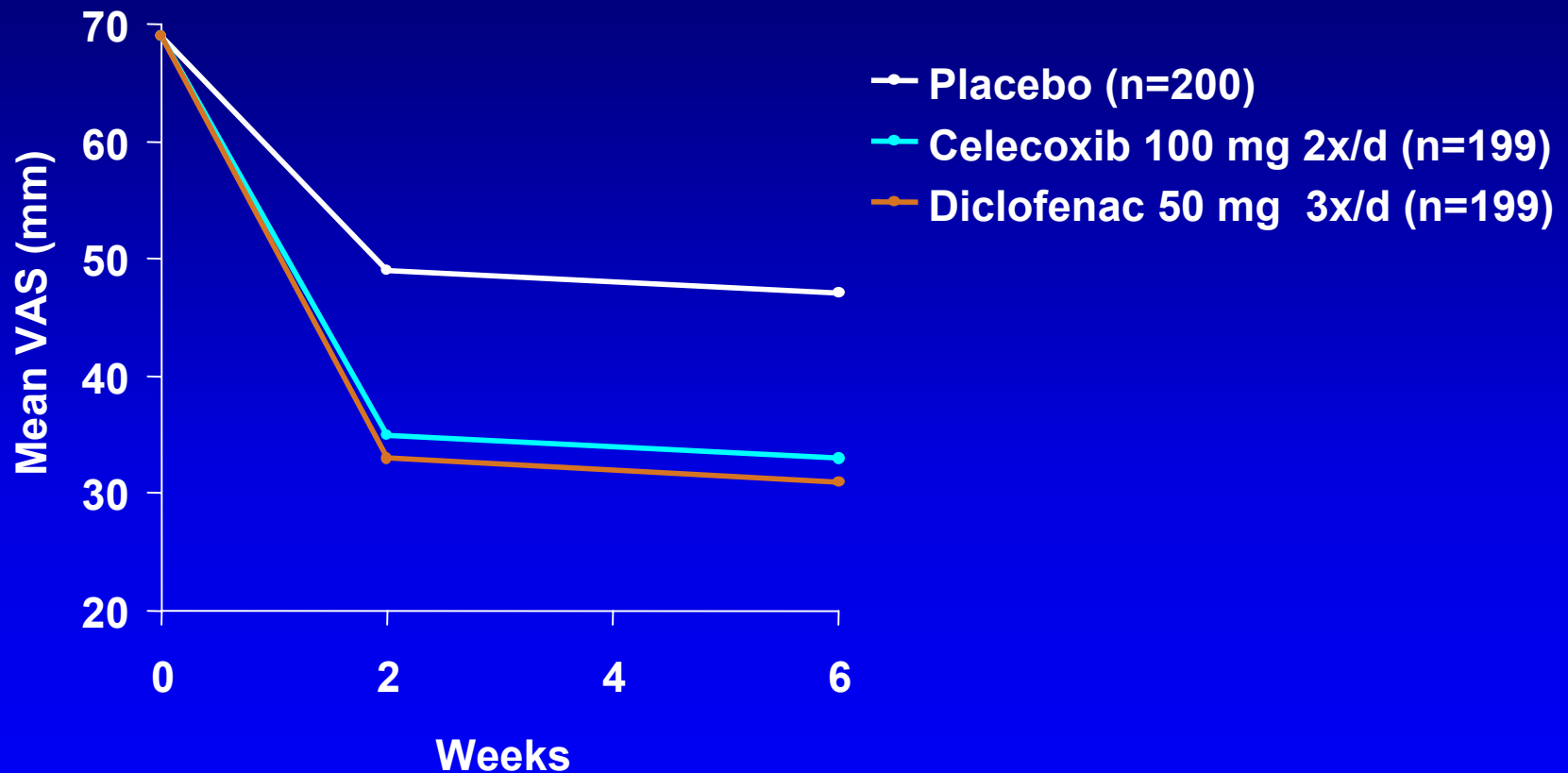


* $P < 0.05$ vs all treatments (except naproxen at Day 1 and celecoxib 100 mg at Day 2)

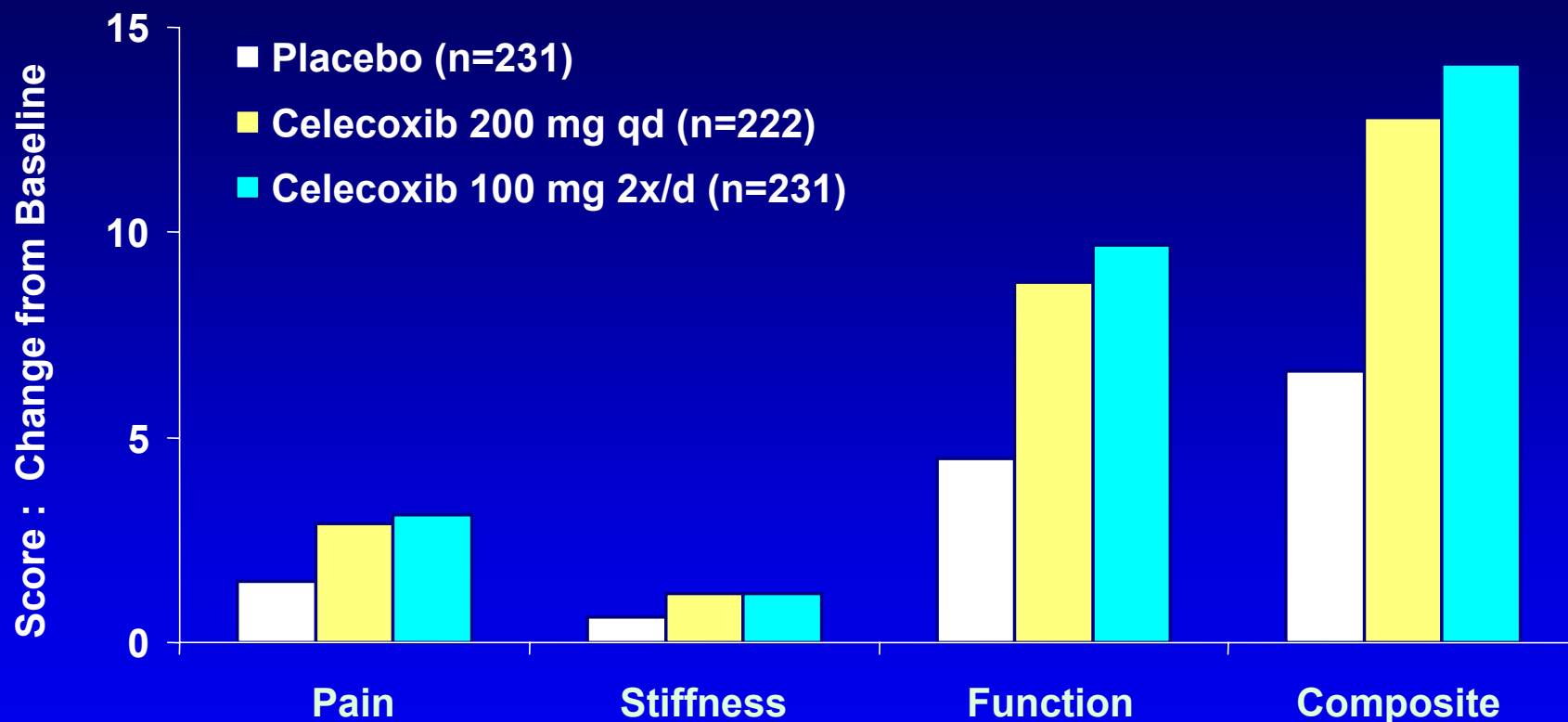
Data on file : Searle Study 020

Celecoxib vs Diclofenac in OA

Patient's Assessment of Pain

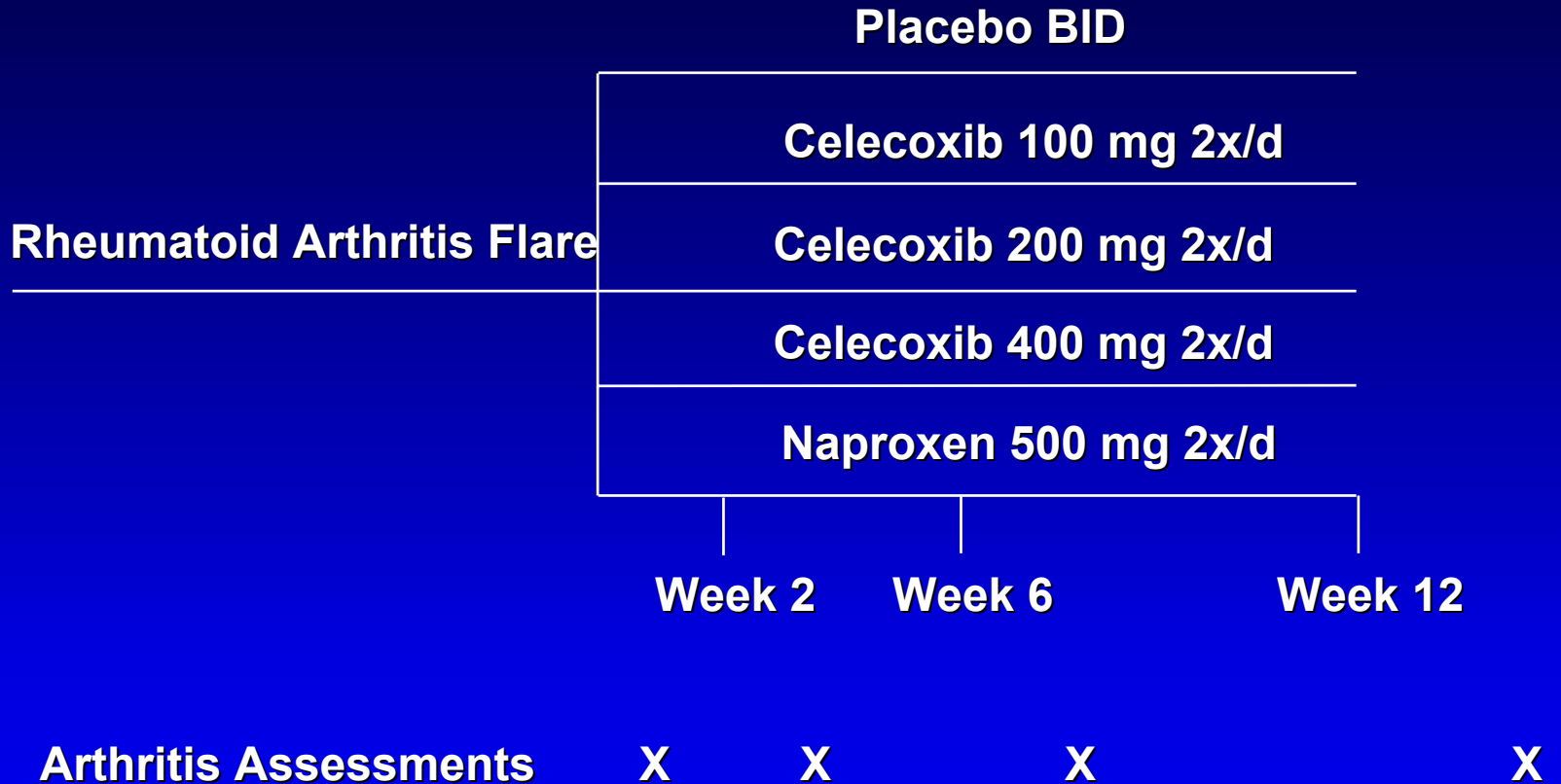


Efficacy of celecoxib 200 mg once a day (qd) in OA



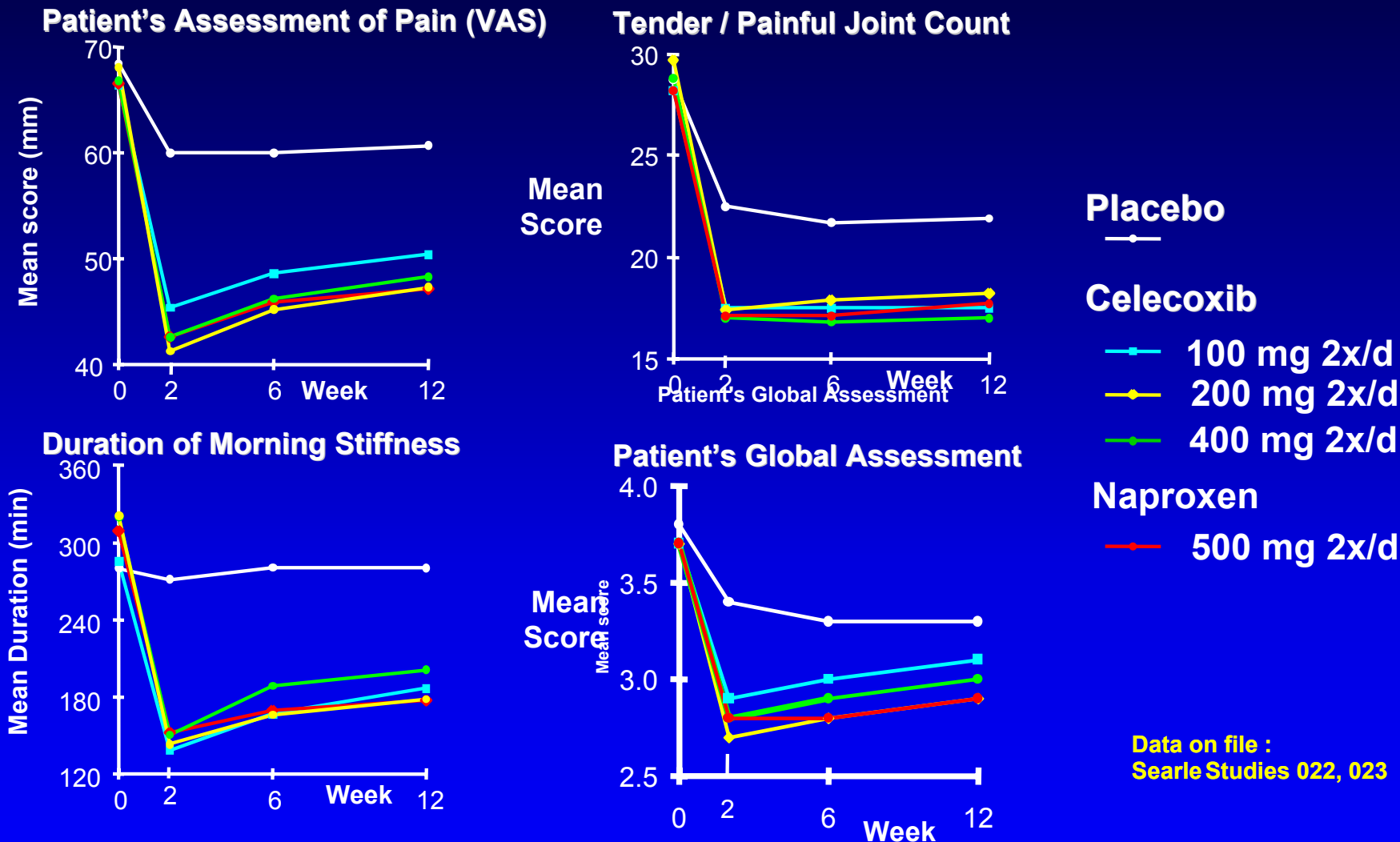
Searle Study 060

Phase III RA Trial Design



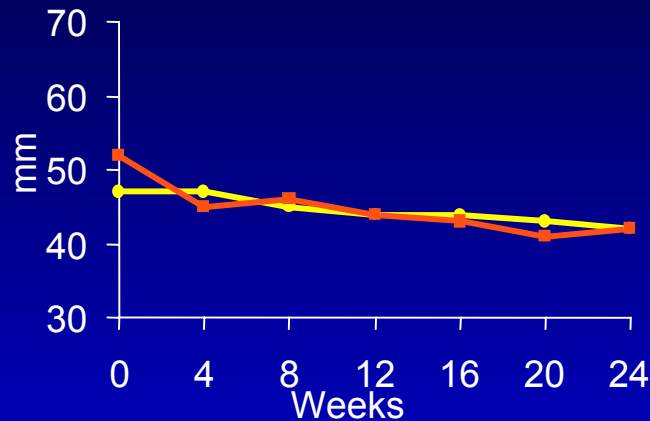
Geis GS et al. *Arthritis & Rheum* 1998;41(9) Suppl:1990A
Searle Studies 022, 023

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

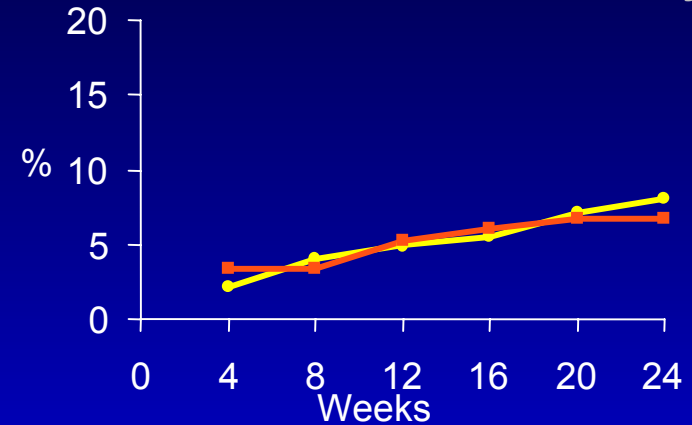


Celecoxib (200 mg 2x/d) vs Diclofenac (75 mg SR 2X/d) in RA (6 months)

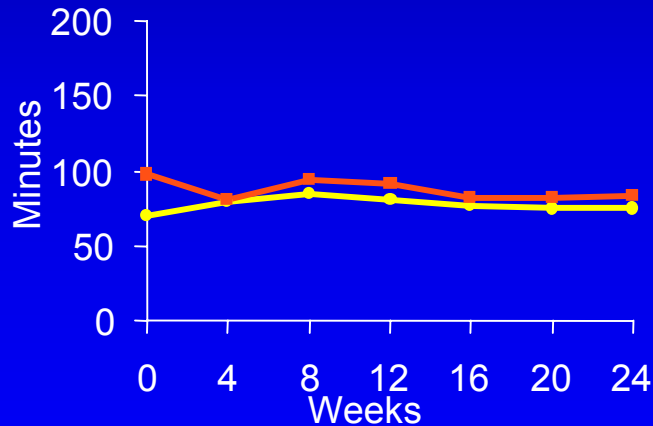
Pain VAS



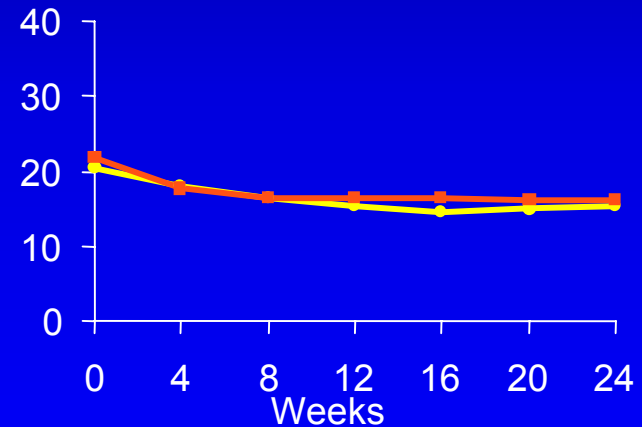
Withdrawal for Lack of Efficacy



Morning Stiffness

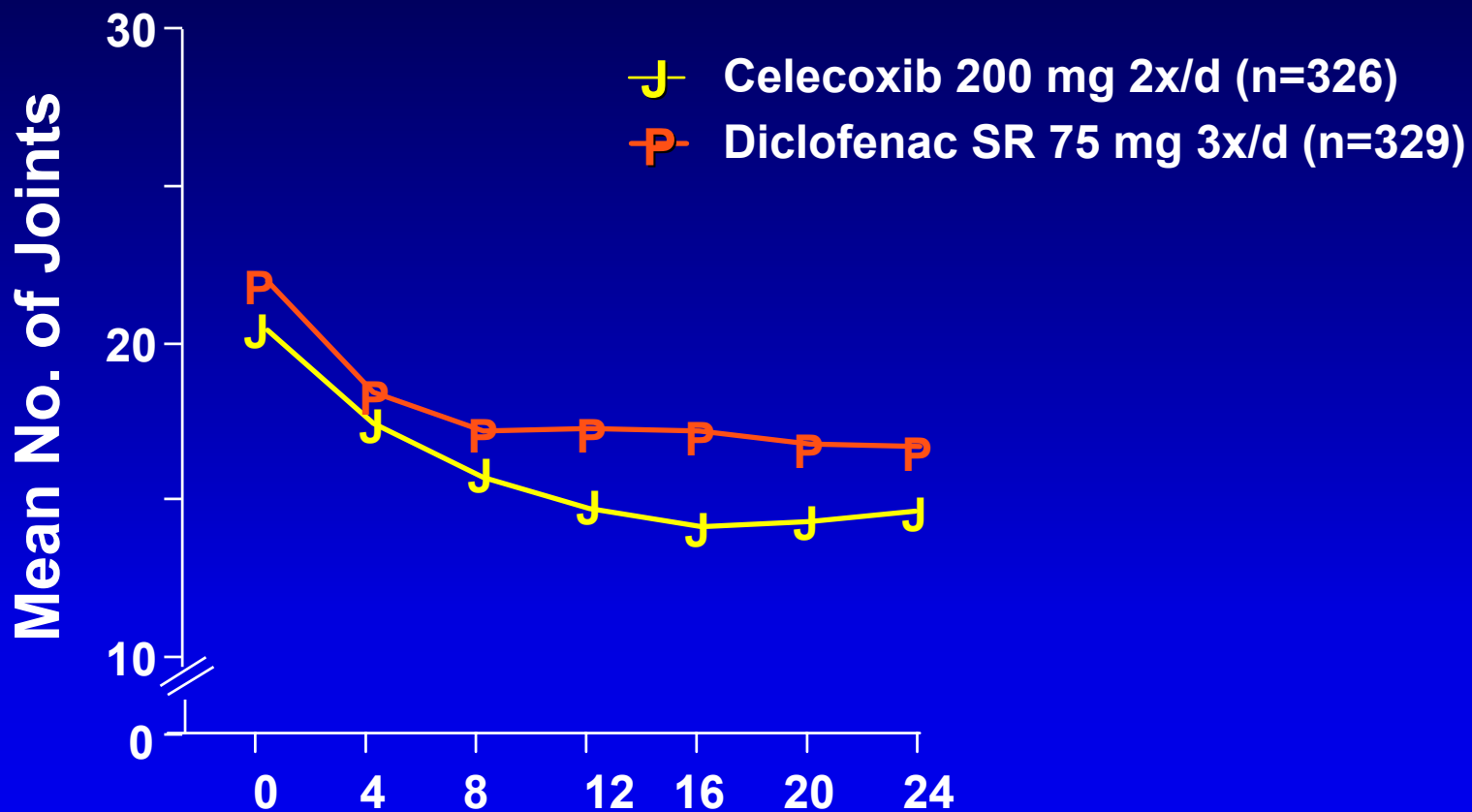


No. of Tender / painful Joints



Data on File : Searle Study 041
Emery P et al, 1999, 354, 2106-2111

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



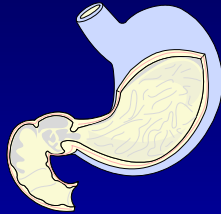
Data on File : Searle Study 041
Emery P et al, Lancet, 1999,2106-2111

Why do need Cox-2 inhibitors ?

Conventional AINS are toxic ...

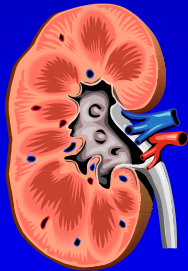
Adverse Effects of common NSAIDs

Upper - GI



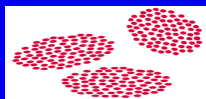
- ➔ Dyspepsia
- ➔ Erosions
- ➔ Anaemia - GI bleeding
- ➔ Ulcers - bleeds/perforations

Renal



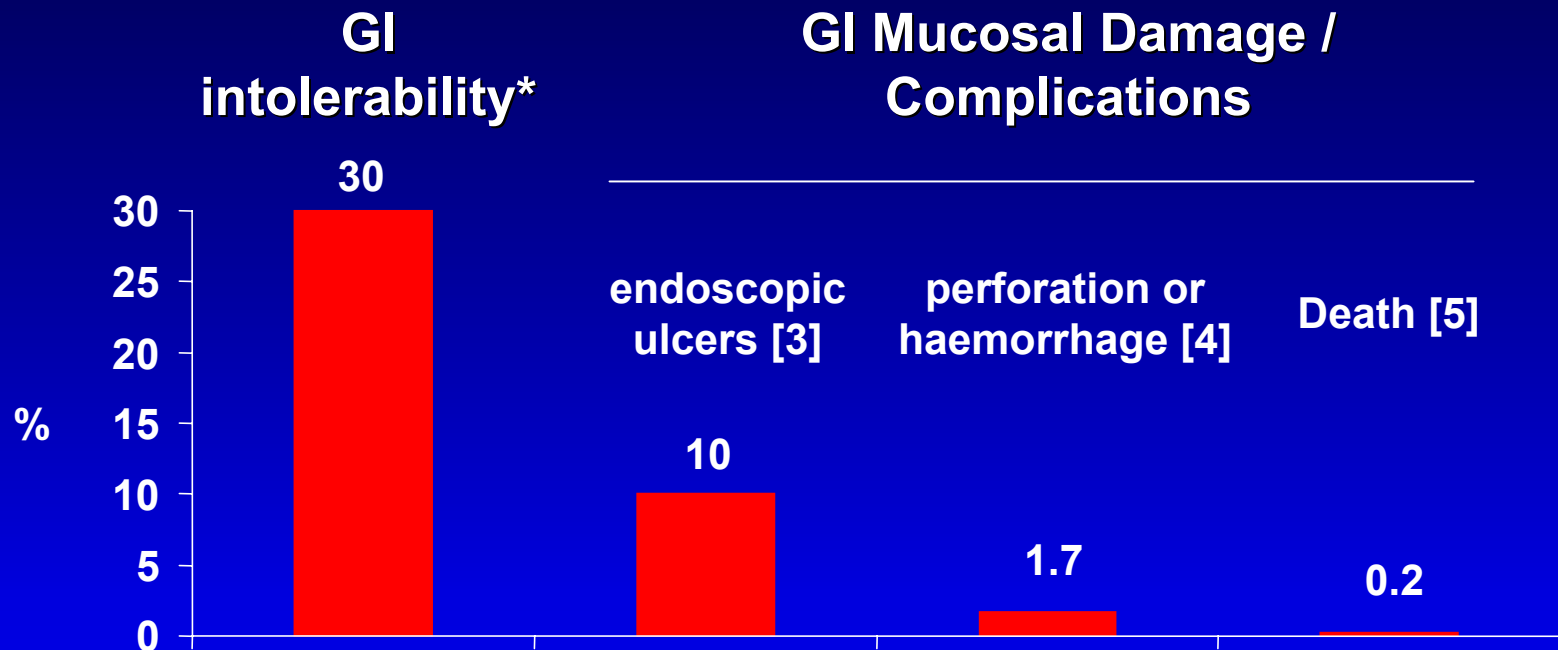
- ➔ Renal dysfunction
- ➔ Renal failure - acute/chronic
- ➔ Blood pressure
- ➔ Heart failure

Anti-platelet effects



- ➔ Contributes to blood loss

NSAIDs toxicity



* Range 20-50% based on
- withdrawals for GI symptoms¹
- community surveys for GI symptoms²

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

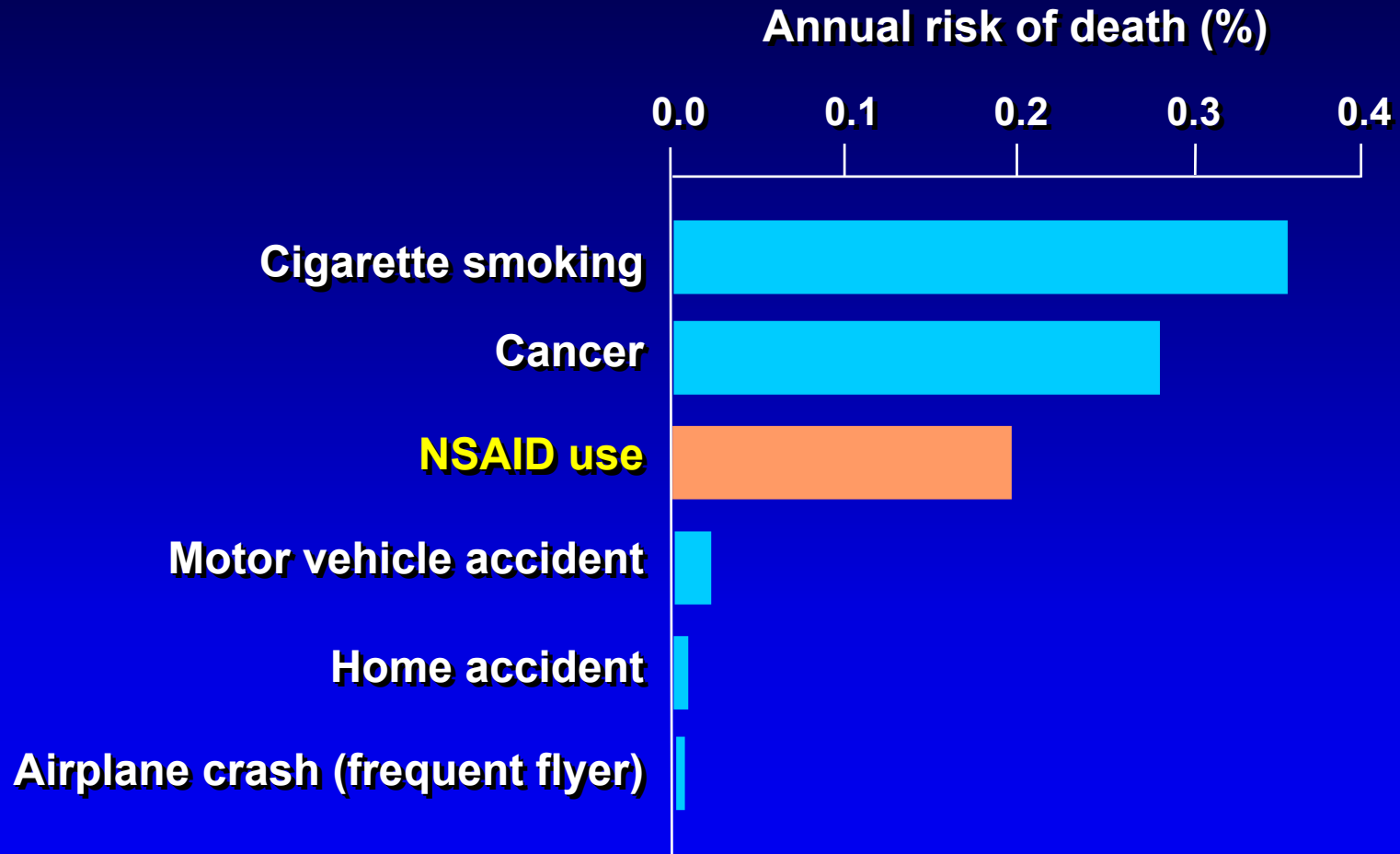
NSAID Ulcers and Ulcer Complications

- **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.

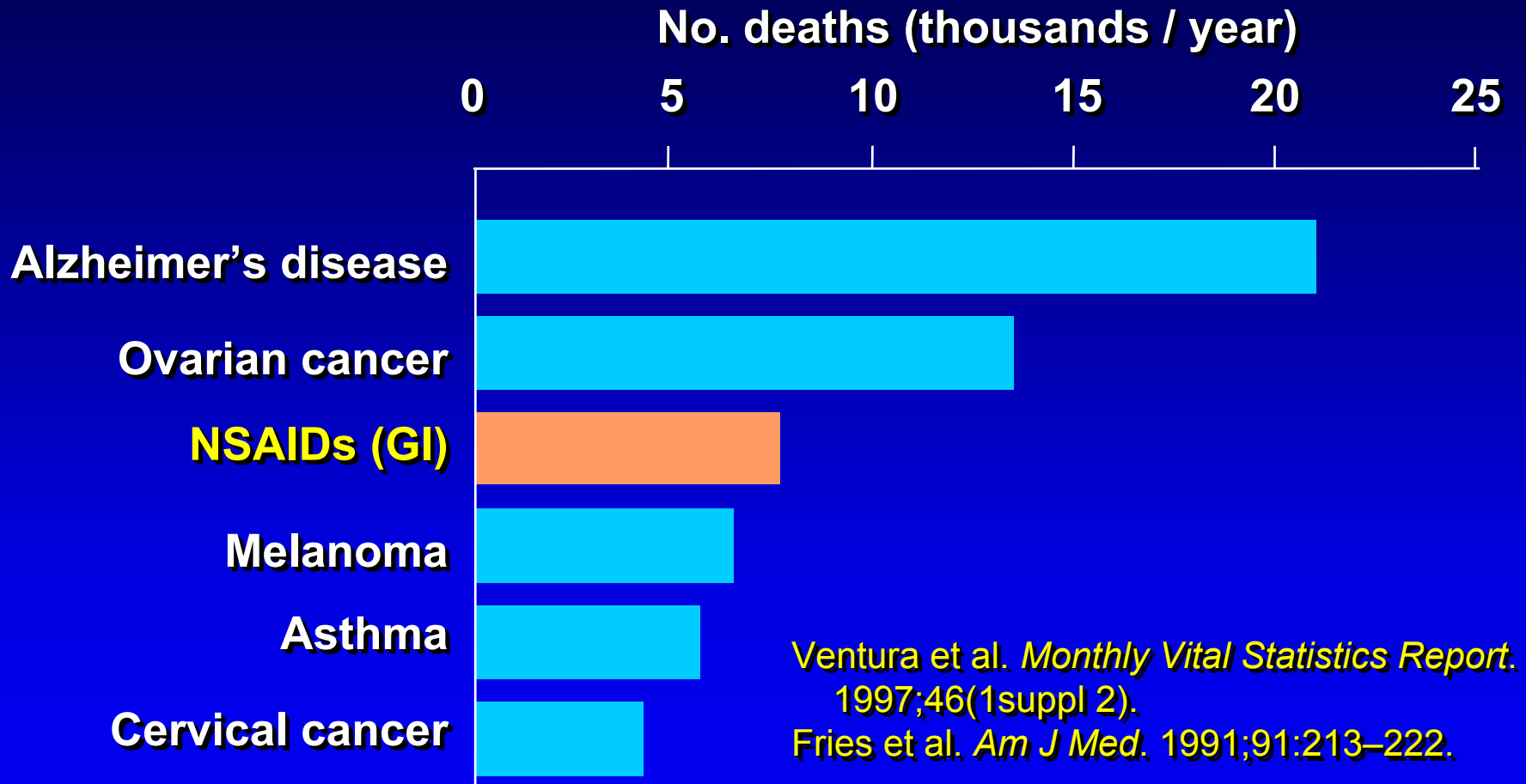
Geis GS et al. *J Rheumatol* 1991;18:11-14.

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

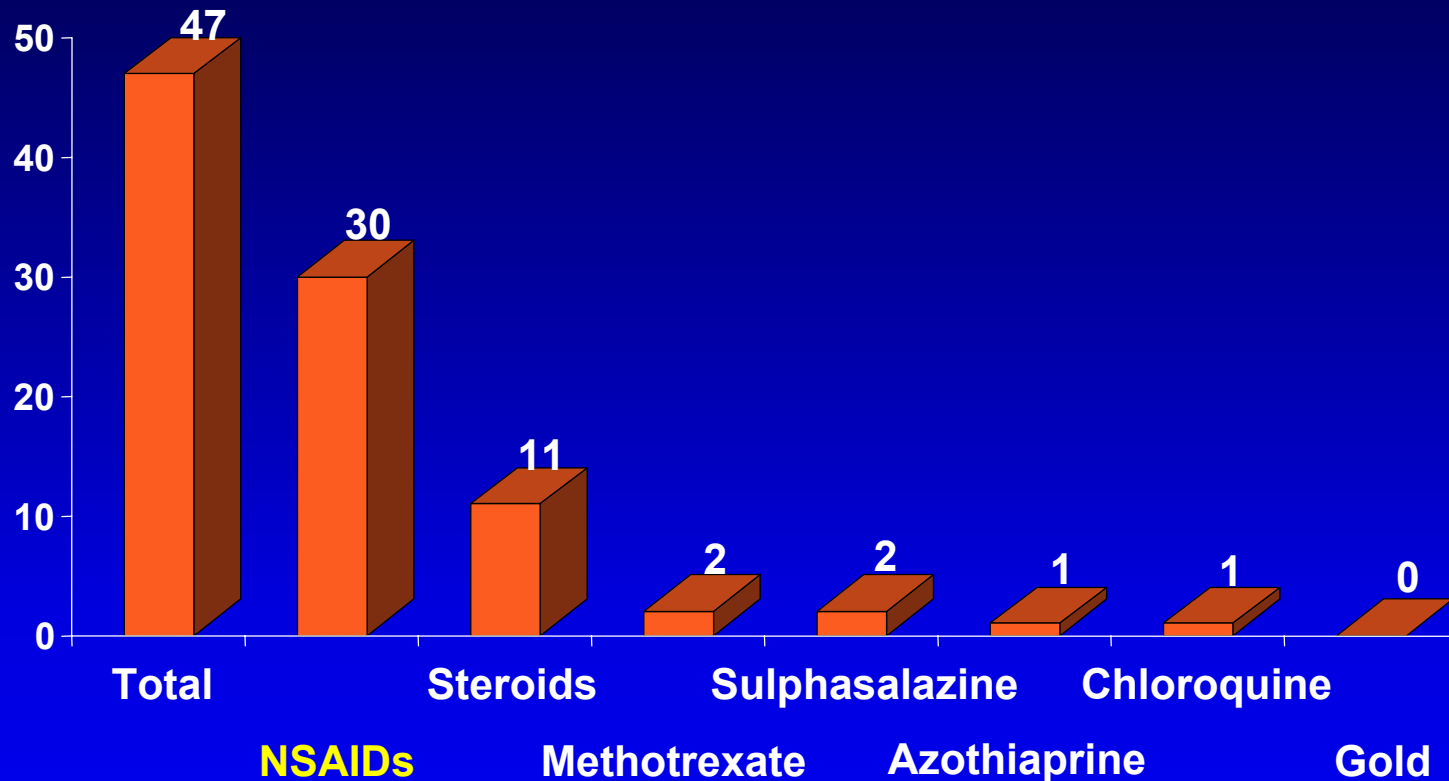


Fries et al. *Am J Med.* 1991;91:213–222;
Wilson, Crouch. *Science.* 1987;236:267–270.

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



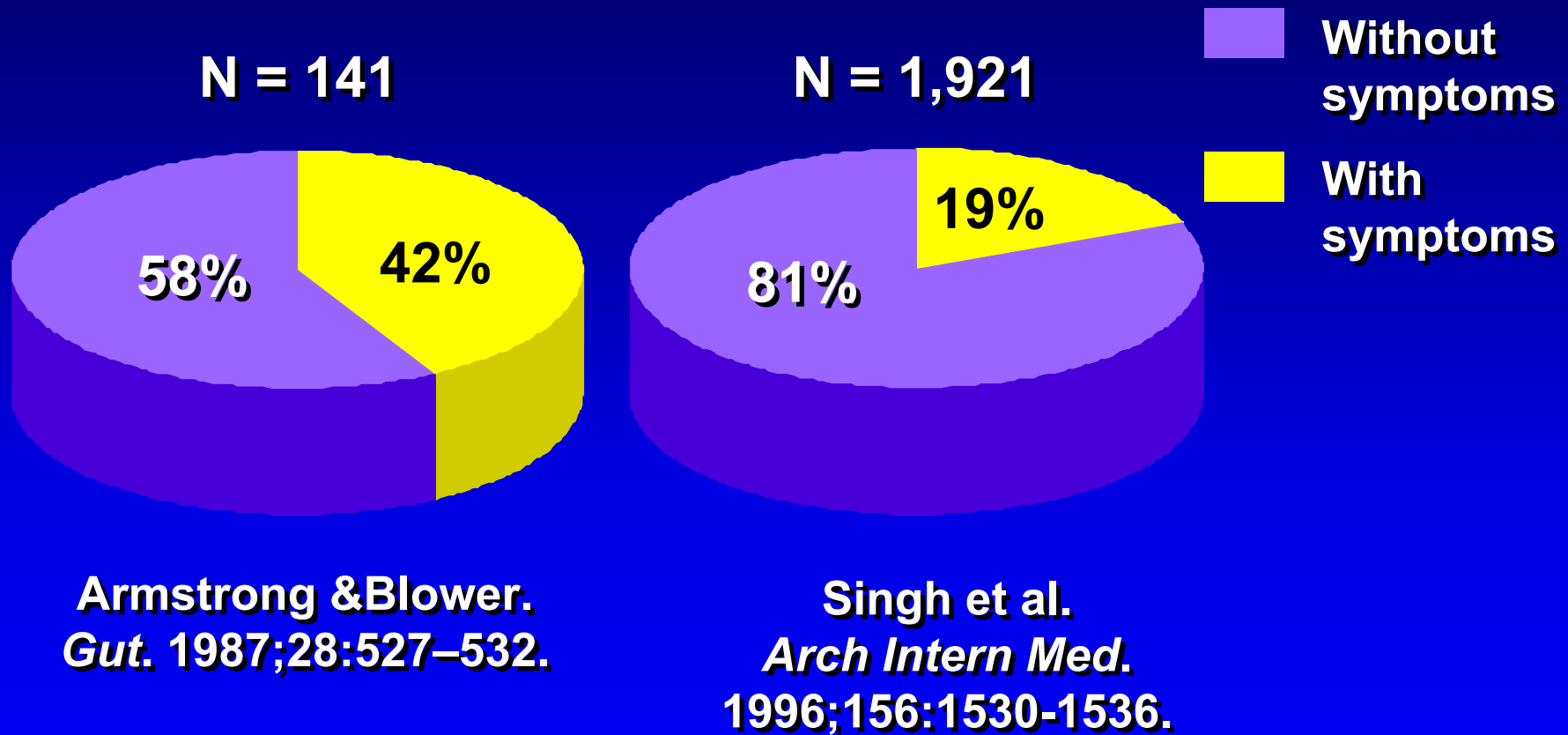
Deaths attributed to anti-rheumatic medication (series of 1666 patients with RA)



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

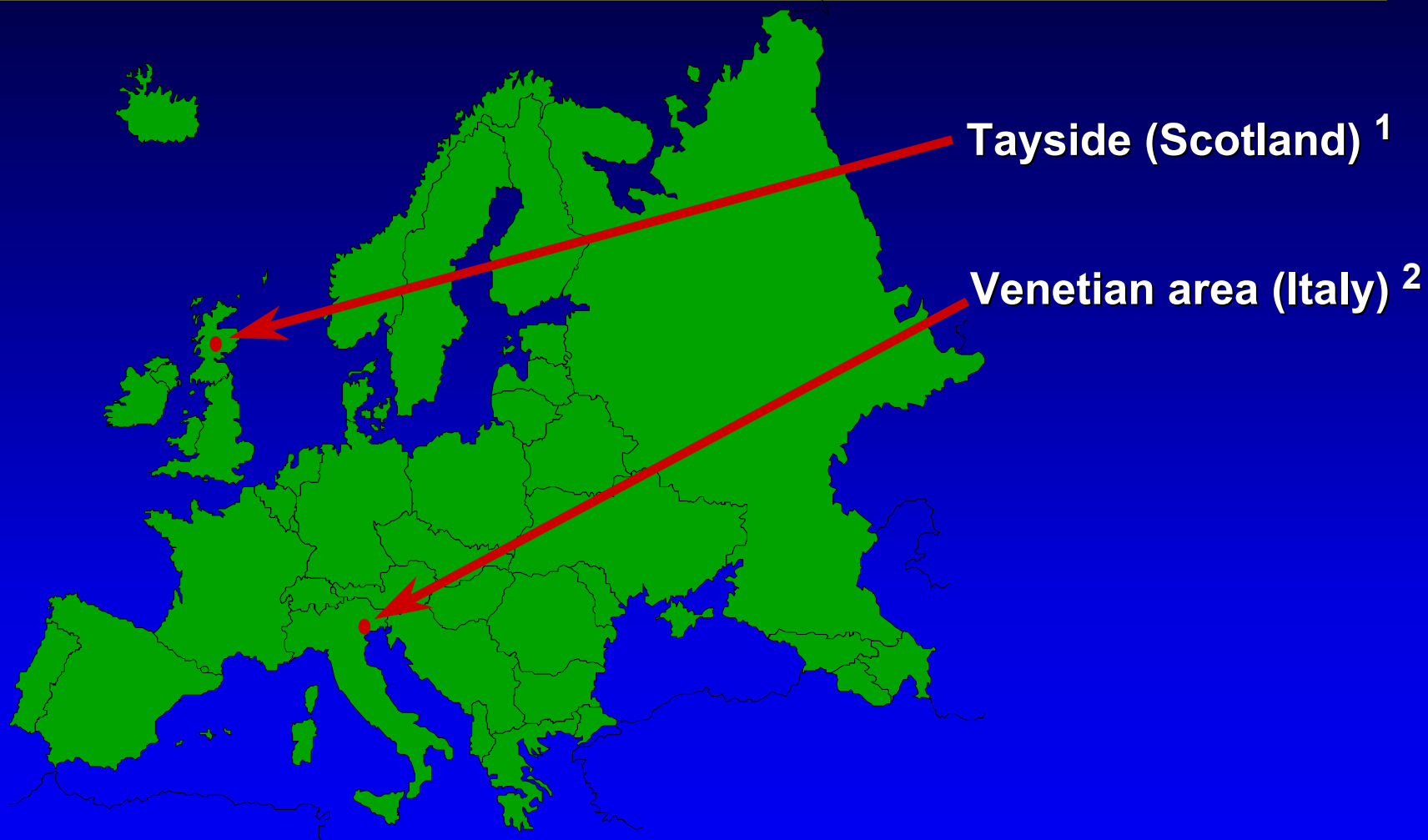
Most patients are asymptomatic prior to a serious NSAID-associated GI event ...

Bleeding, perforation, and gastric outlet obstruction



Pharmaco-epidemiological studies in Europe

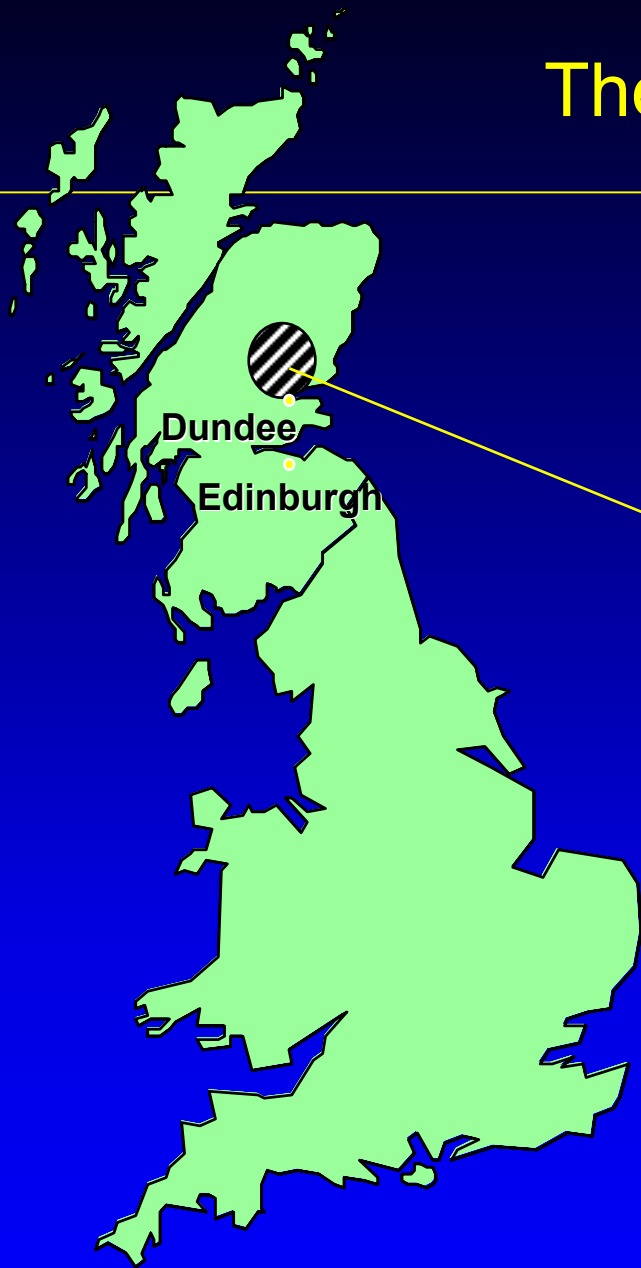
NSAIDs and GI events



1 : MacDonald et al, BMJ, 1997, 315,1333-1337

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

The Tayside study

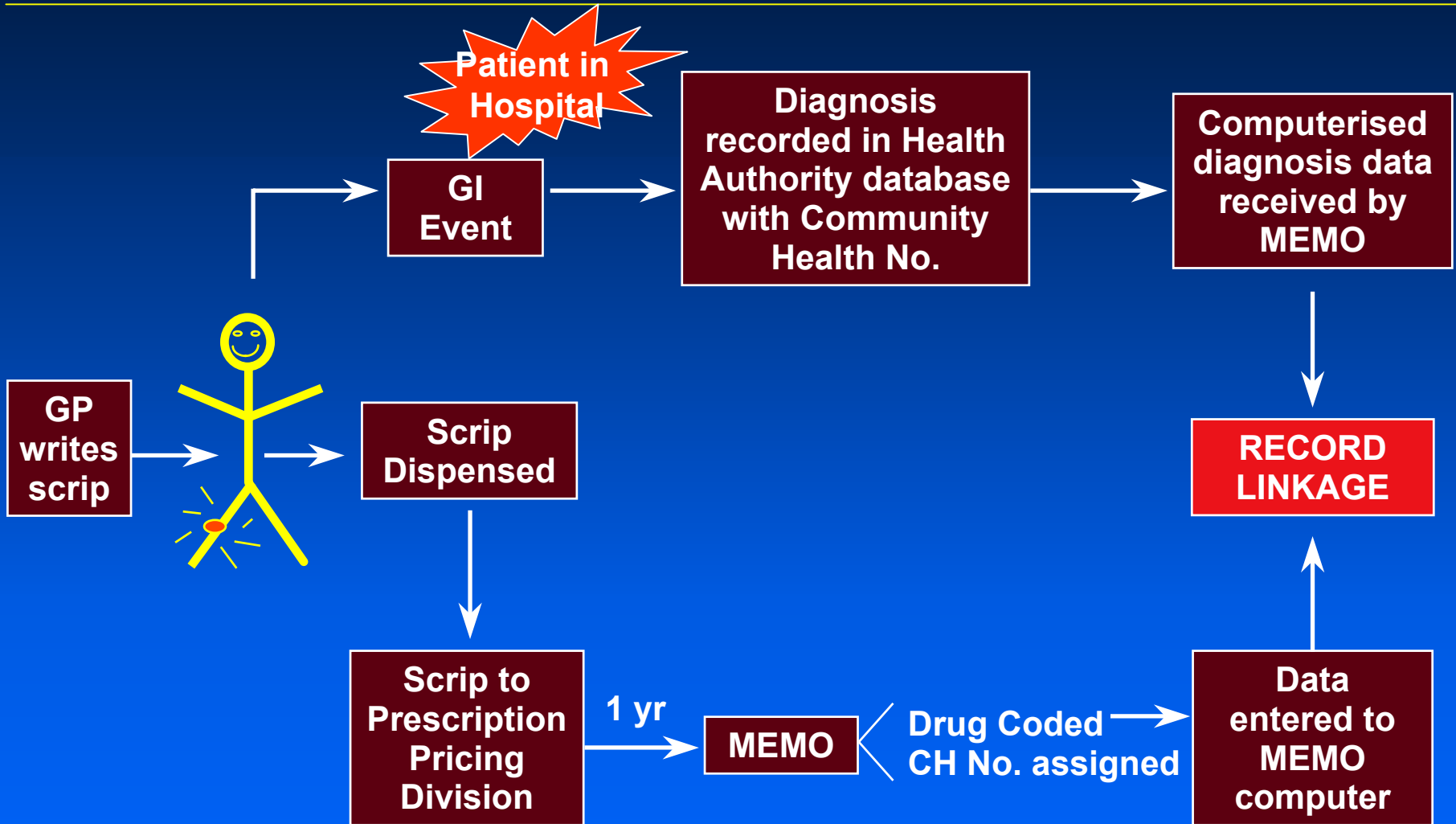


Tayside Area of Scotland

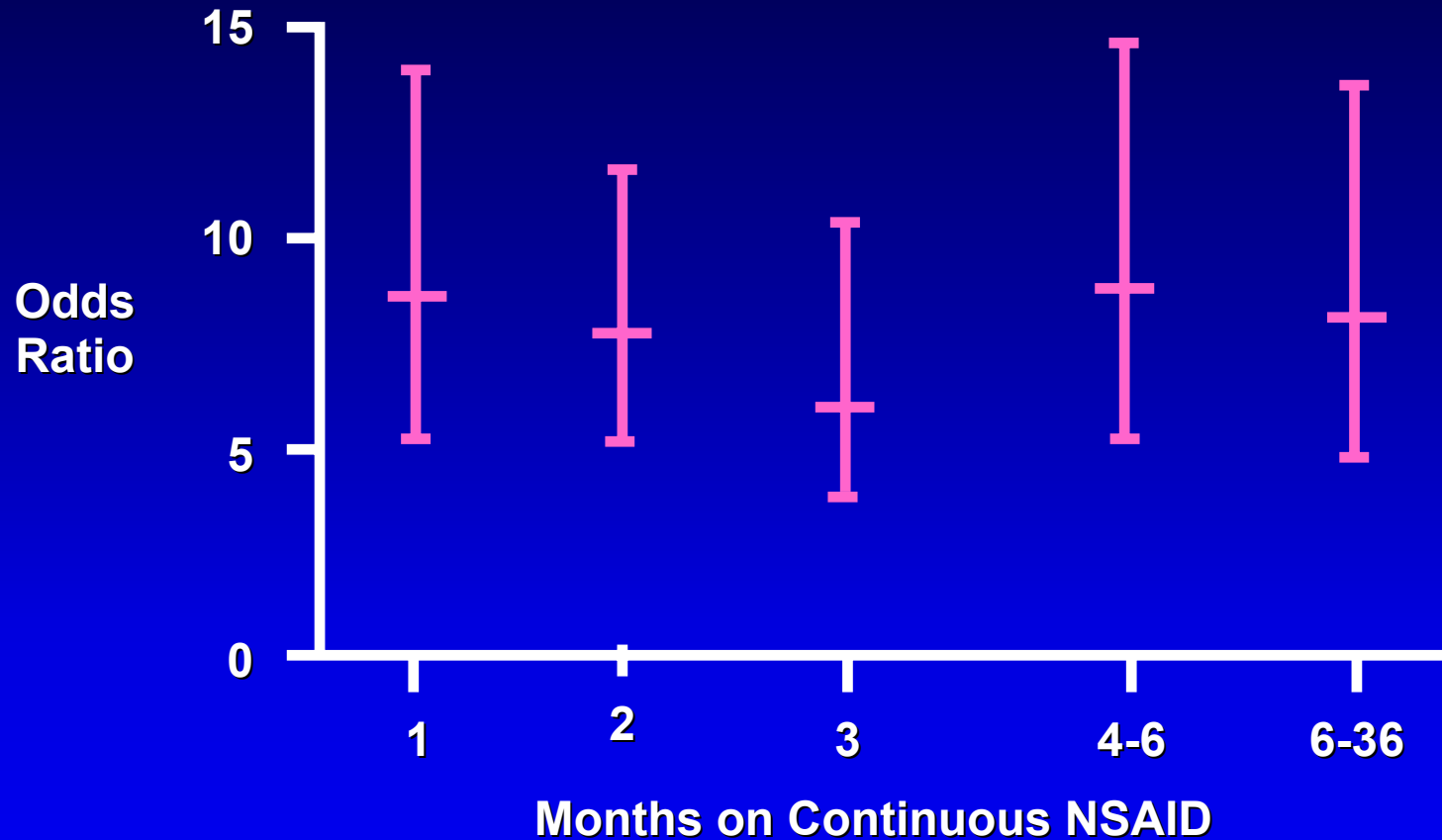
Unit for Medicines Monitoring (MeMo)

- 400,000 population
- Monitored all NSAIDs for 3yr
- 107,000 NSAID-users

The Tayside Record Linkage System



NSAID Induced GI Complications - Constant Risk



MacDonald et al, BMJ 1997, 315,1333-1337

*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)
<i>Ketorolac</i>	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 every day 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**

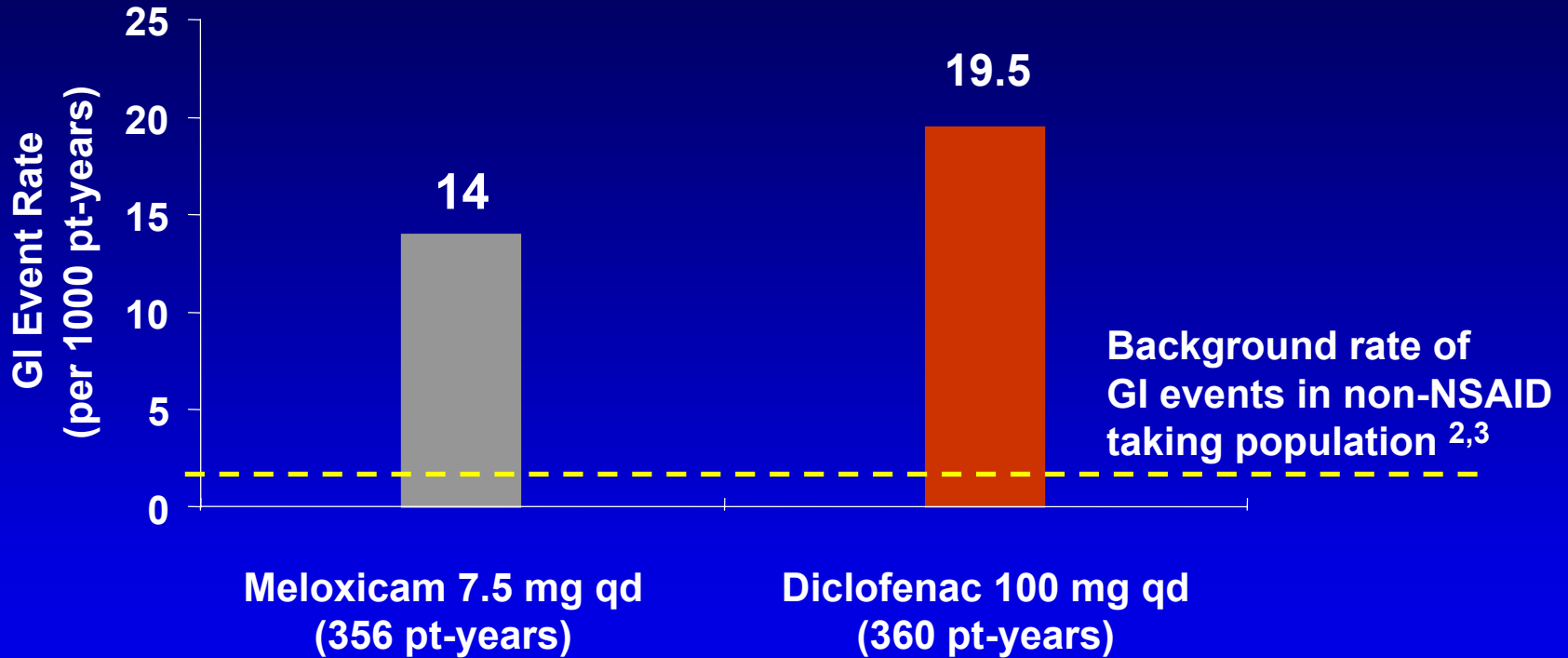
Calculated from :

Blower AL et al, Aliment Pharmacol Ther, 1997, 11, 283-291

MacDonald T et al, BMJ, 1997, 315, 1333-1337

Meloxicam : clinically significant GI events

Upper GI perforation, ulceration or bleeding



1. Hawkey et al, BJR, 1998, 37,937-945
2. McDonald et al, BMJ, 1997, 315,1333-1337
3. Singh et al, Am J Med, 1998,105(1B),31S-38S

**qd = quaque die
daily dose in one
administration per day**

Meloxicam : influence of the dose

- 341 patients with RA treated with 15 mg meloxicam daily for up to 18 months (66%)
- 28% experienced GI adverse events
- 13.7% discontinued for adverse events
- 3.9% discontinued for GI adverse events
- 0.8% serious GI complications

Huskisson EC et al, BJR, 1996, 35 (Suppl.1) 29-34

This is why ...

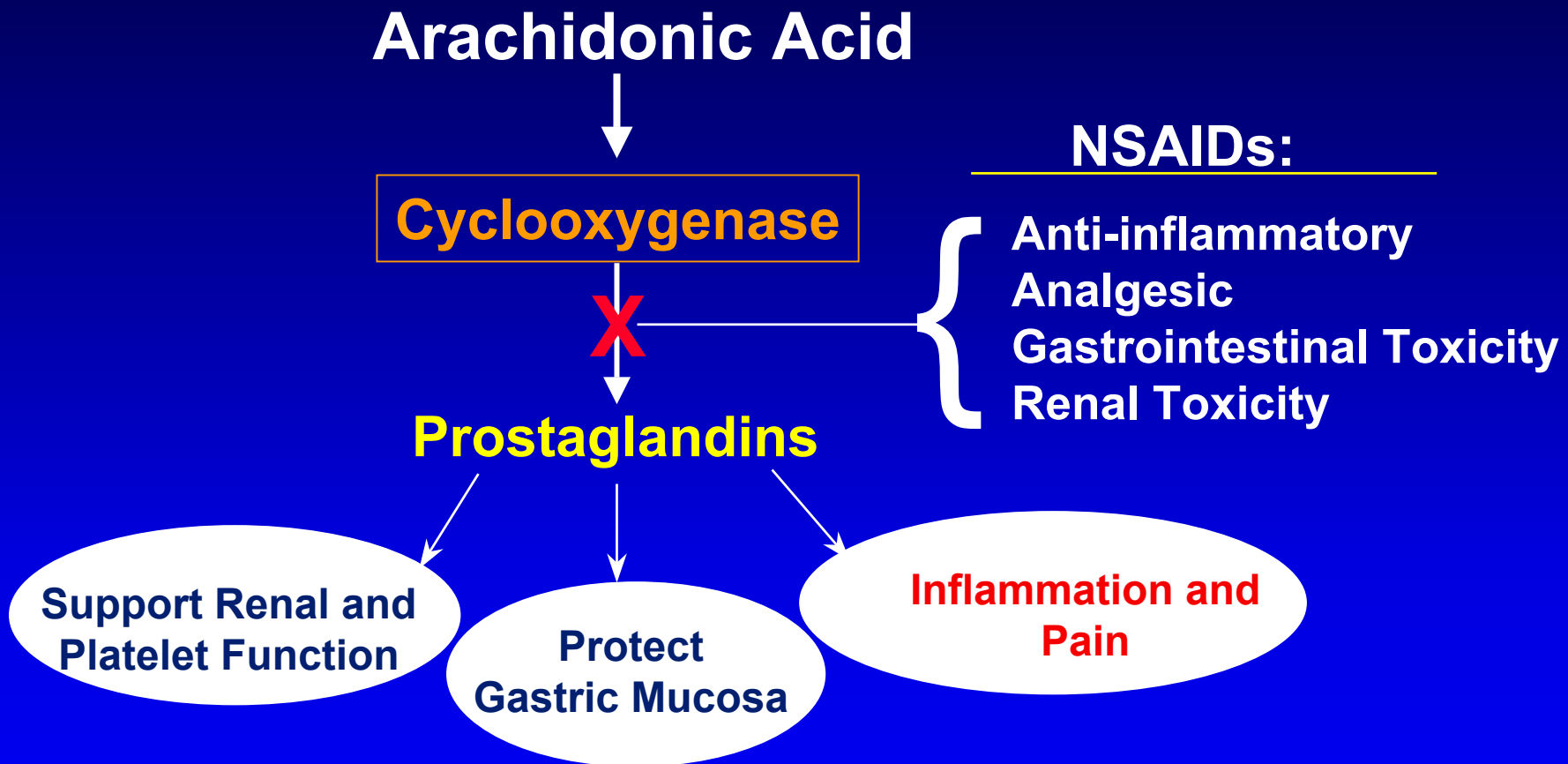
“Toxicity is the major reason for not recommending the use of NSAIDs as first-line therapy for patients with OA of the hip”

**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

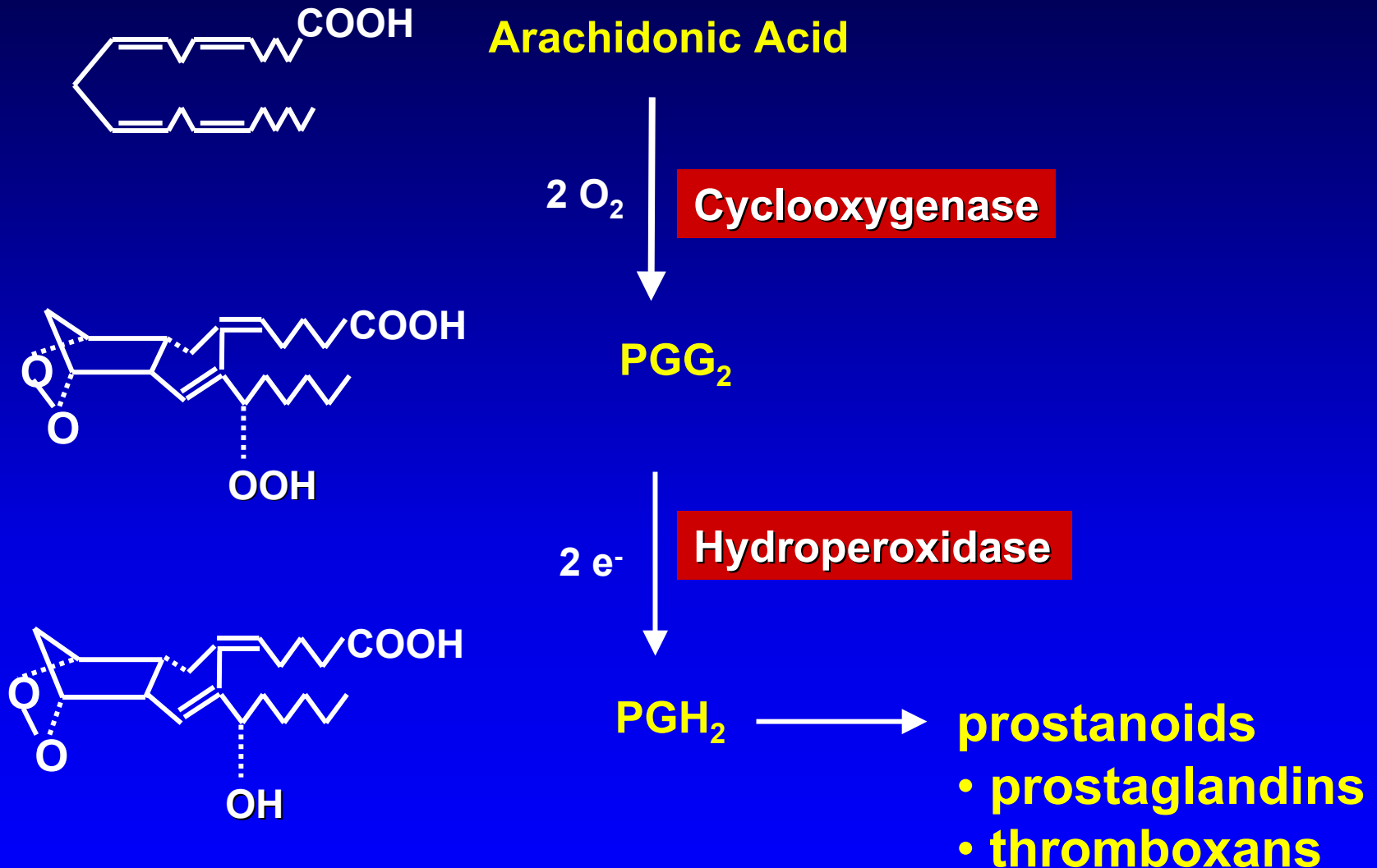


Shorrock CJ et al. *Am J Med* 1988;84 (Suppl):25-34.

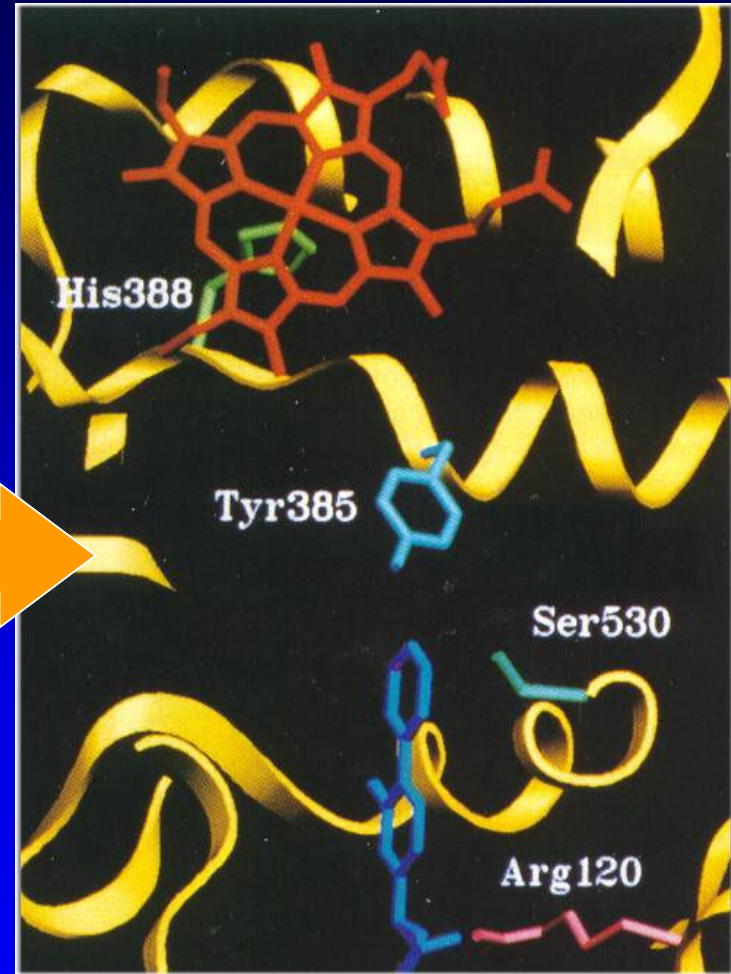
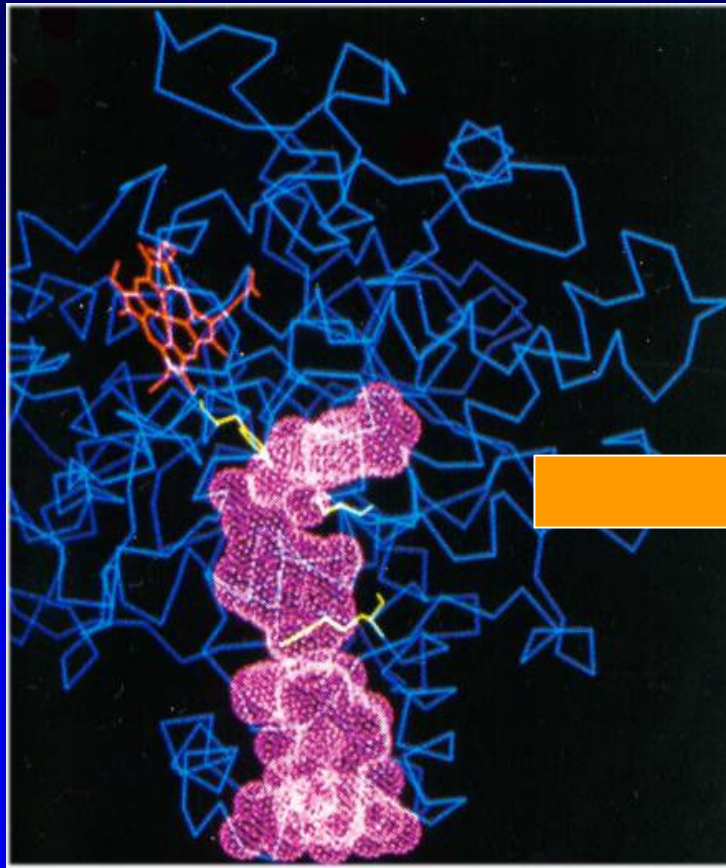
The Discovery of the role of cyclooxygenase

- **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

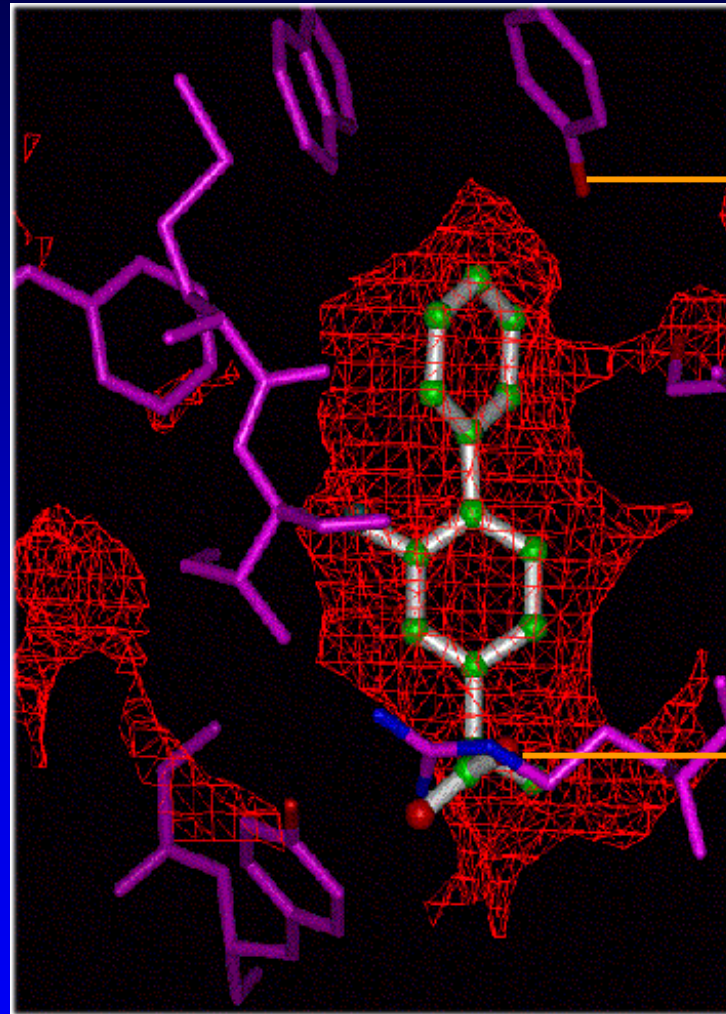


Mapping of the cyclooxygenase active site



Mapping of the cyclooxygenase active site

**COX-1 Active Site
occupied by
flurbiprofen**

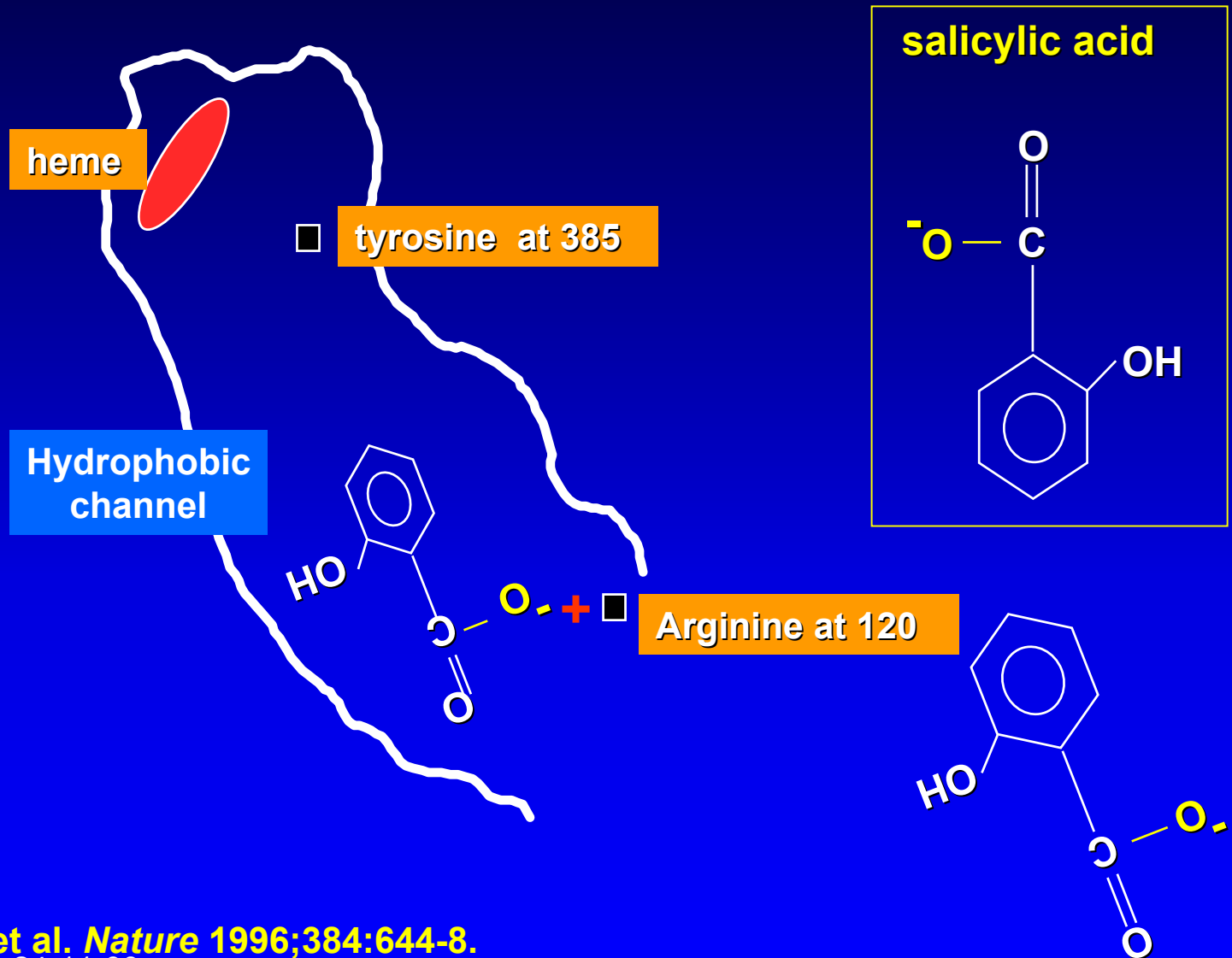


tyrosine 385

arginine 120

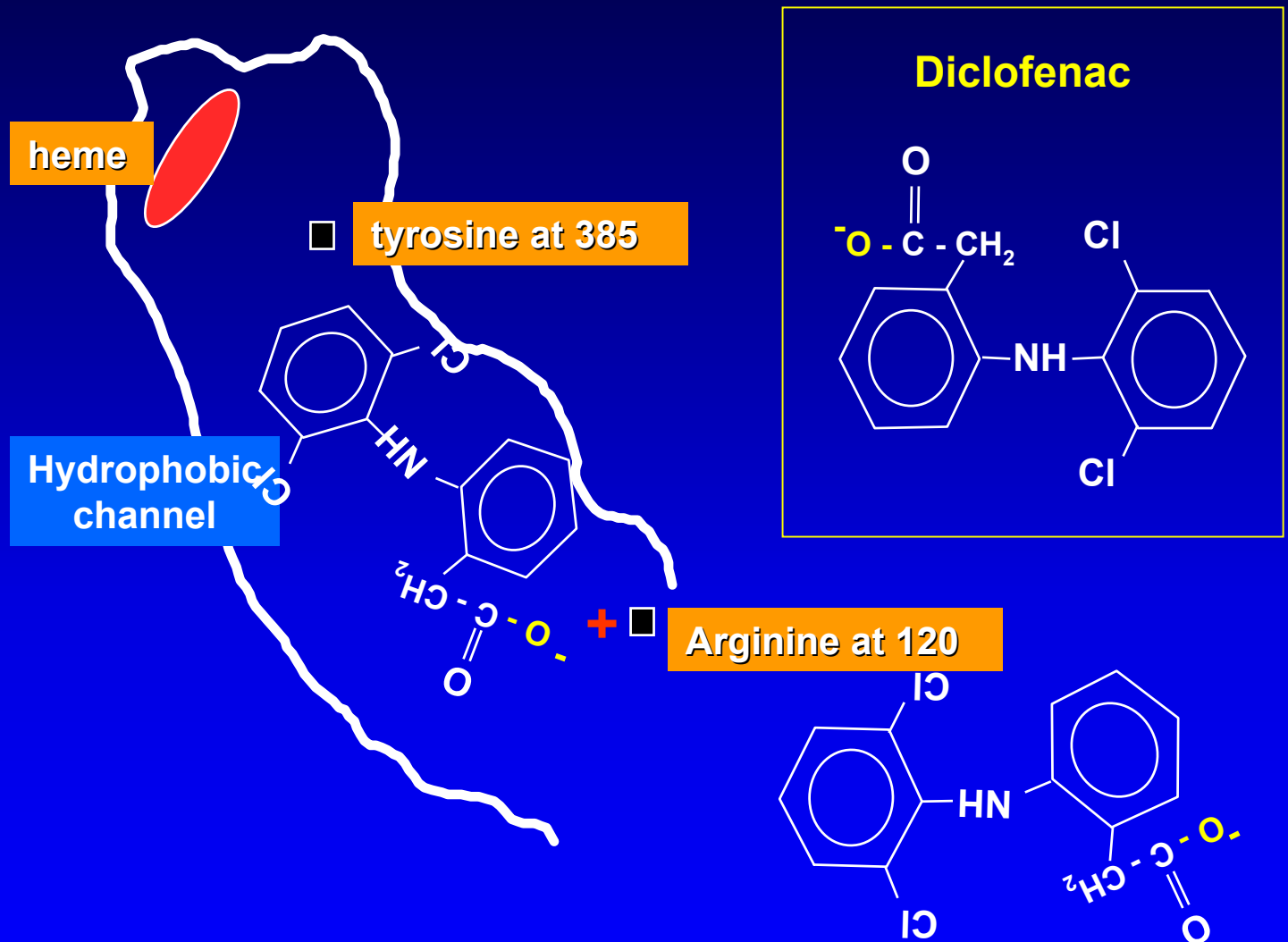
Picot, Loll and Garavito: Nature 1994; 367:243.

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



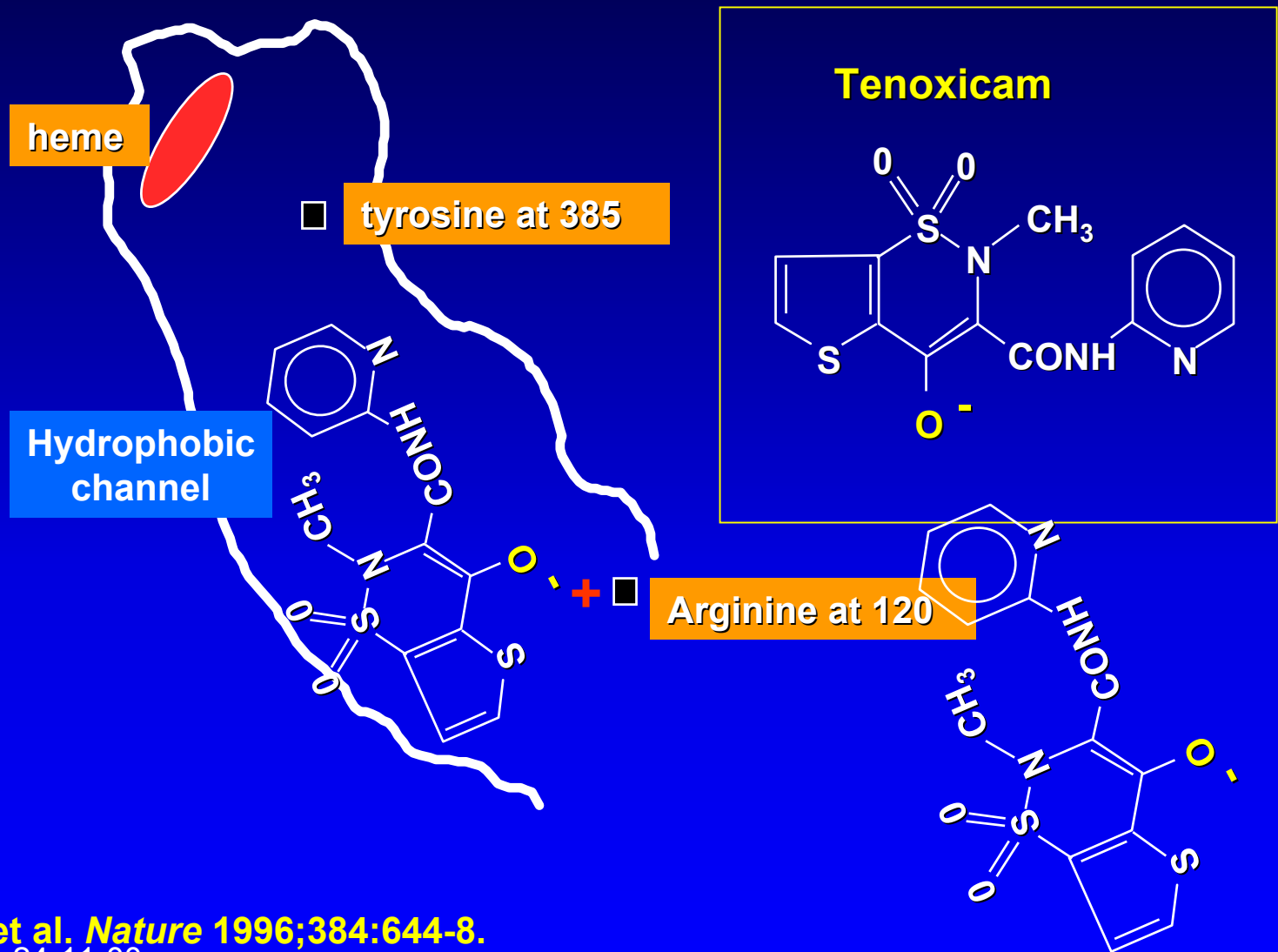
Kurumbail RG et al. *Nature* 1996;384:644-8.

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



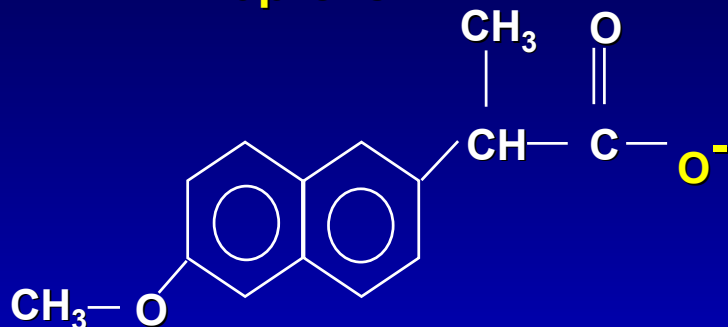
Kurumbail RG et al. *Nature* 1996;384:644-8.

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

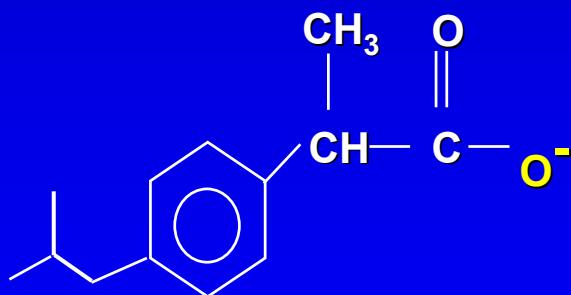


Similarities of structures ...

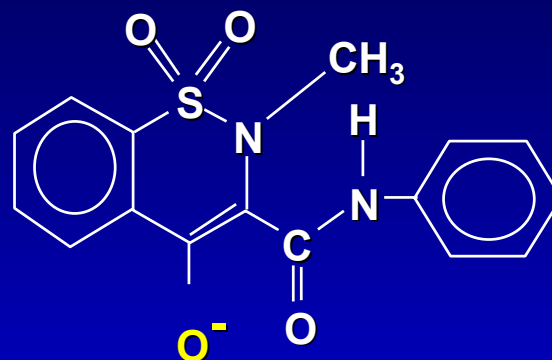
naproxen



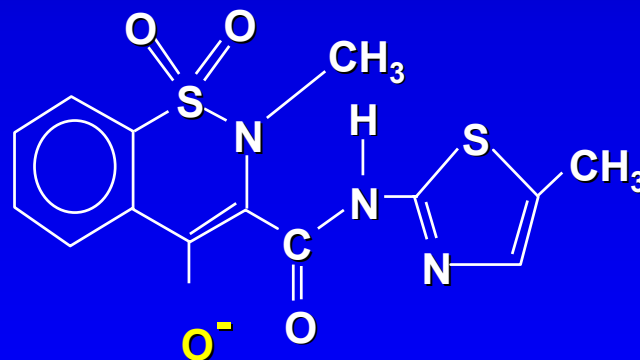
ibuprofen



piroxicam



meloxicam



Discovery of two forms of cyclooxygenase

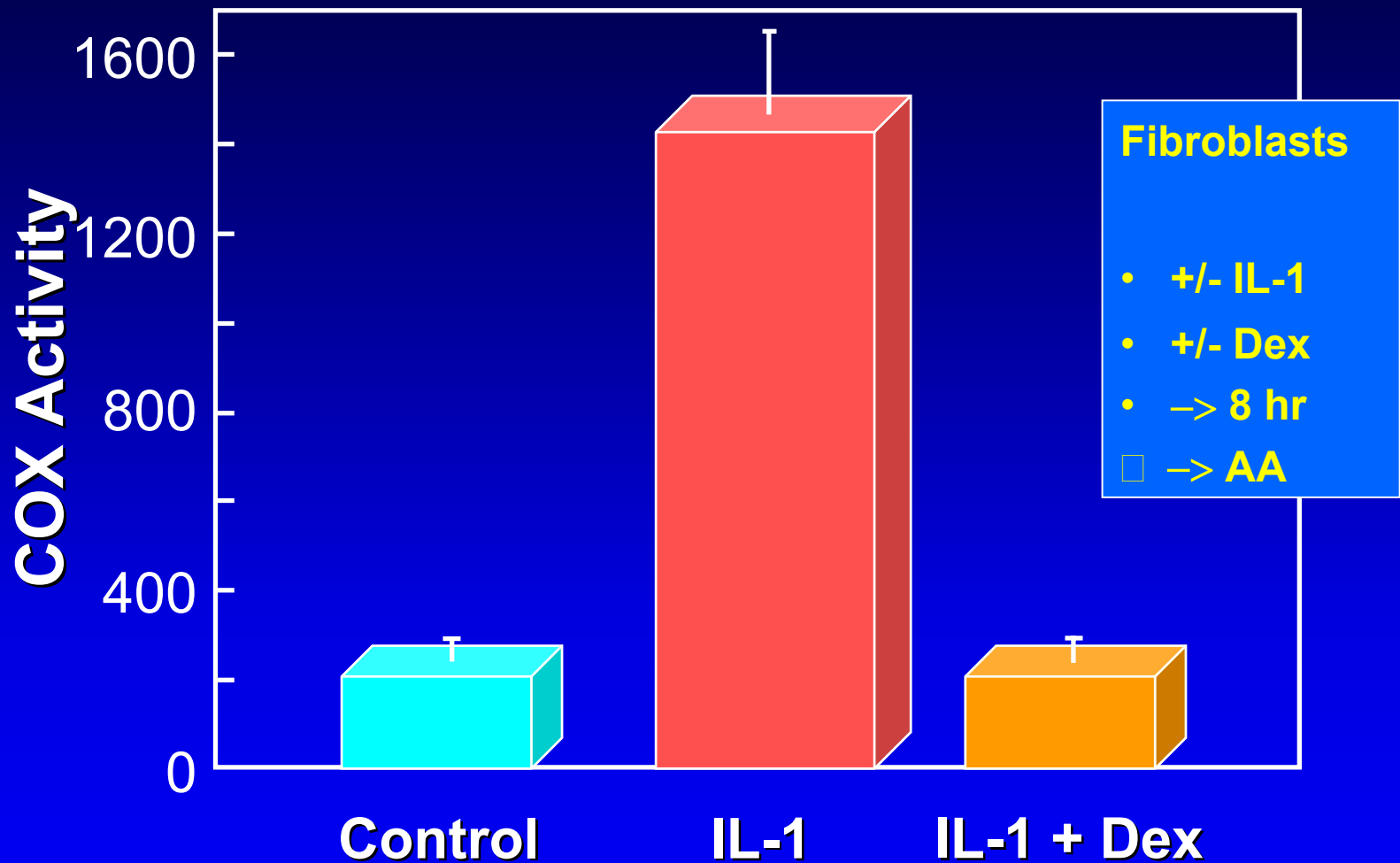
- **1989 ... IL-1 induces COX activity in fibroblasts ¹**
- **1990 ... the inducible COX activity is inhibited by steroids ²**
steroids had no effect on basal cyclooxygenase activity
- **1991 ... the inducible cyclooxygenase is cloned ³**
 - 60% identical to COX-1
 - certain important amino acid differences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

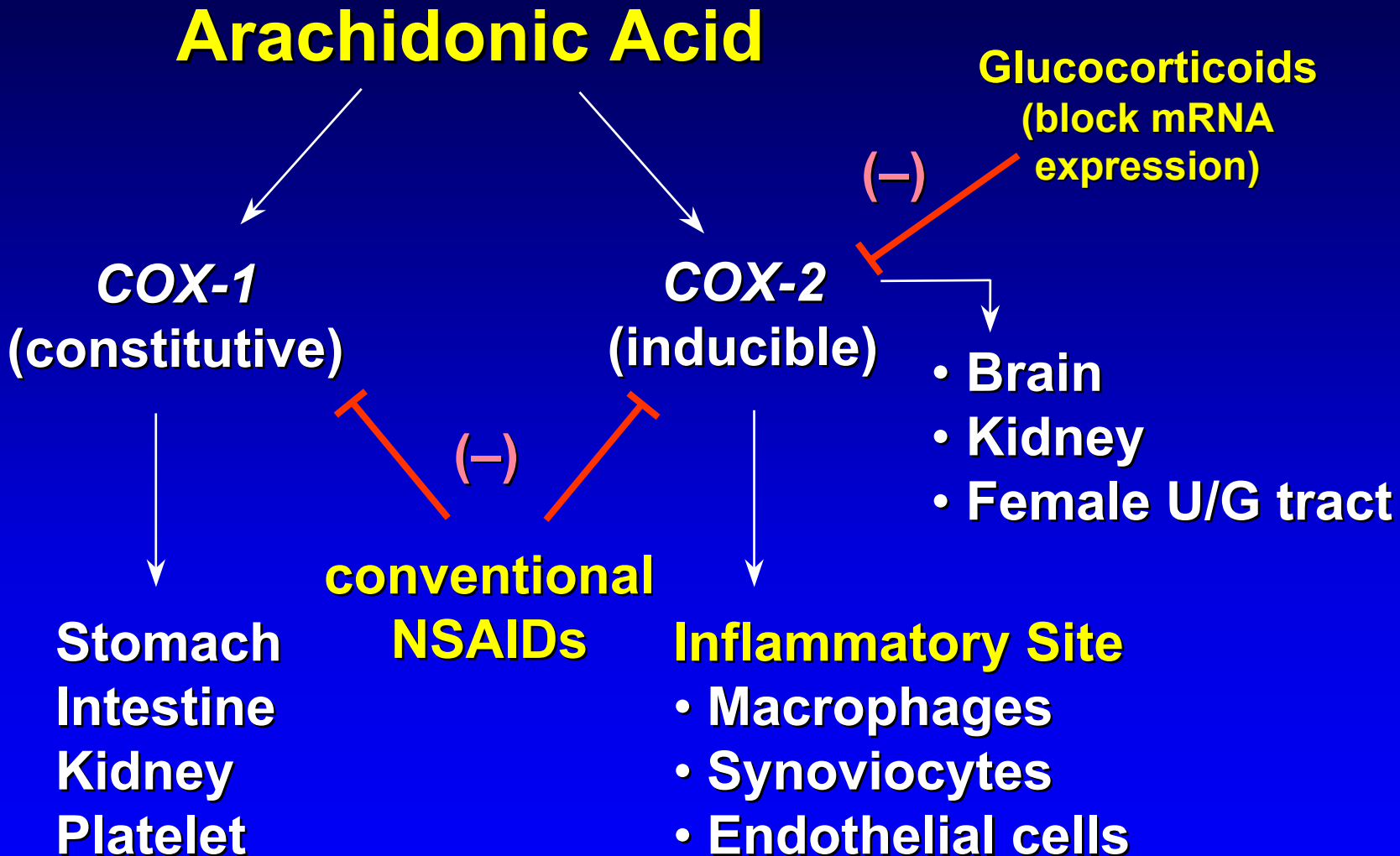
3 : Xie et al, 1991, PNAS, 88, 2692-6

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



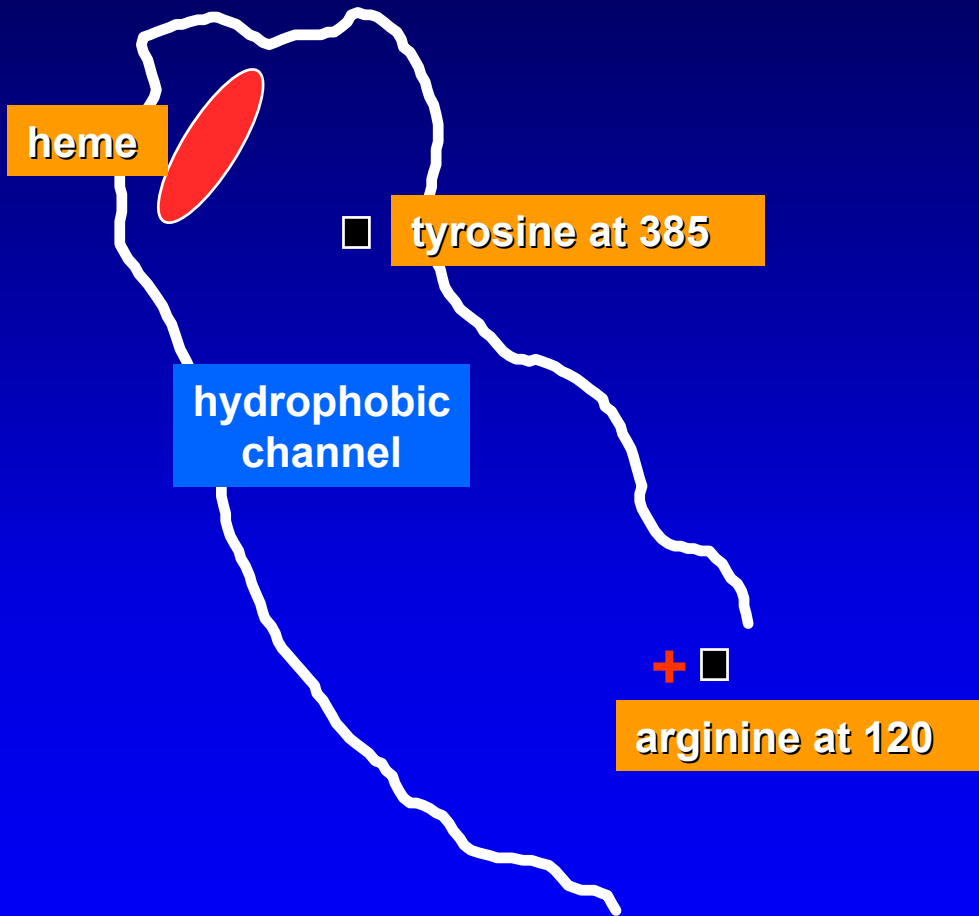
Raz et al, PNAS, 86,1657-1661

COX-2: a new anti-inflammatory drug target

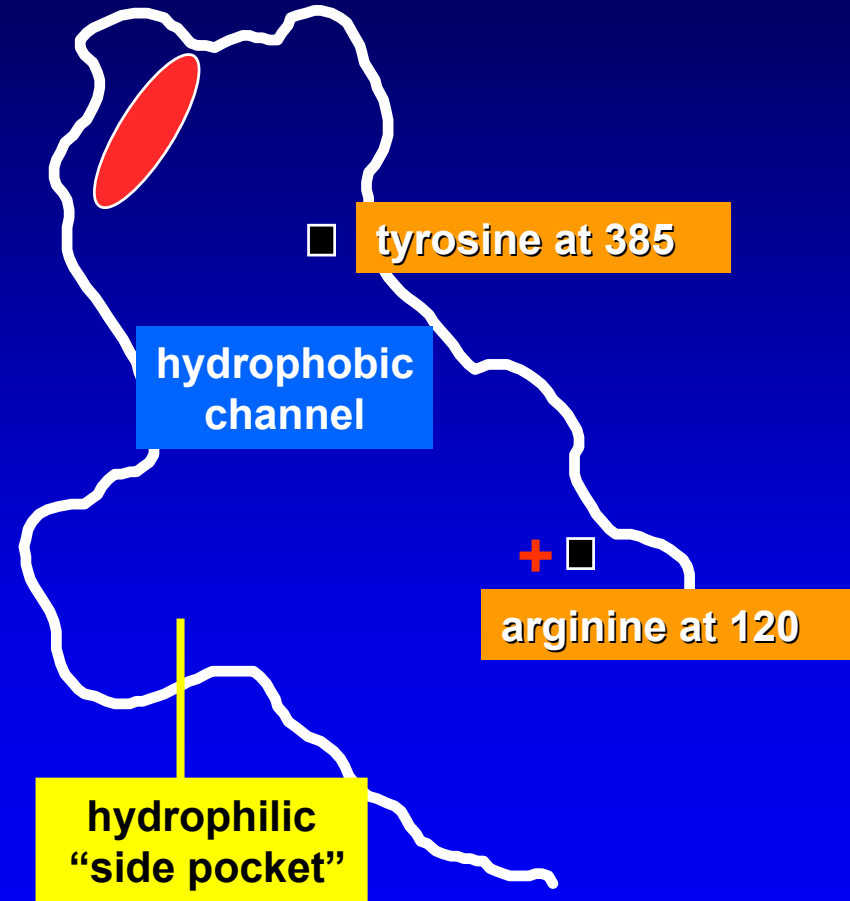


Structures of COX-1 and COX-2

COX-1



COX-2

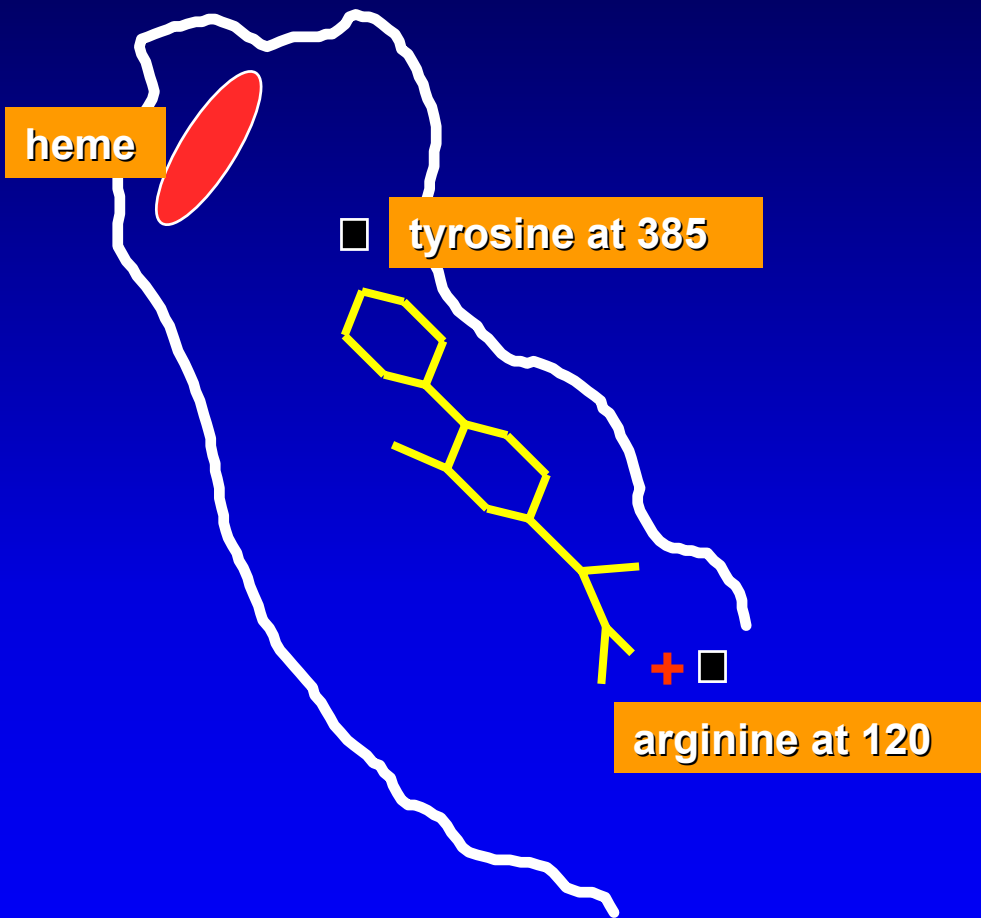


Kurumbail RG et al. *Nature* 1996;384:644-8.

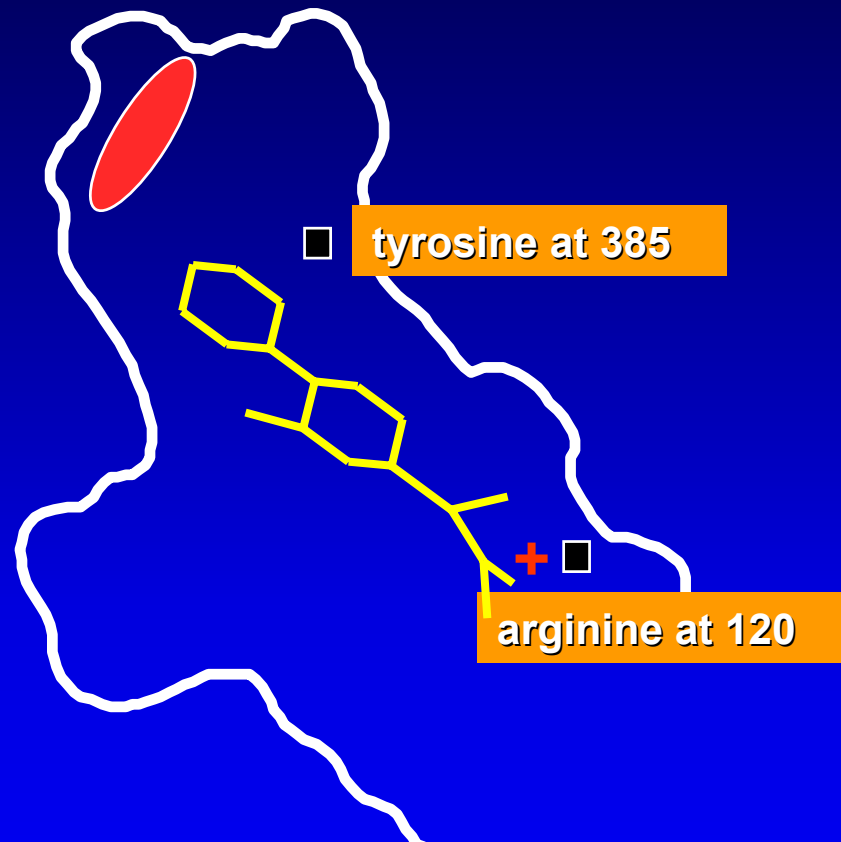
Newcastle meeting 24-11-00

Conventional NSAIDs inhibit both COX-1 and COX-2

COX-1



COX-2



binding to Arg 120
through carboxylate is enough...

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

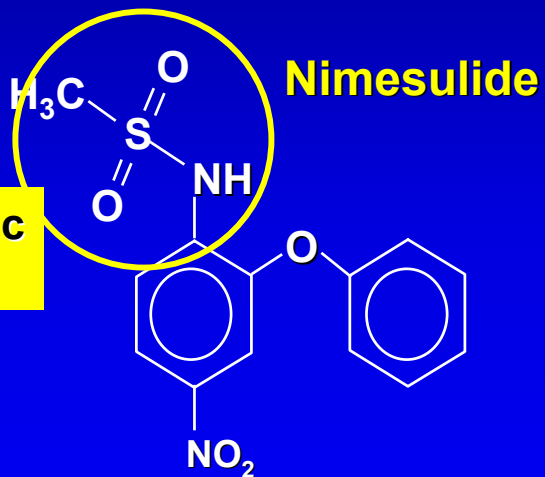
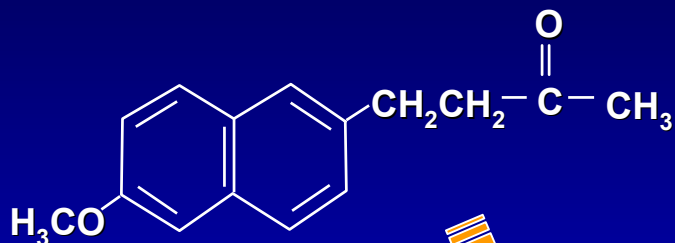
Chemistry and Activity



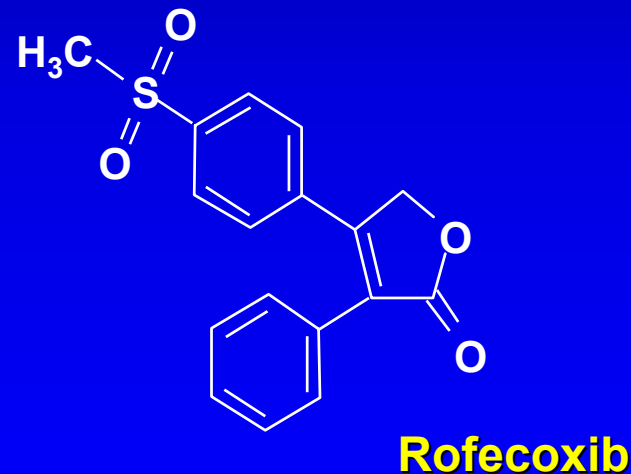
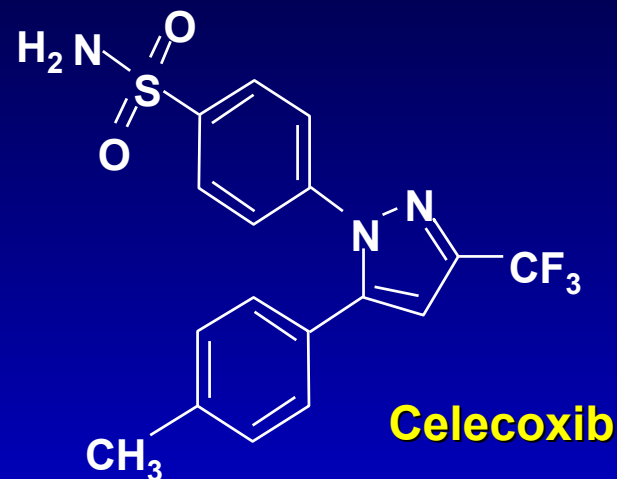
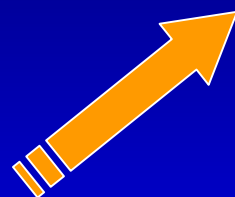
This is where all begins...

Pharmacochemistry of the COX-2 inhibitors

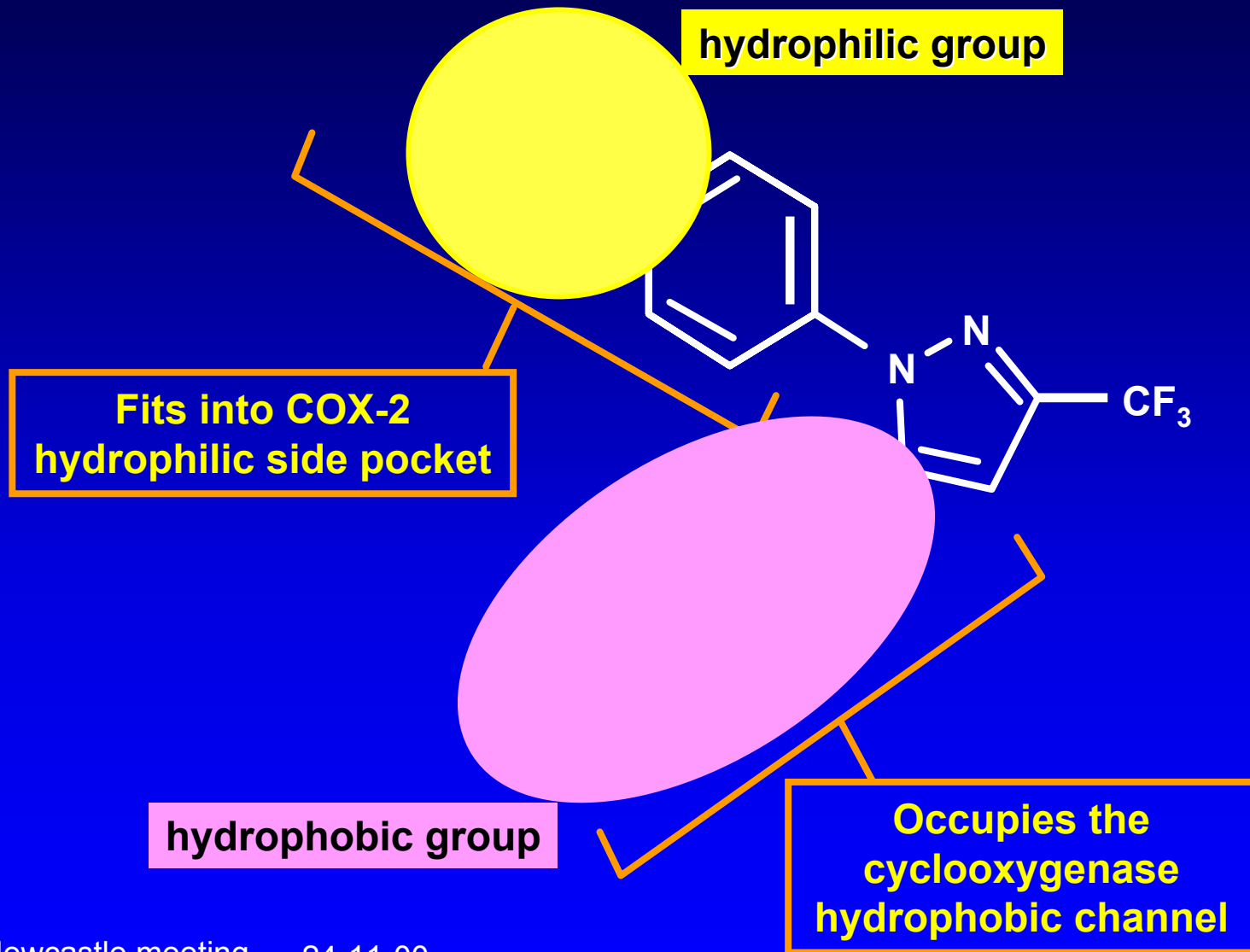
Nabumetone



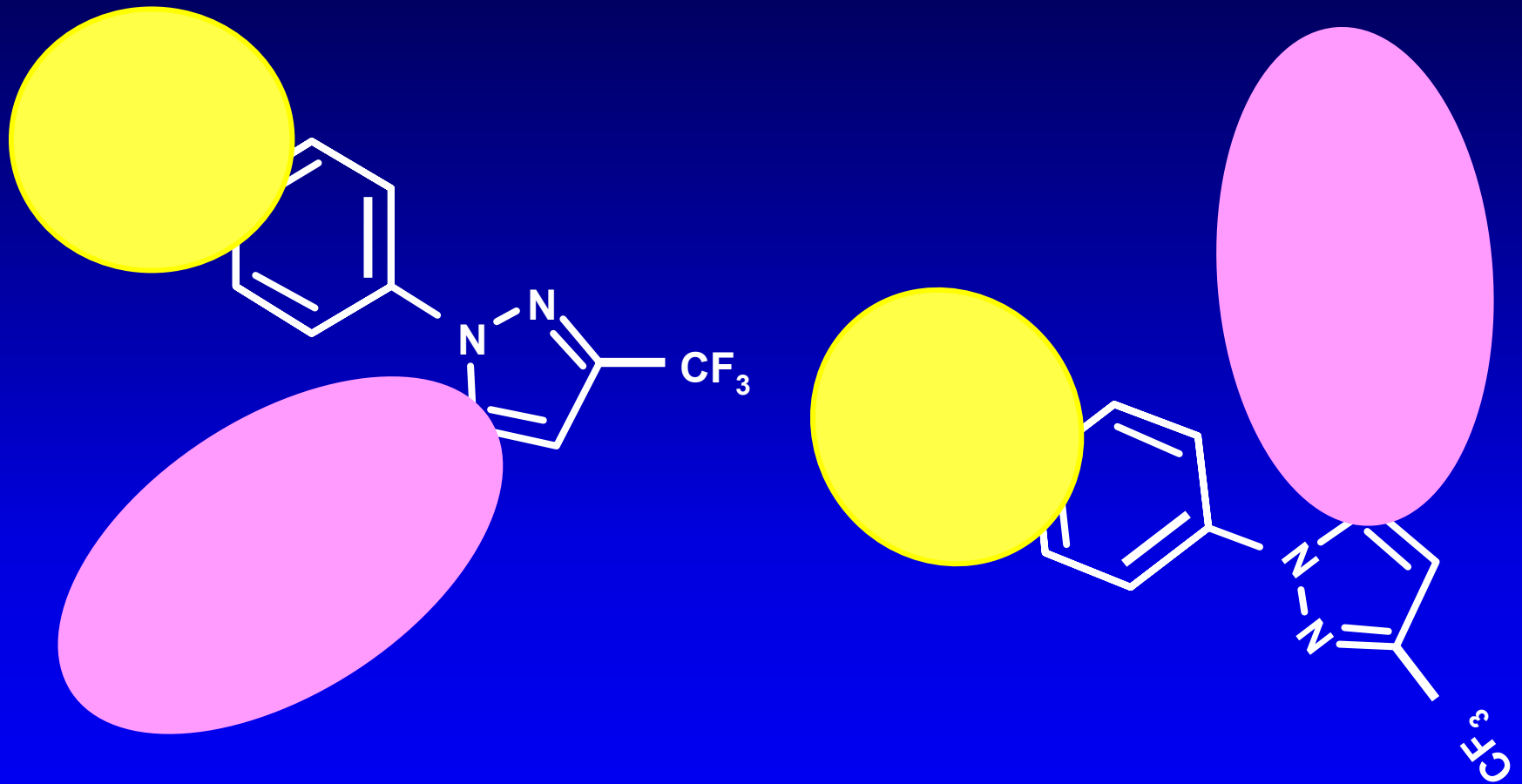
hydrophilic group



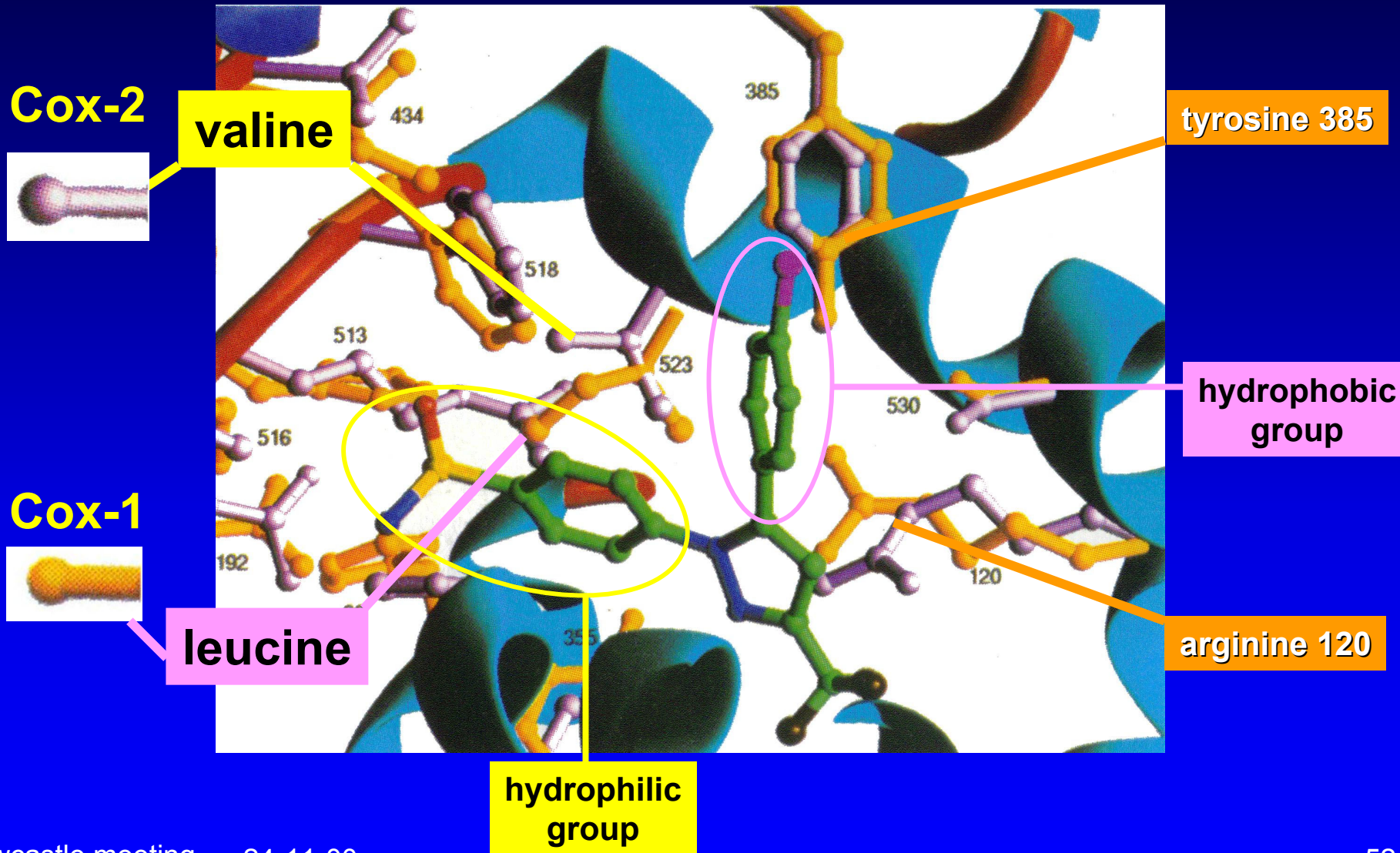
Pharmacochemical determinants in “coxibs”



Fitting "coxibs" in cyclooxygenases ...

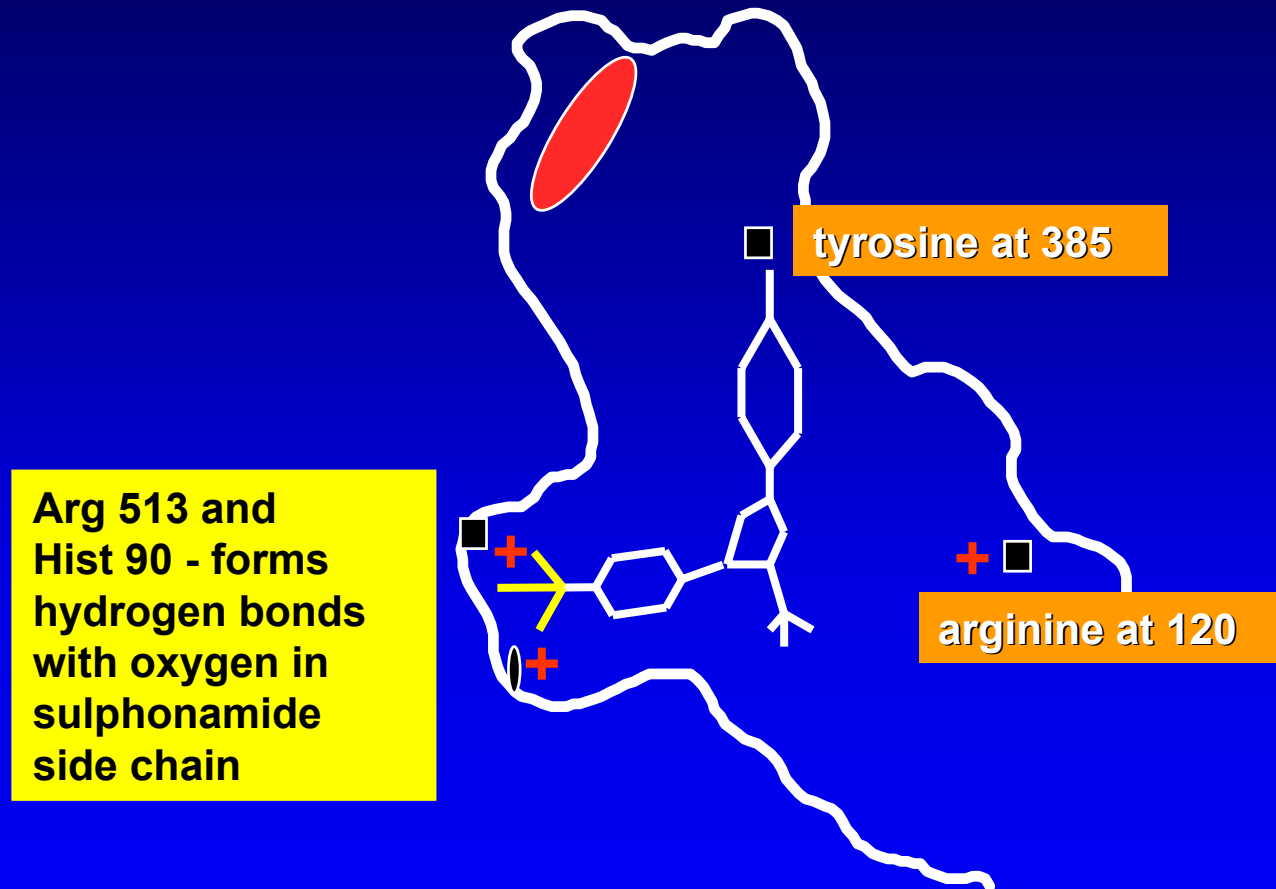


Structures of COX-1 and COX-2 with celecoxib

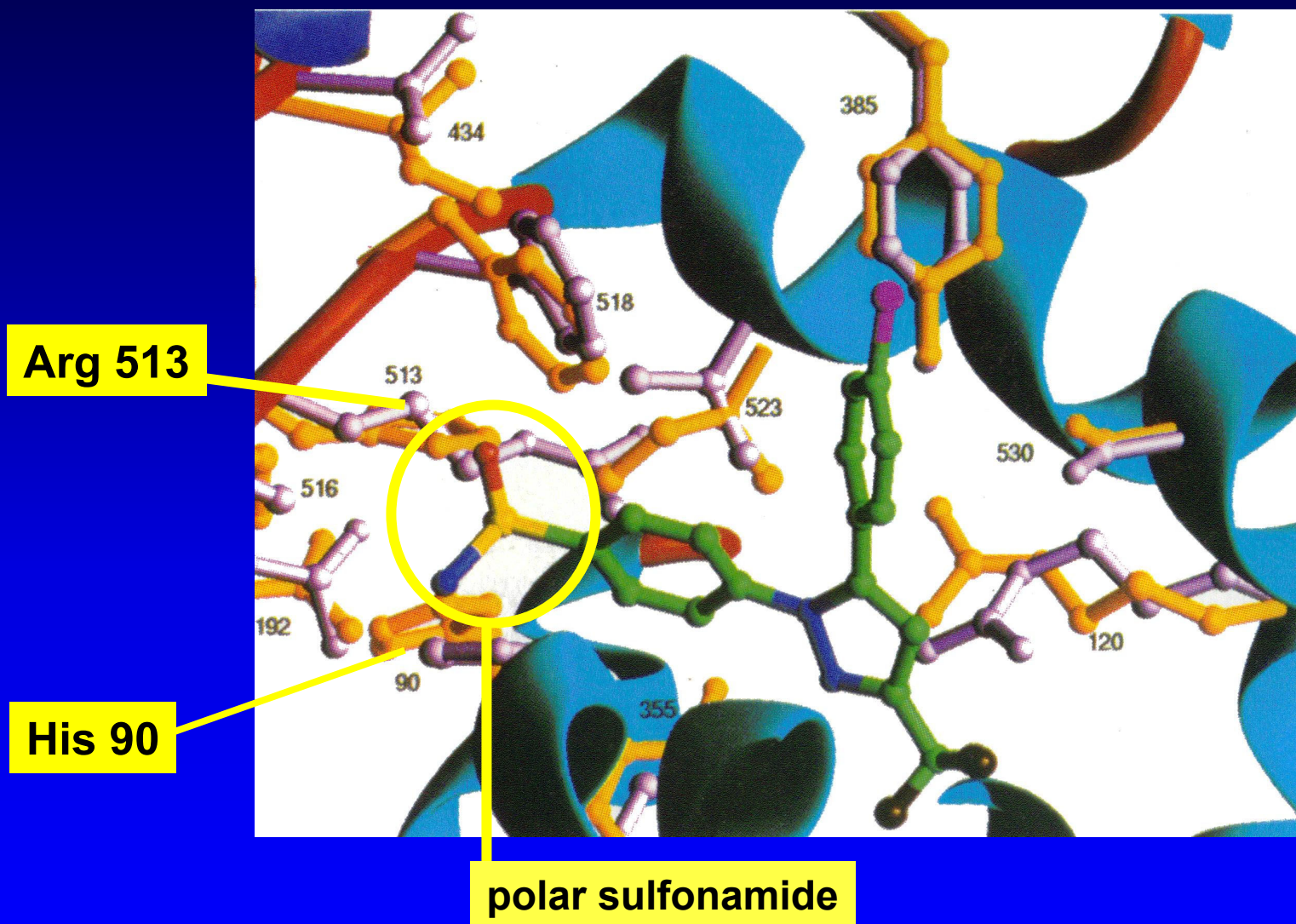


Why do “coxibs” bind so tightly to cyclooxygenase-2 ?

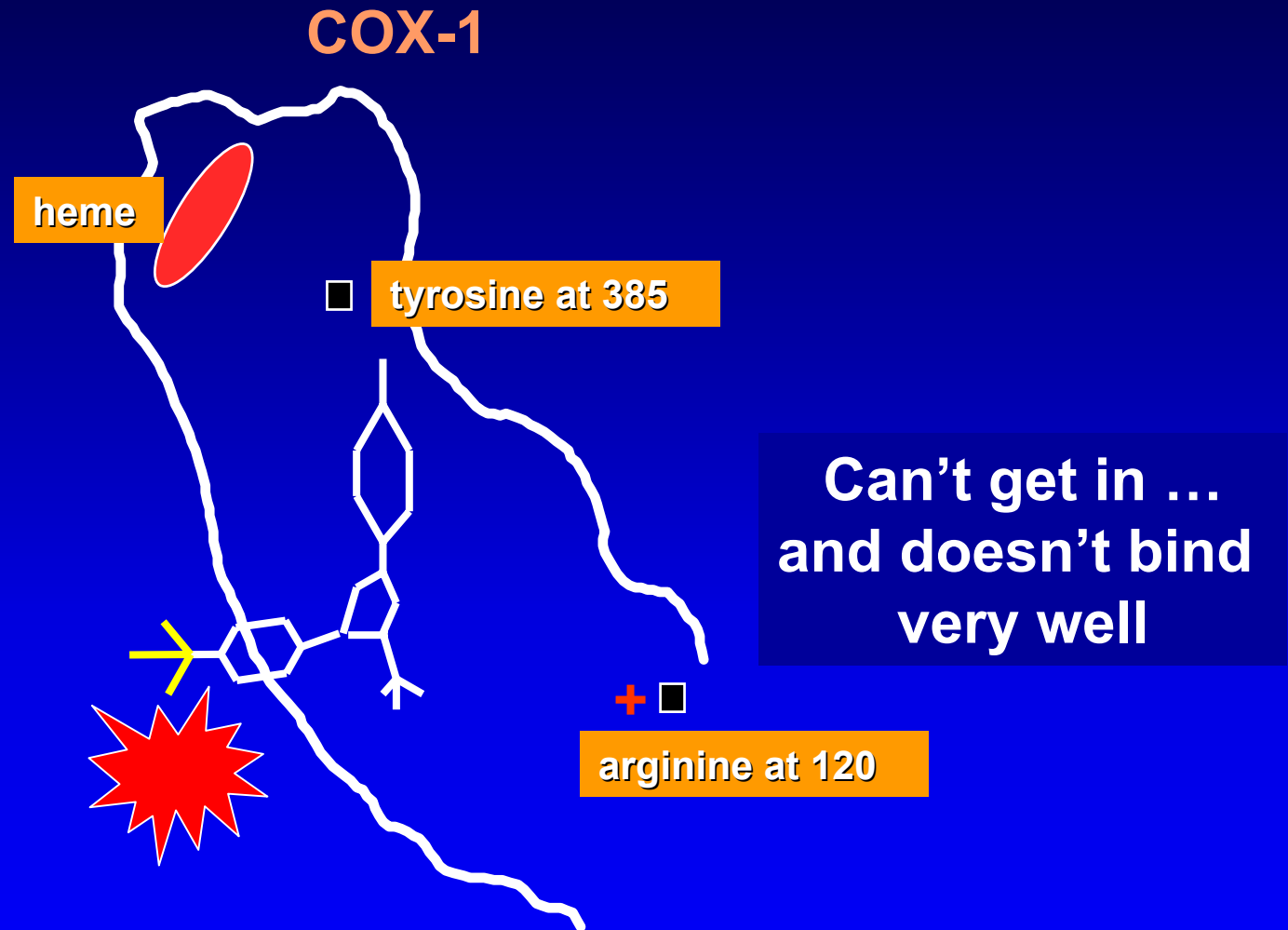
the polar sulphonamide side chain tightly bind to hydrophilic “side pocket”



Binding of the slide chain to Arg 513 and His 90

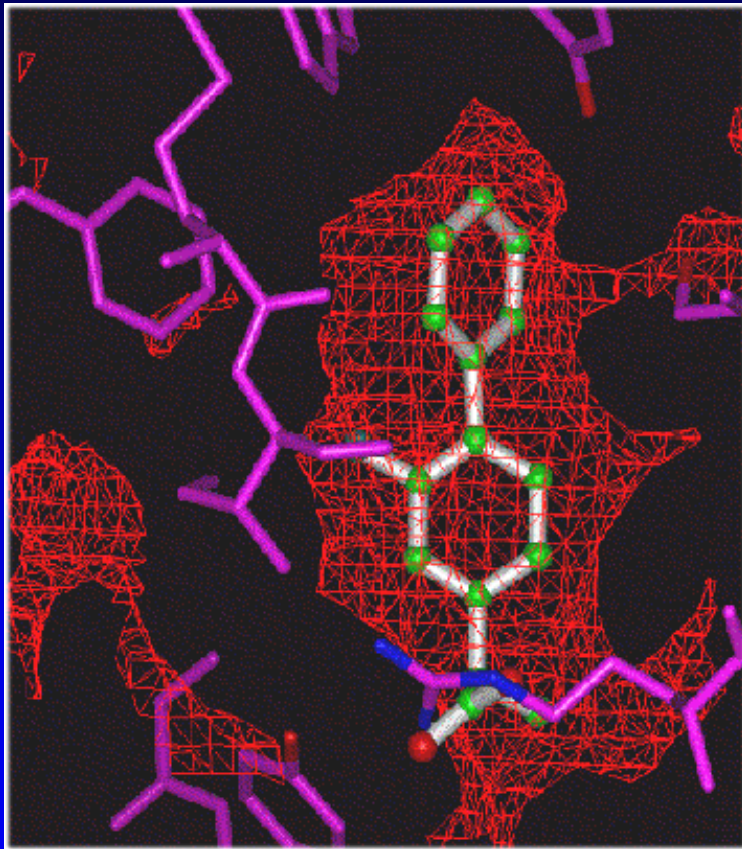


Why do “coxibs” fail to inhibit cyclooxygenase-1 ?



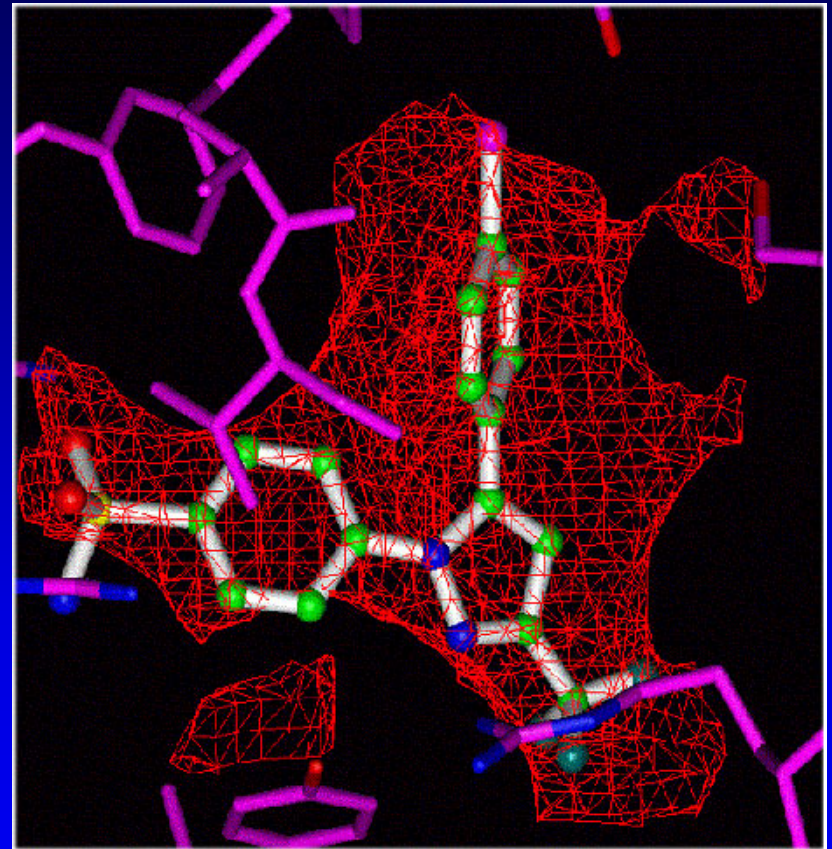
Cox-1 vs Cox-2 ...

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)**

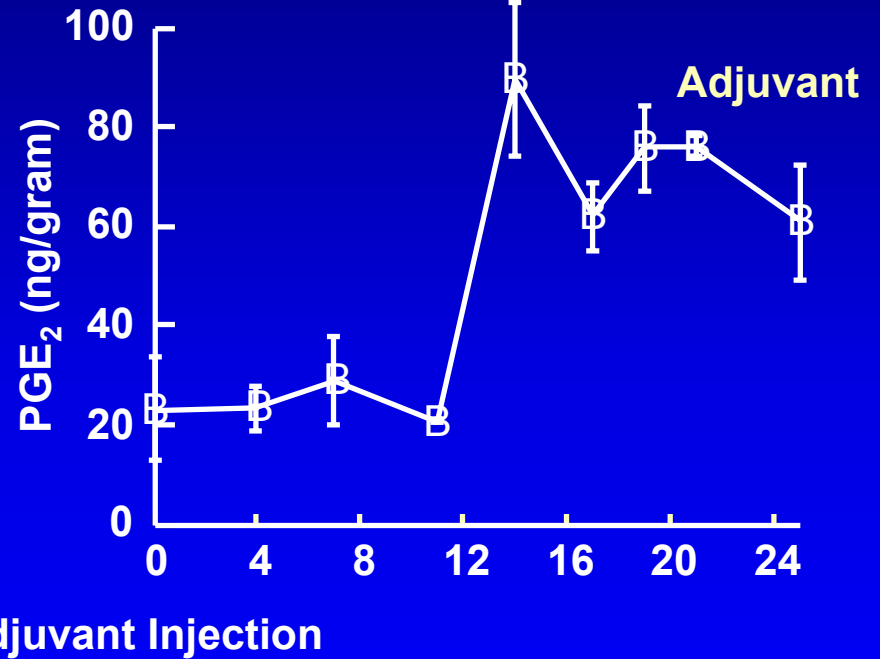
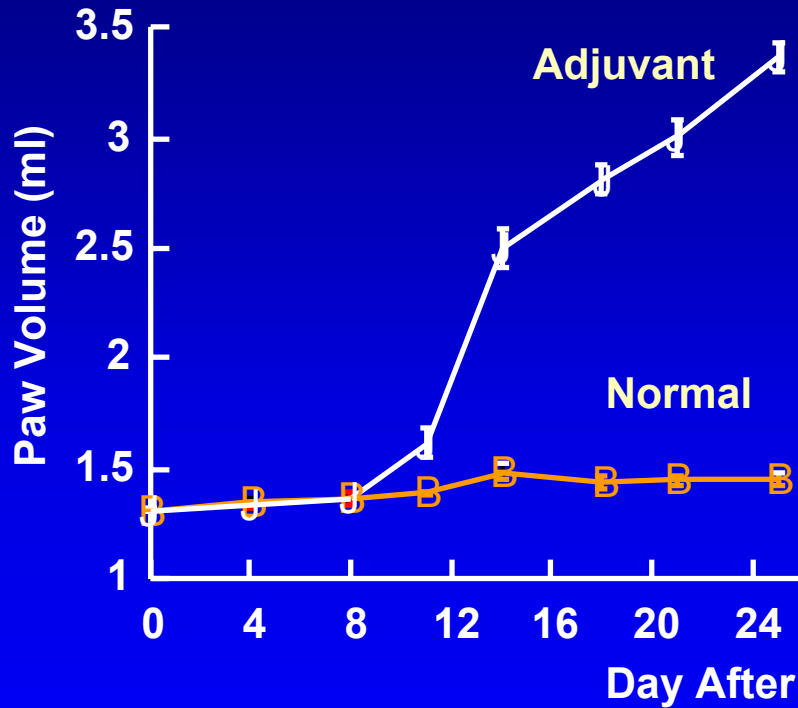
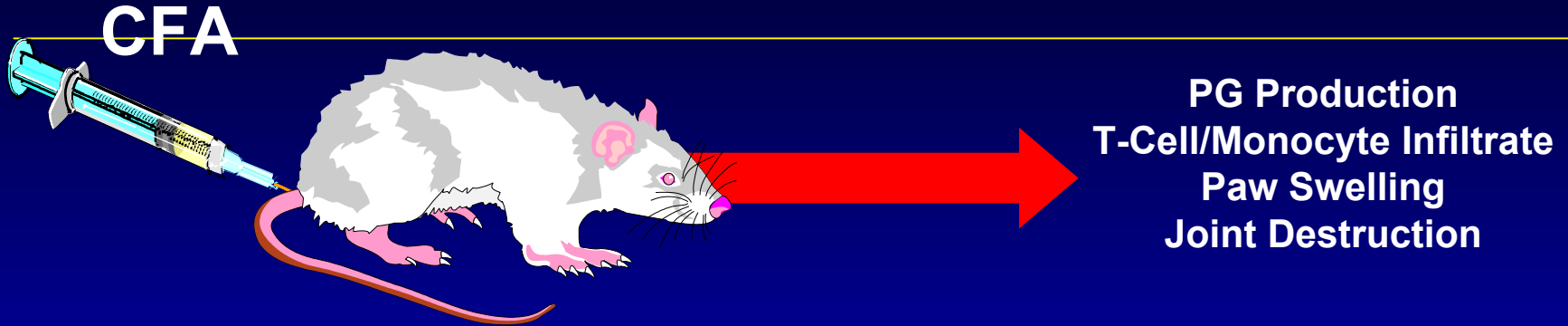
Specificity of coxibs in real life ...

- Specificity is an in-vivo concept and reflects the ability of a drug to provide clinically relevant inhibition of COX-2 **without** clinically-relevant inhibition of COX-1.
- It has to be demonstrated using clinically relevant measures

Categories of COX Inhibitors

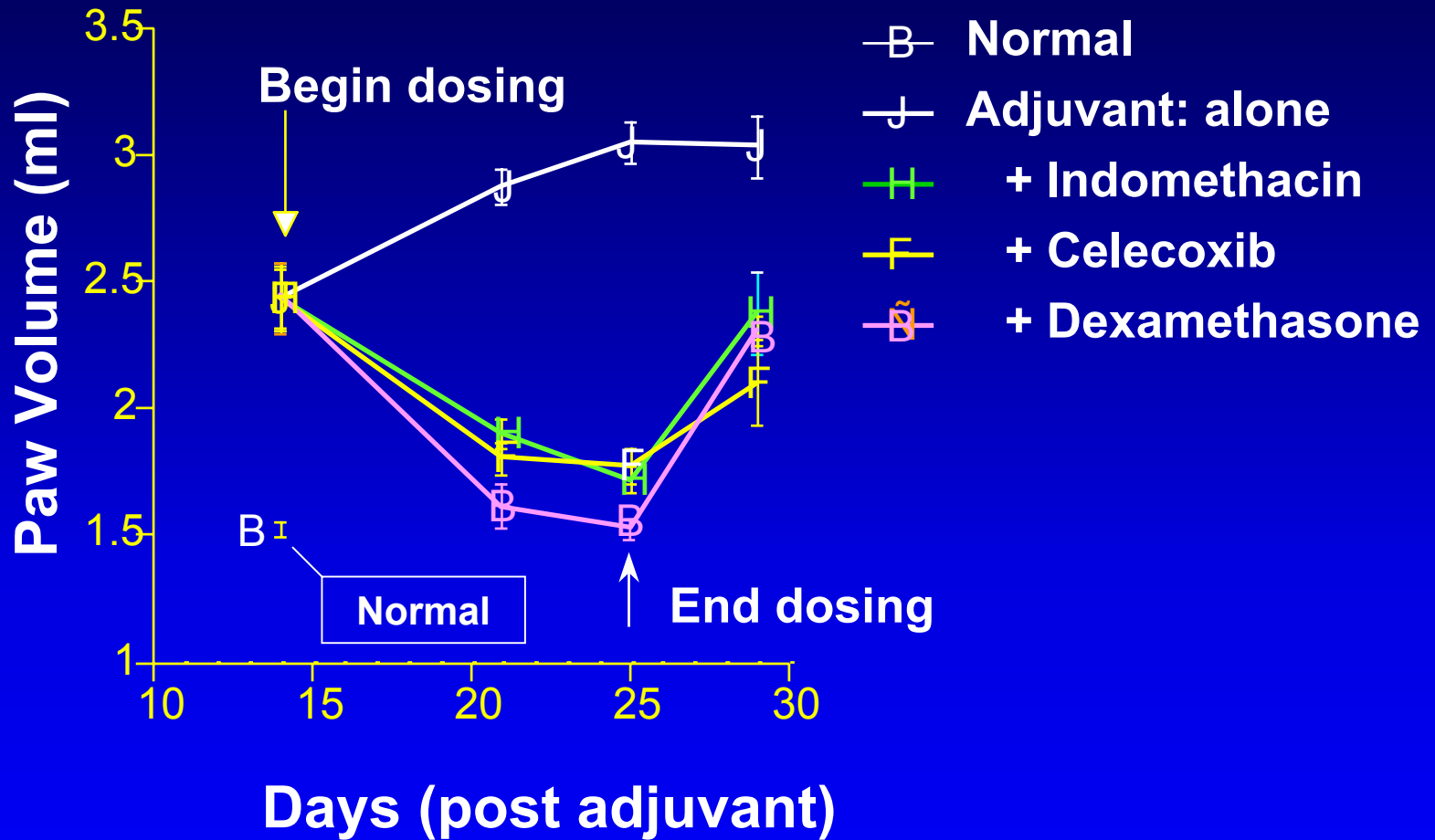
- 1. COX-1 specific** Low dose aspirin
- 2. COX non-specific** All current NSAIDs
- 3. COX-2 preferential*** Agent with some anti-inflammatory or analgesic activities at a dose that inhibits COX-2 but causes no significant inhibition of COX-1
- 4. COX-2 specific** Agent which at maximal therapeutic dosing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

Rat Adjuvant Arthritis Model



CFA = Complete Freund's Adjuvant

Reversal of inflammation in rat adjuvant arthritis

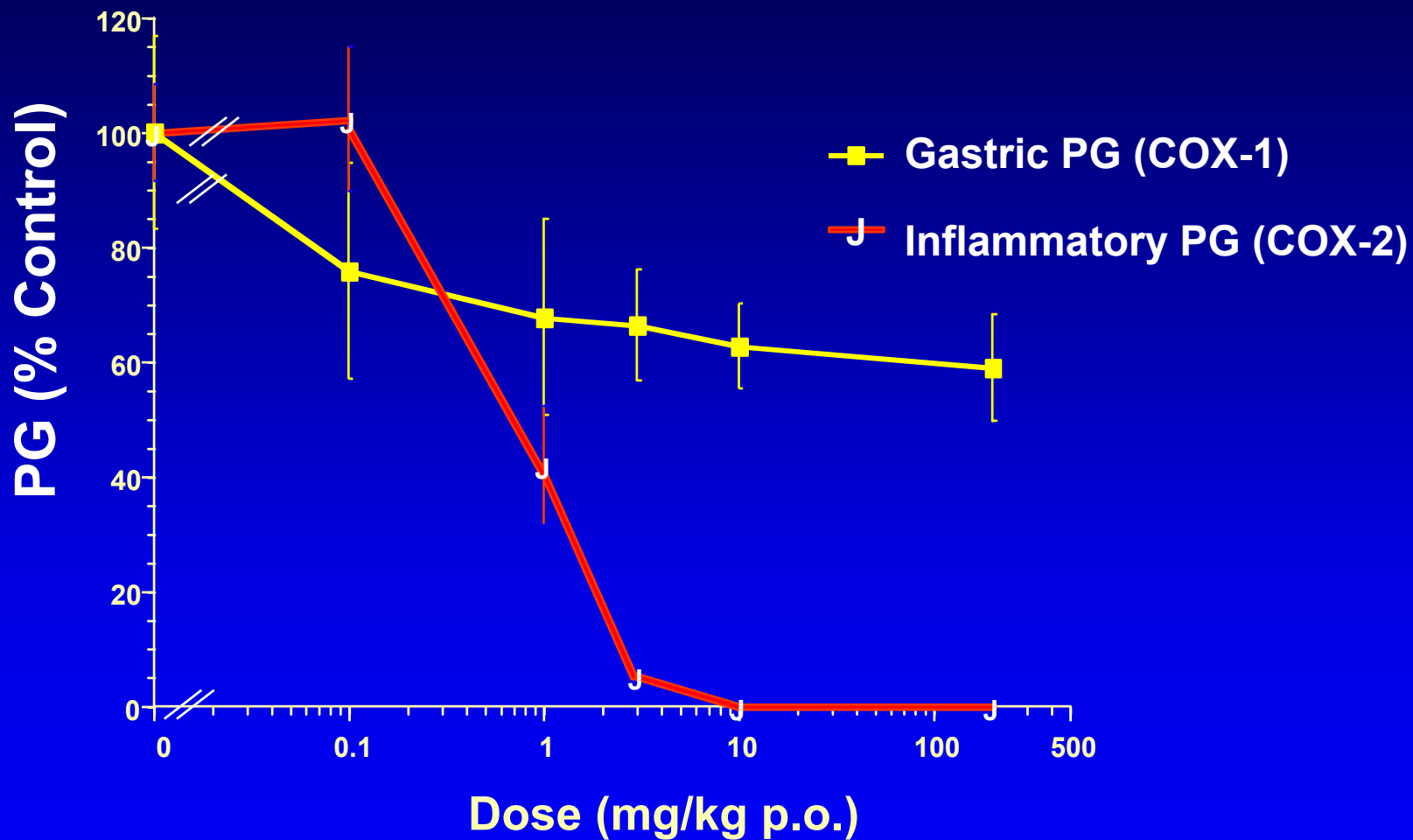


Selectivity of COX Inhibitors *in vivo*

- Carrageenan air pouch
 - High levels of PG produced via COX-2
 - Provides a biochemical measure of COX-2 inhibition *in vivo*
- Gastric prostaglandin production
 - GI mucosa expresses COX-1 exclusively
 - Measure of the effect of COX inhibitors on steady state PG levels

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

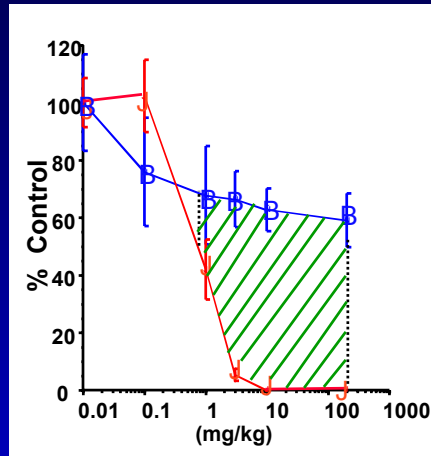
Specificity of Celecoxib *in vivo*



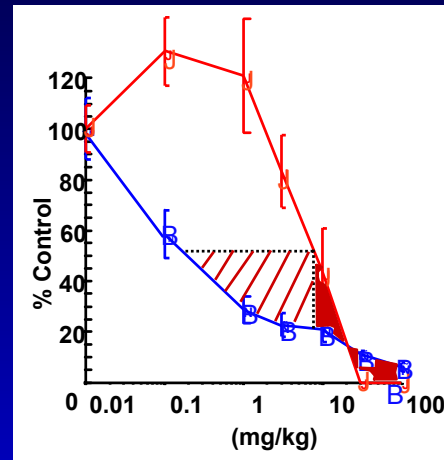
Smith CJ, PNAS, 1998, 95, 13313-18

Specificity of COX inhibitors In Vivo

Celecoxib

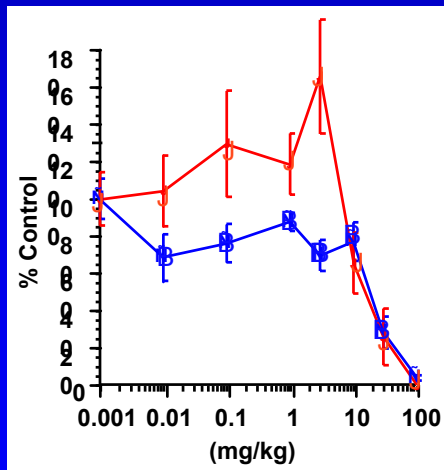


Etodolac

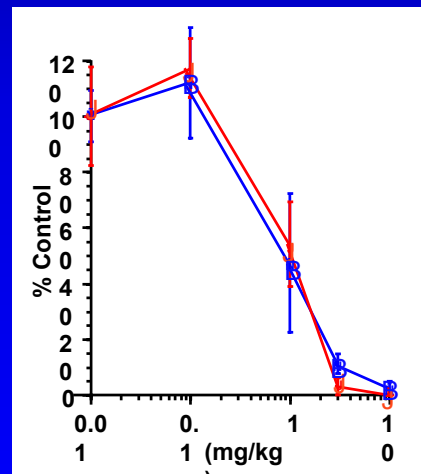


—■ Gastric PG (COX-1)
—■ Inflammatory PG (COX-2)

Nabumetone



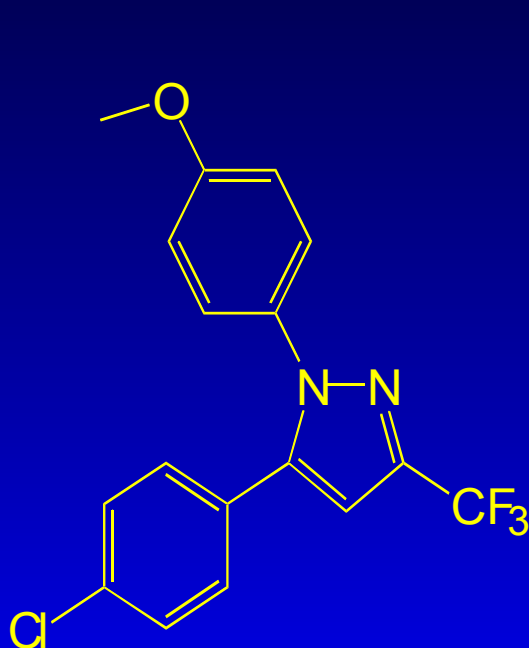
Meloxicam



Efficacy without GI toxicity
 GI toxicity without efficacy
 Efficacy with GI toxicity
 No efficacy, no GI toxicity

Data on File : Searle

Selective cyclooxygenase inhibitors



SC-560

IC₅₀	COX-1	0.009
(μM)	COX-2	6.3

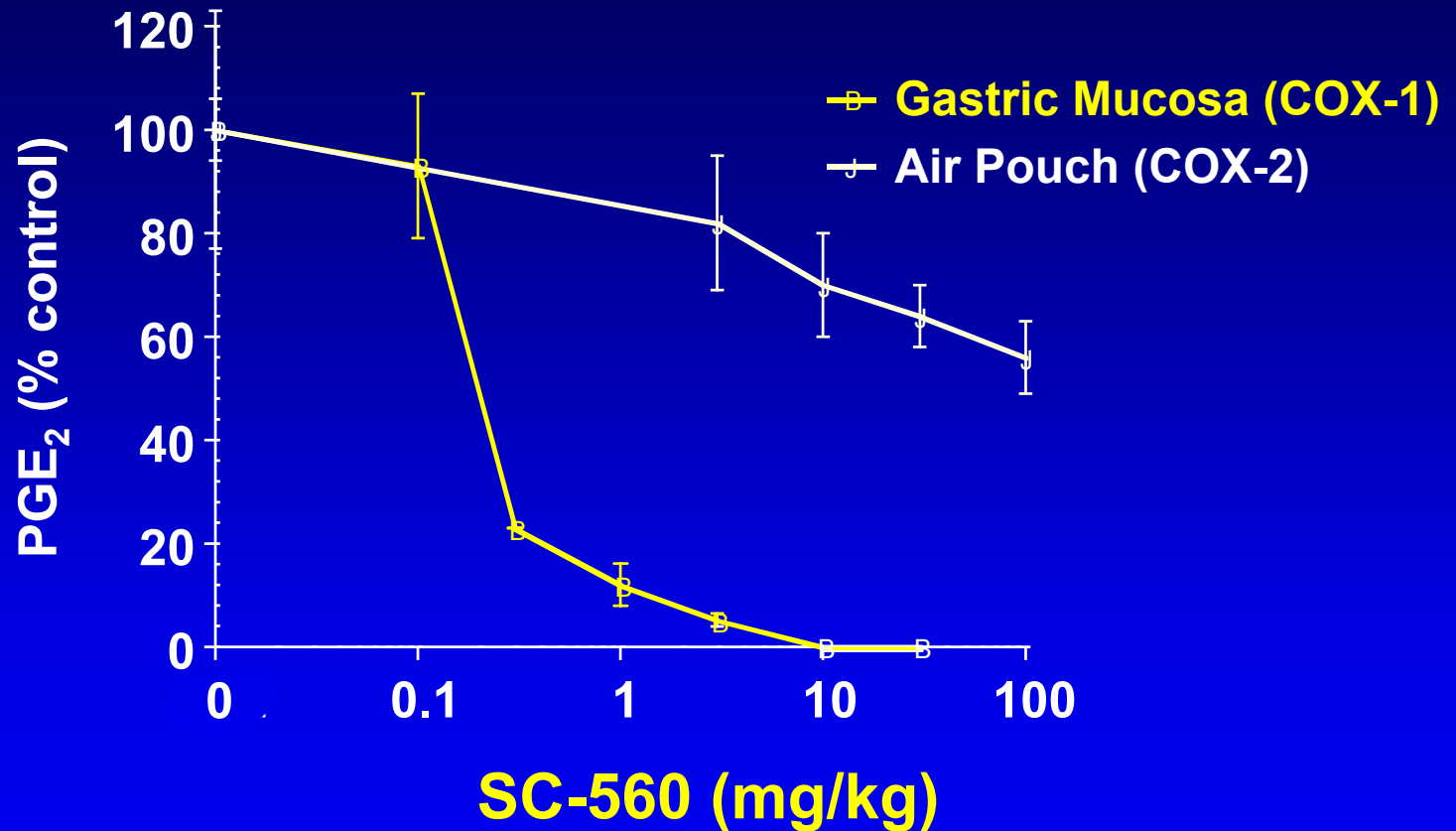


celecoxib

15
0.04

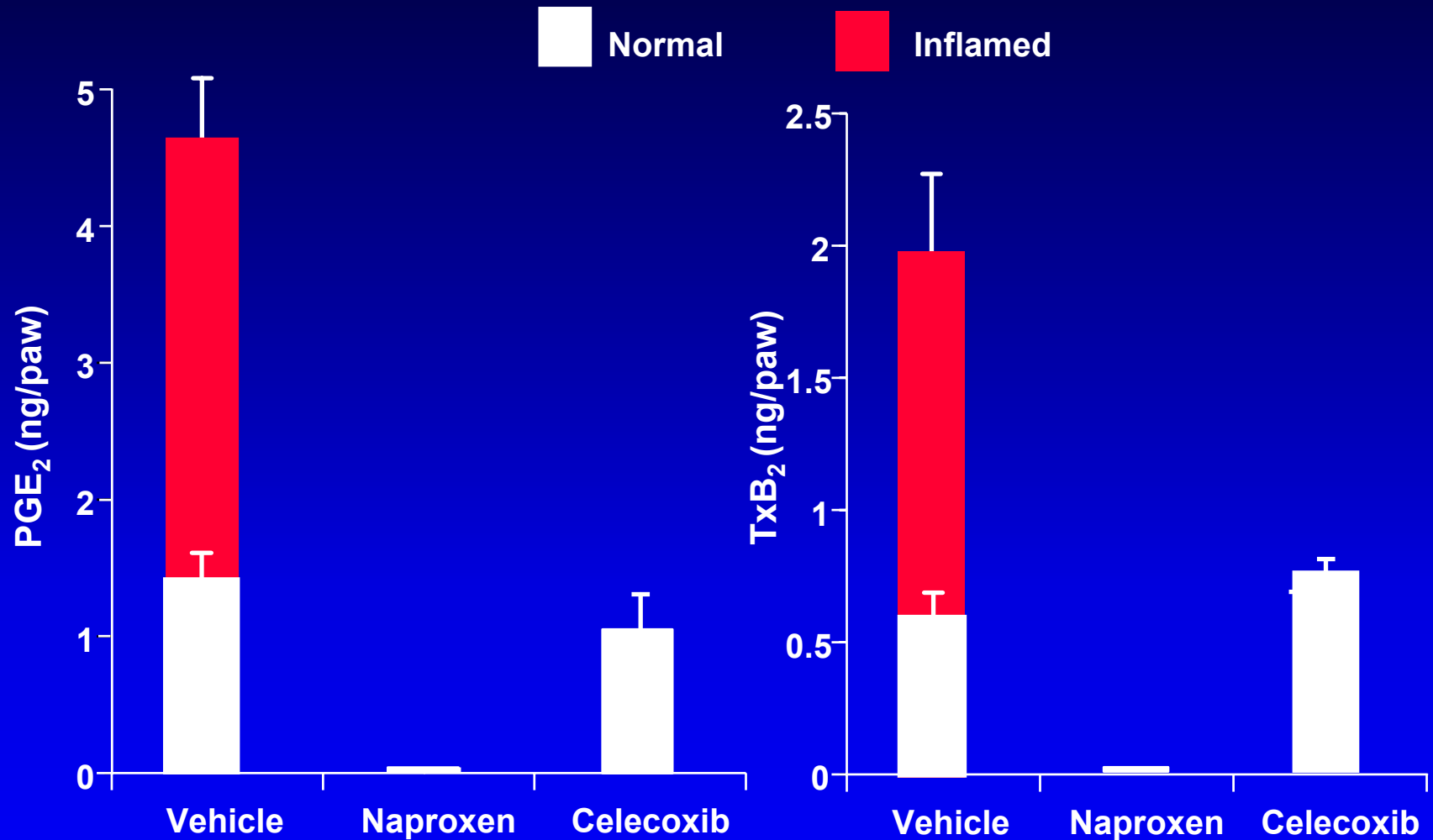
Smith CJ, PNAS, 1998, 95, 13313-18

In vivo Specificity of SC-560



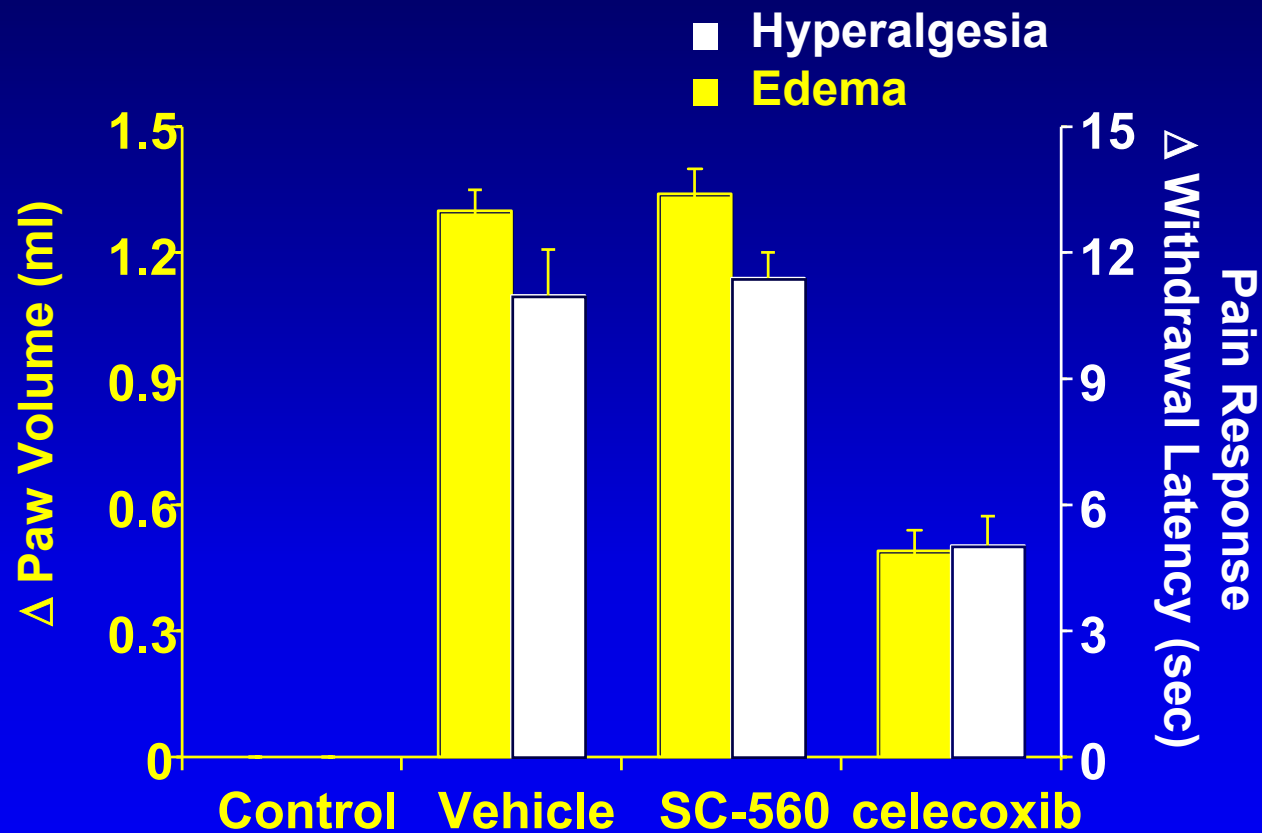
Smith CJ, PNAS, 1998, 95, 13313-18

Effect of celecoxib or naproxen on prostanoïd levels in normal and inflamed tissue (carageenan)



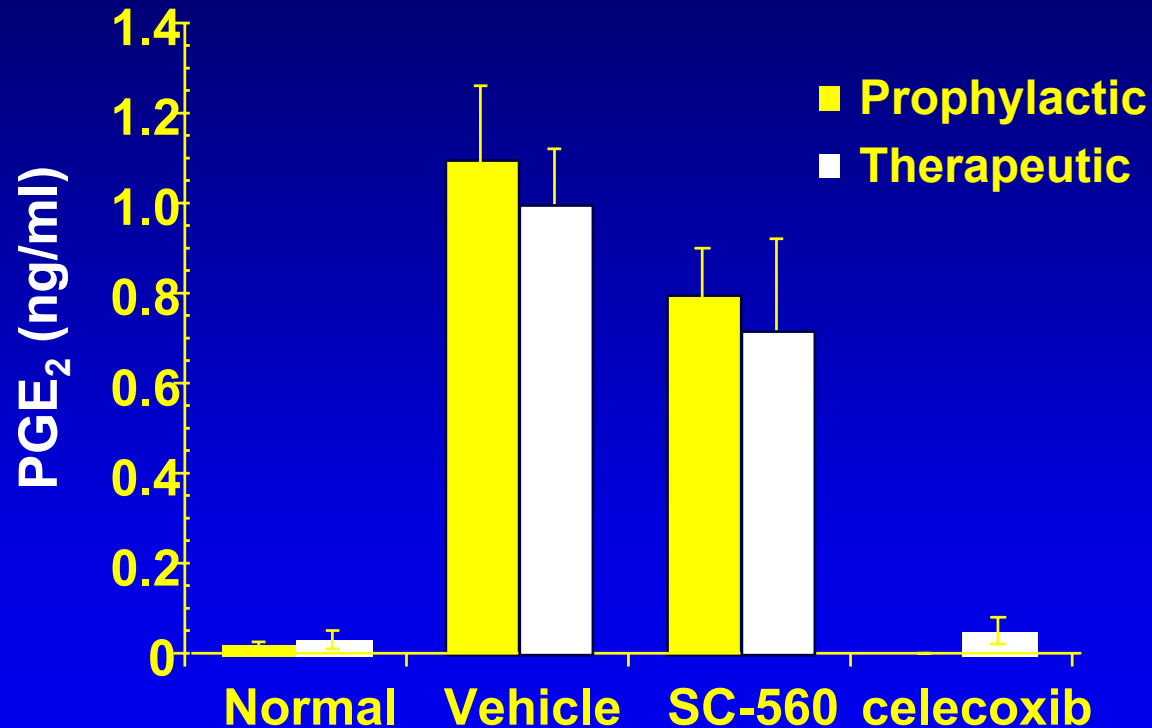
Smith CJ, PNAS, 1998, 95, 13313-18

Inhibition of COX-1 is not anti-inflammatory or analgesic



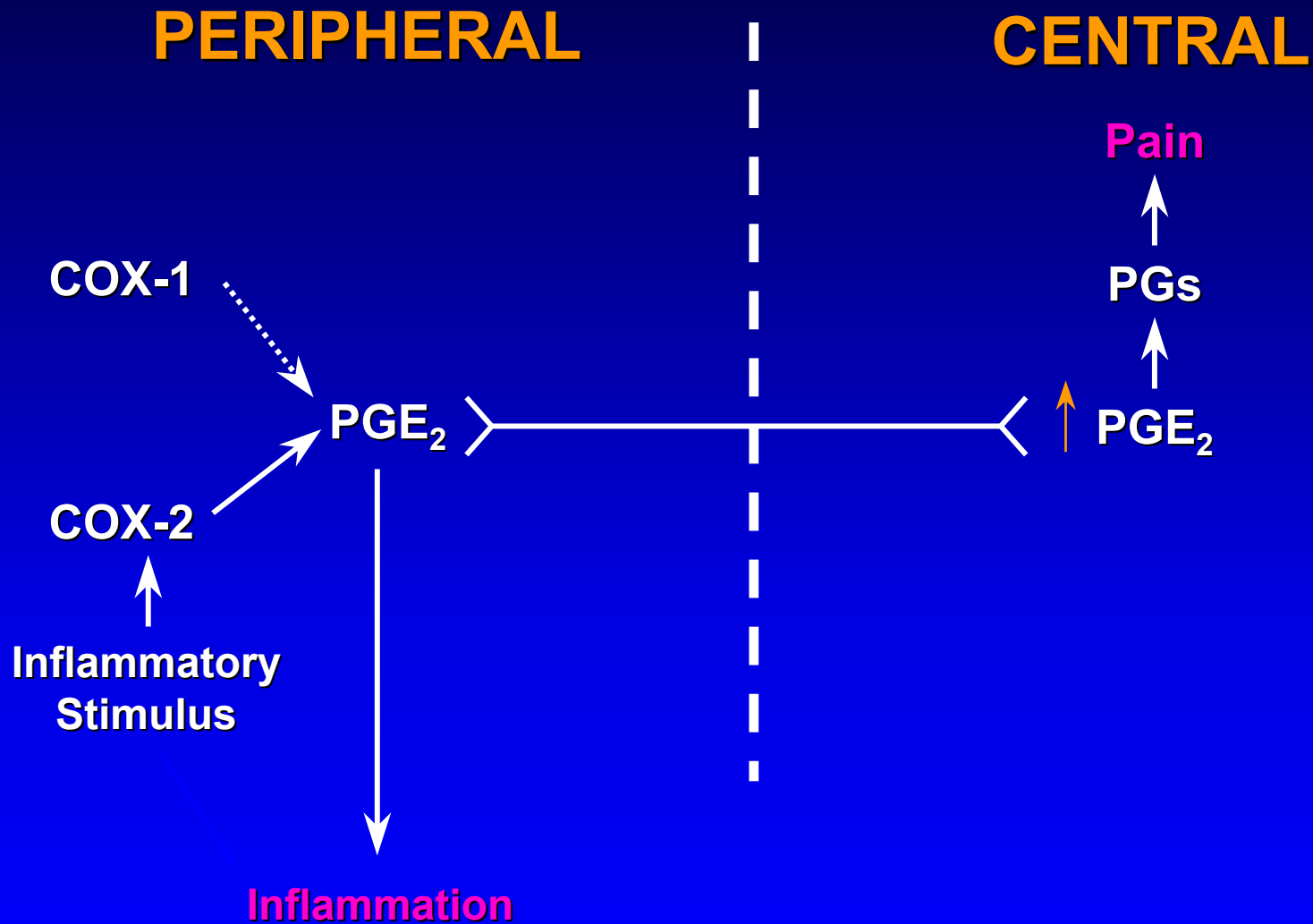
Smith CJ, PNAS, 1998, 95, 13313-18

Specific COX-1 inhibition does not inhibit inflammation-induced PGE₂ levels in CSF



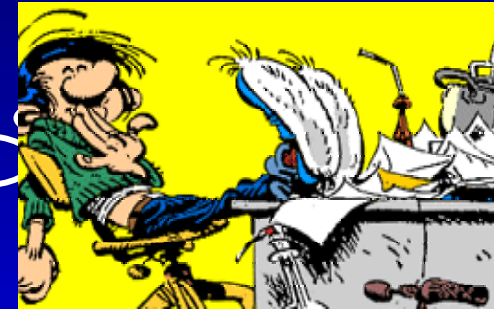
Smith CJ, PNAS, 1998, 95, 13313-18

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**

Pharmacokinetics of celecoxib

- **Metabolism**

- hepatic metabolism by cytochrome P450 2C9
- inactive metabolites

- **Excretion**

- 57% faecal
- 29% of excretion is the carboxylic acid metabolite in the urine
- <1% unchanged drug in the urine

Pharmacokinetic profile in special populations

- **2x AUC in older age population vs young (females > males)**
- **2x AUC in patients with moderate hepatic impairment**
- **Increase in AUC in black population and low weight individuals**
- * **None of these changes are sufficient to require dosage alteration and plasma levels are well within the margin to retain COX-2 specificity**

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)**

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

Phase III Endoscopy Safety Trials

Mucosal Grading Scale

<u>Grade</u>	<u>Description</u>
0	No visible lesions (normal mucosa)
1	1-10 petechiae
2	>10 petechiae
3	1-5 erosions*
4	6-10 erosions
5	11-25 erosions
6	>25 erosions
7	Ulcer**

* An erosion is defined as any break in the mucosa without depth

** An ulcer is defined as any break in the mucosa at least 3 mm in diameter with unequivocal depth

Phase III Endoscopy Safety Trials

Baseline Demographics - Study in OA

	Placebo (n=247)	Celecoxib BID			Naproxen BID
		50 mg (n=258)	100 mg (n=240)	200 mg (n=237)	500 mg (n=233)
Hx of GI bleeding	4%	2%	4%	1%	1%
Hx of GI ulcer	19%	16%	15%	15%	18%
Hx of CV disease	65%	59%	57%	58%	63%
H. pylori positive	35%	41%	33%	38%	39%
Aspirin use (\leq 325 mg/d)	14%	12%	13%	16%	17%

Data on File: Searle Study

021

Phase III Endoscopy Safety Trials

Baseline Demographics - Study in RA

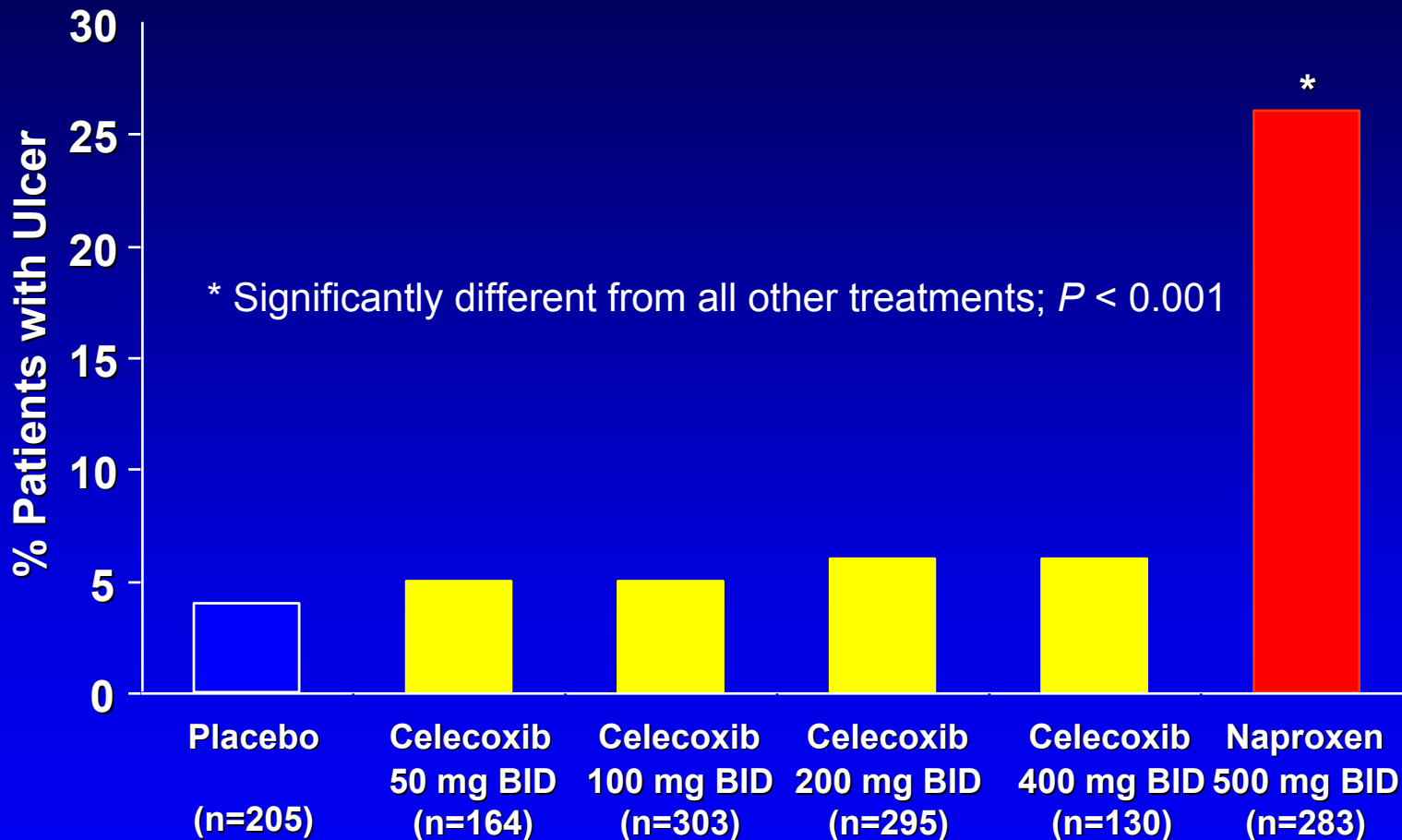
	Placebo (n=231)	Celecoxib BID		Naproxen BID	
		100 mg (n=240)	200 mg (n=235)	400 mg (n=218)	500 mg (n=225)
Hx of GI bleeding	3%	3%	2%	1%	2%
Hx of GI ulcer	13%	18%	16%	14%	15%
Hx of CV disease	45%	47%	44%	39%	42%
H. pylori positive	34%	32%	32%	23%	25%
Aspirin use (≤325 mg/d)	8%	10%	11%	7%	8%

Data on File: Searle Study 022

Simon LS et al, JAMA, 1999, 282, 1921-28

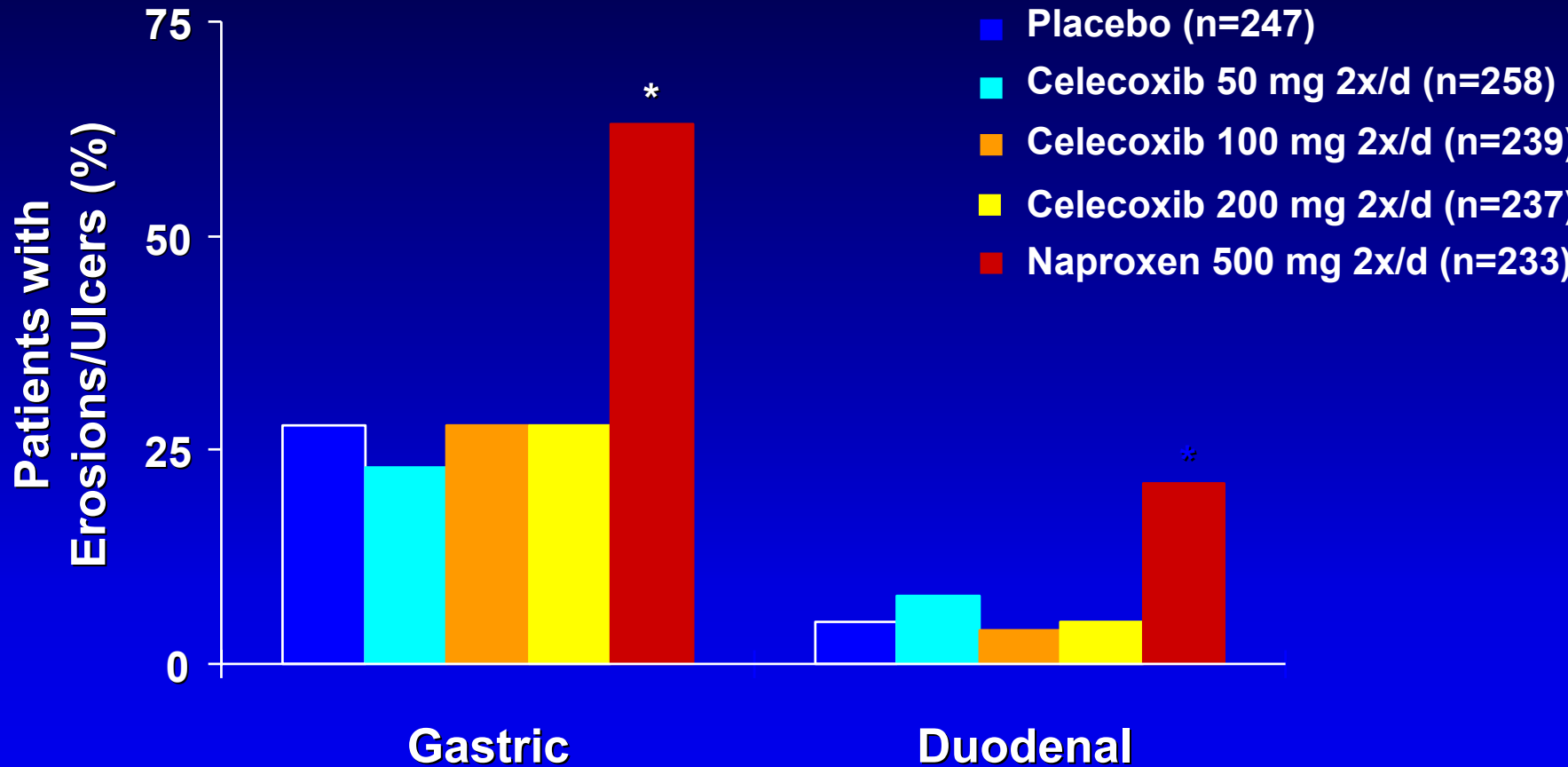
Incidence of gastroduodenal ulcers - week 12

Celecoxib - Phase III RA and OA UGI Safety Trials



Data on File: Searle (Studies 021 & 022)

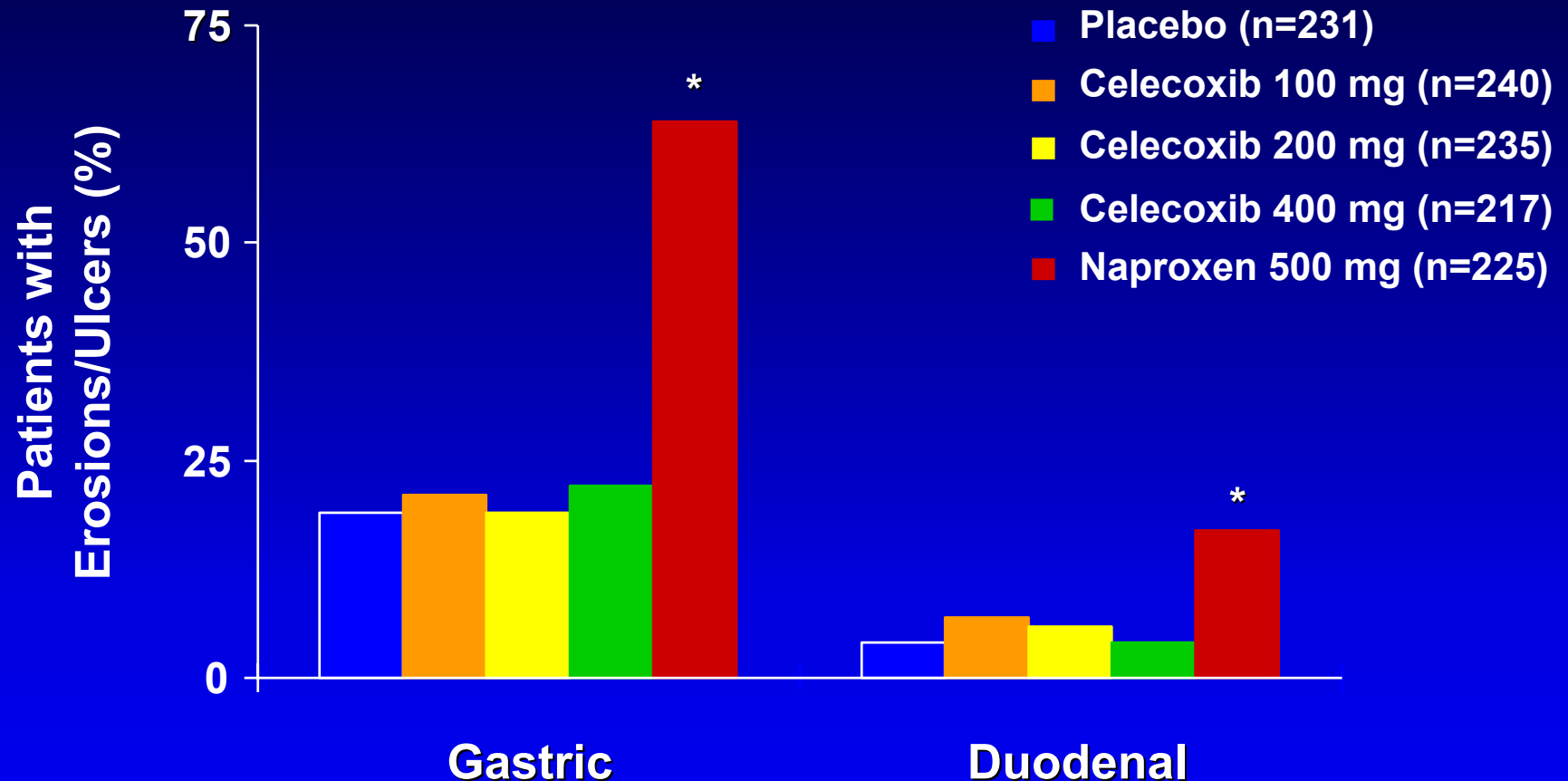
Incidence of erosions / ulcers in patients with OA



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

Data on file : Searle Study 021

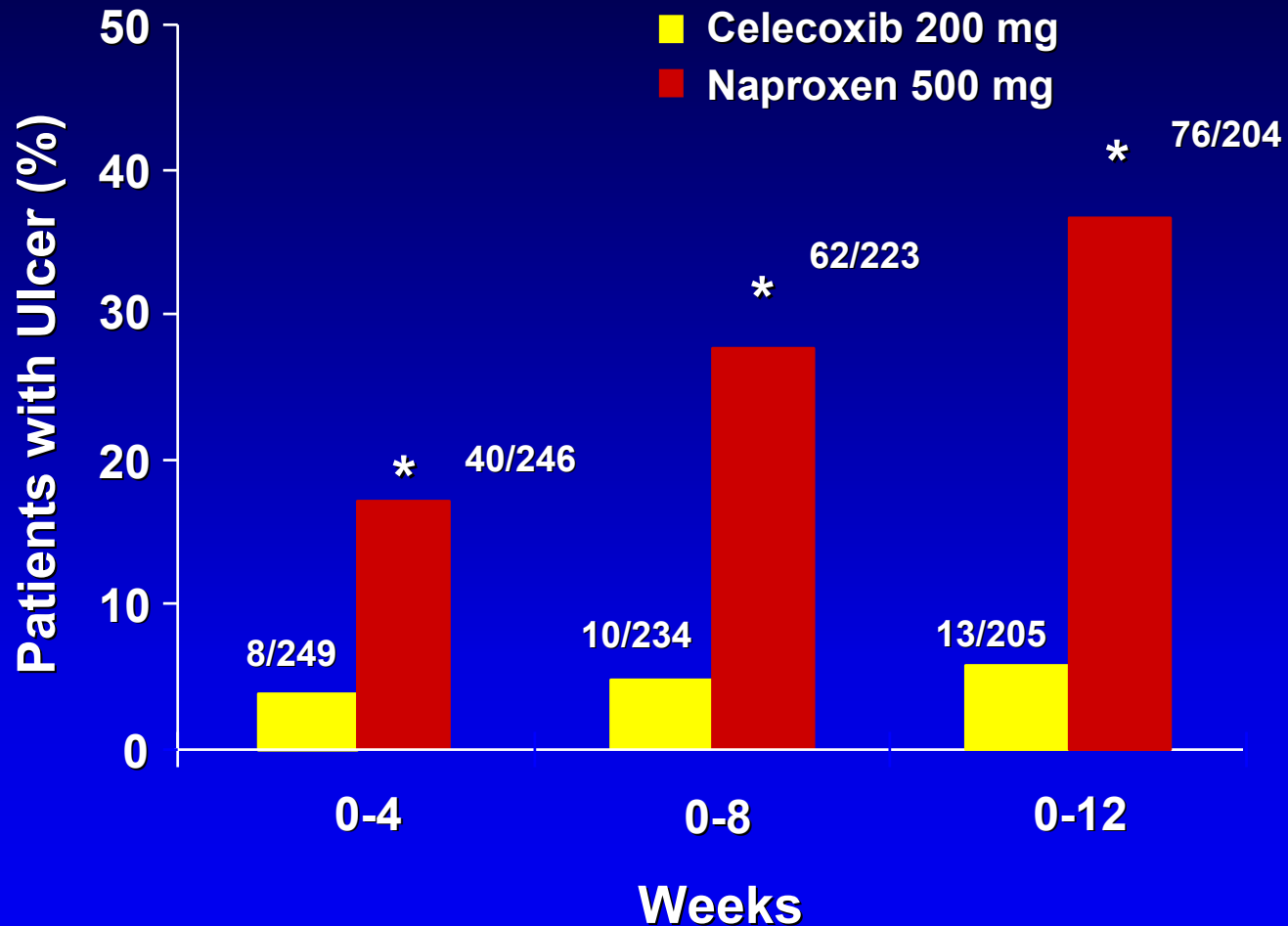
Incidence of Erosions / Ulcers in Patients with RA



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

Data on file : Searle Study 022

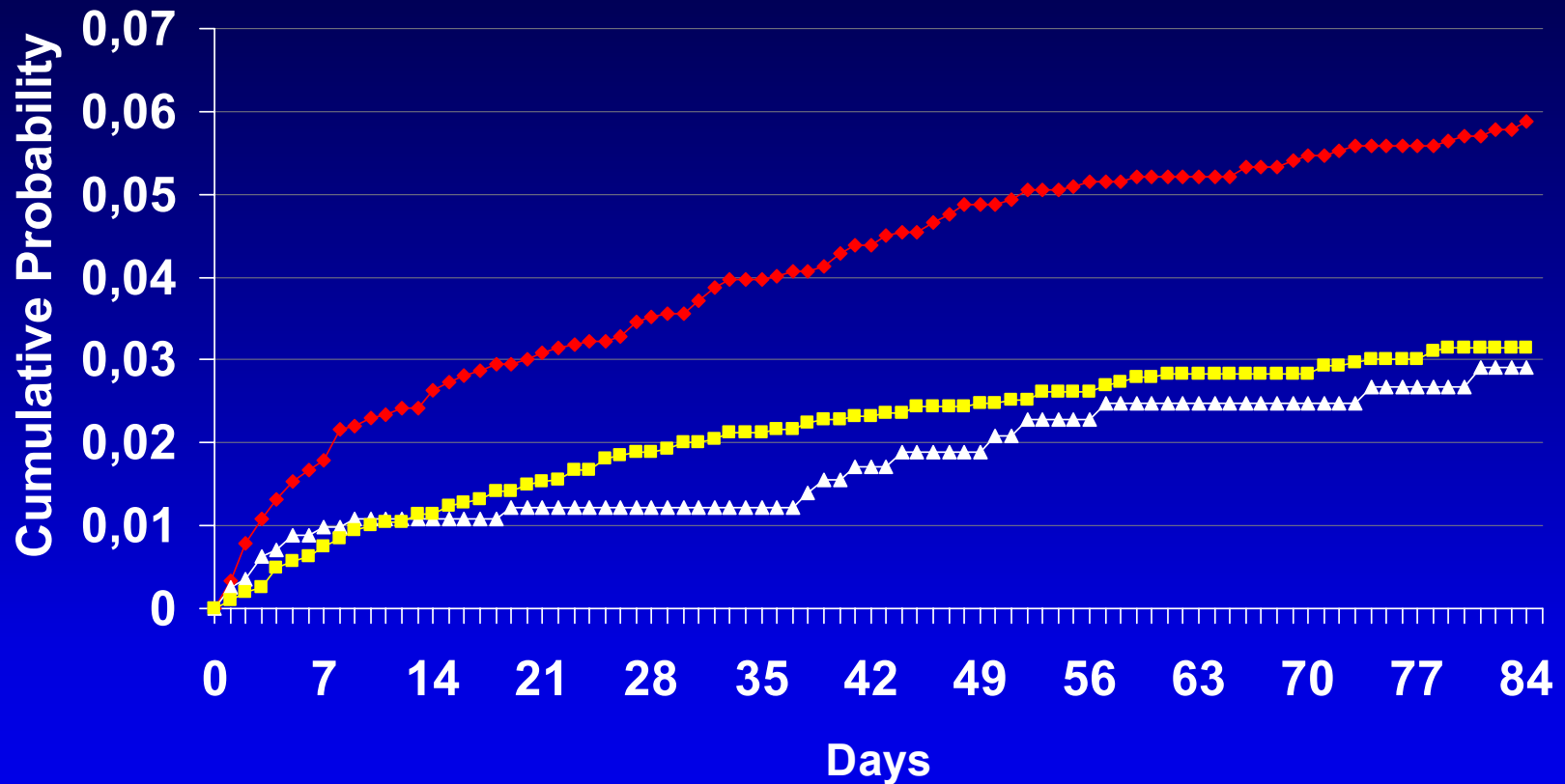
Cumulative Incidence of Gastric Ulcers



* Significantly different from celecoxib; $P < 0.001$

Data on File : Searle Study 062

Abdominal Pain Moderate-Severe



—◆— NSAIDs n=2,427 —▲— Placebo n=1,136 —■— Celecoxib 200-400 mg/day n=3,216

NSAIDs compared to Celecoxib or placebo;
 $p < 0.001$

Data on File: Searle

Assessment of adverse events in relation to age

- **11,009 patients in the 14 Phase II / III trials in OA and RA**
- **4073 (37%) \geq 65 yr; 2366 on celecoxib**
- **Celecoxib treated older age groups showed same tolerability profile as young population and better than NSAID comparator (4% vs 9.2% incidence of abdominal pain in North American arthritis trials)**

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)	+ <u>±</u>	+	+ +	+ +
Glomerulus			+	+
Macula Densa	+ (++++)	+ (++++)	(-)	
Interstitialium	+ +	+ +	+	+
Thick Ascending Loop	+ (++++)	+ (++++)		
Collecting Ducts	+ + +	+ + +	+ +	+ +

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

Conclusions from Renal Function Assessments

- **GFR decrease observed with naproxen (500 mg BID) in older subjects (65-85 yrs) but not celecoxib (200 mg or 400 mg BID)**
- **Small, consistent transient reductions in fractional excretion of sodium on both celecoxib and naproxen**
- **Small increase in peripheral oedema, 2.1% vs 1.1% placebo (same observed on NSAID)**
- **No evidence of clinically relevant renally-mediated events**
 - No effect on incidence of hypertension
 - No increased incidence of hypertension with ACE inhibitors, β -blockers, calcium antagonists, diuretics

Shall we have a bright future ?

look for long term safety ...

look for superior activity ...

but looking beyond the past ...



Shall we have a bright future ?

Look to the future...



A new bridge has arrived in Newcastle on 20th of November

