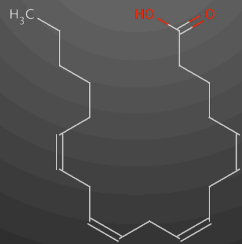
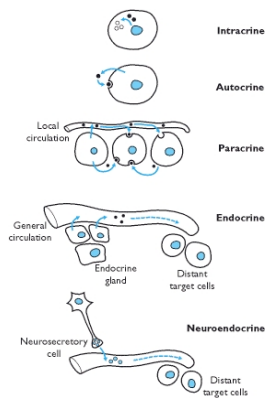


Eicosanoids are specialized signaling molecules primarily derived from arachidonate (from linoleate)

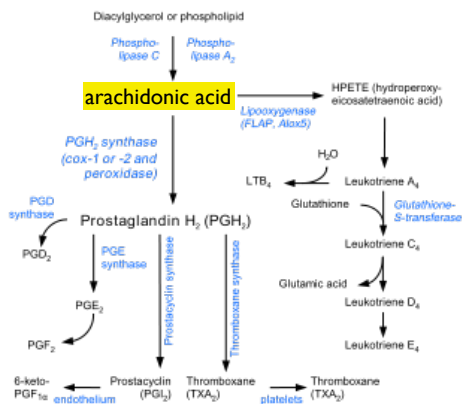


Eicosanoids are short-lived local signalling molecules

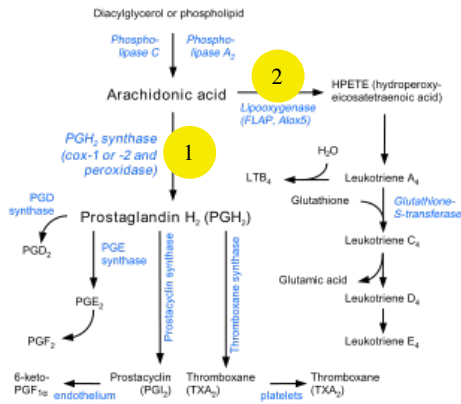


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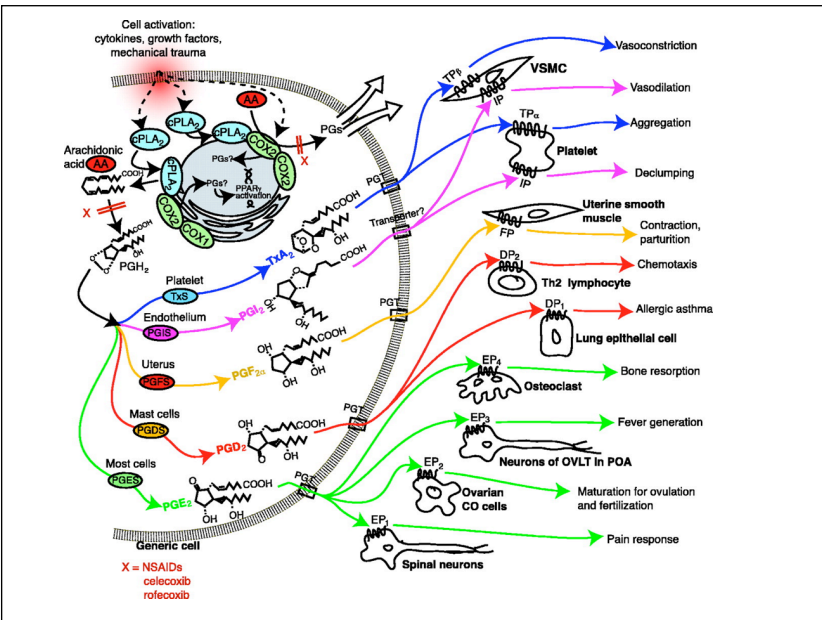
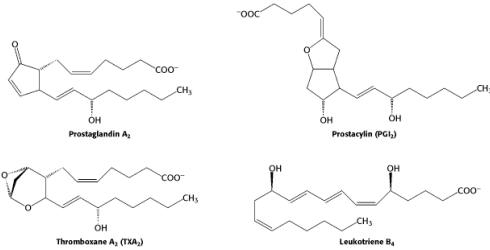
Eicosanoids are divided into 4 classes: Prostaglandins, Prostacyclins, Leukotrienes, Thromboxanes



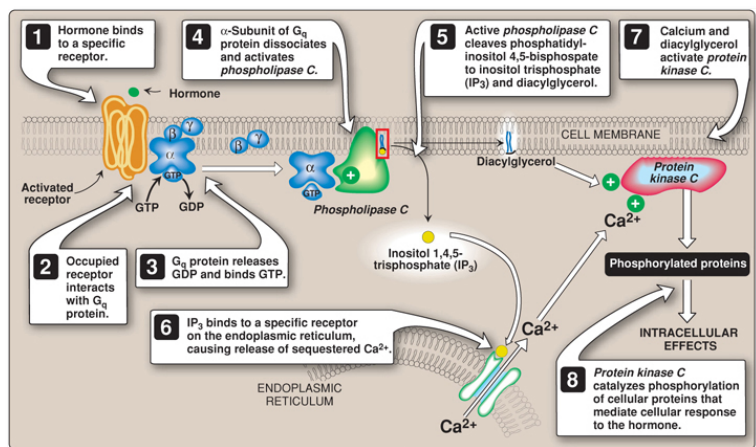
They are derived from Arachidonic acid through two main pathways: cox pathway, lipoxygenase pathway



Prostaglandins: 5 point ring  
 Thromboxanes: 6 point ring with O  
 Prostacyclins: double ring  
 Leukotrienes: absent ring, ≥3 dbl bonds



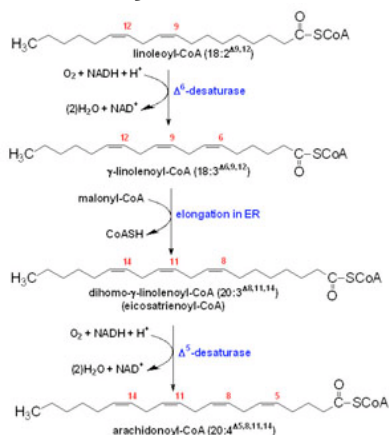
## Eicosanoids typically interact with specific G-protein coupled receptors



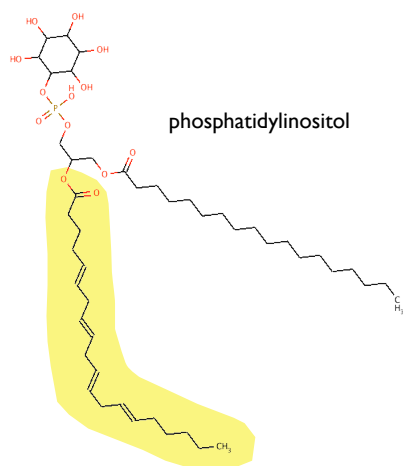
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## Linoleic acid and Arachidonate are essential fatty acids

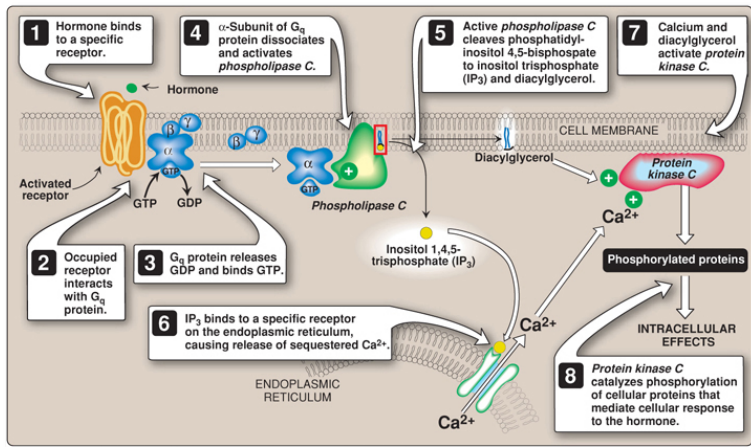
Some arachidonate can be derived from linoleic acid in the ER



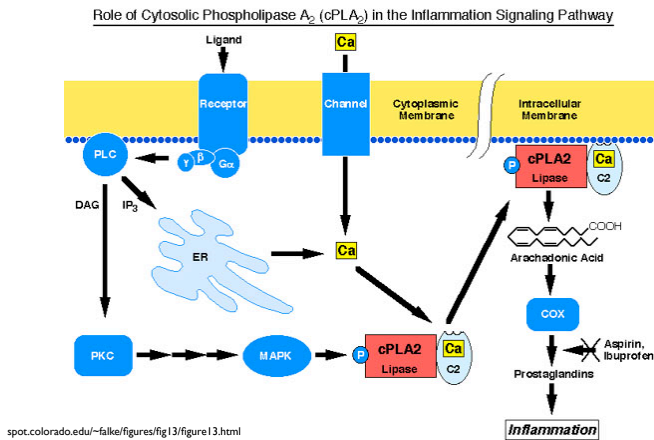
## Arachidonate is incorporated into phospholipids



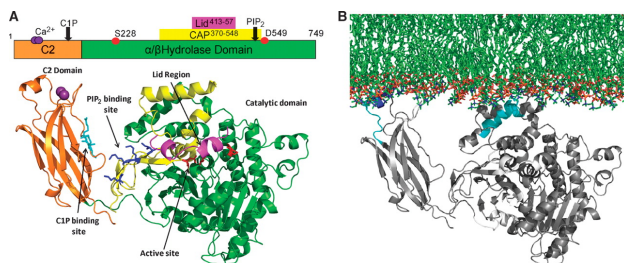
# Phospholipase C cleaves phosphatidylinositol to release DAG



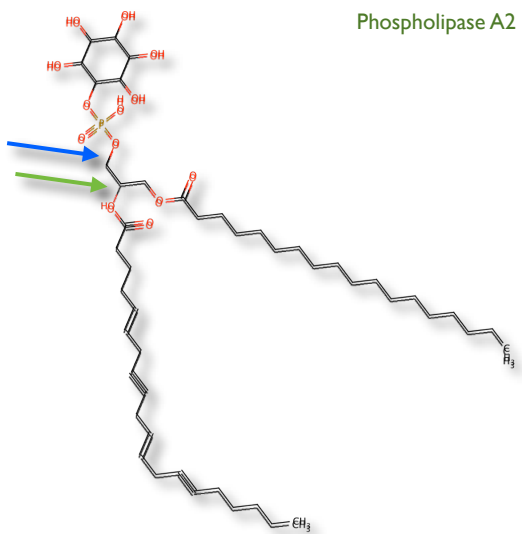
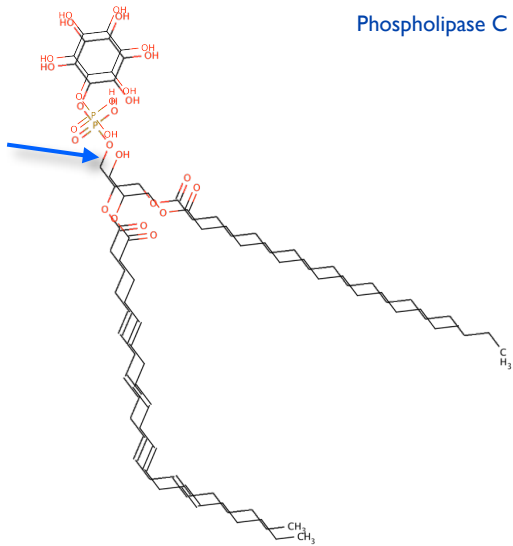
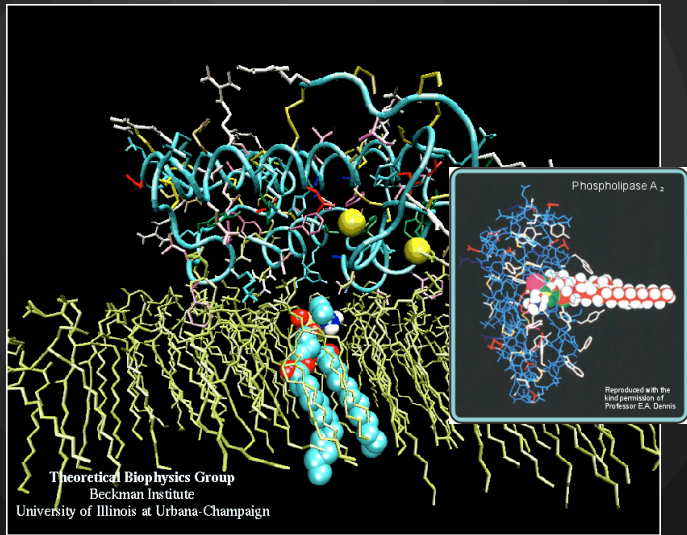
# Cytoplasmic phospholipase A2 cleaves arachidonate from phosphatidyl inositol in the outer ER membrane

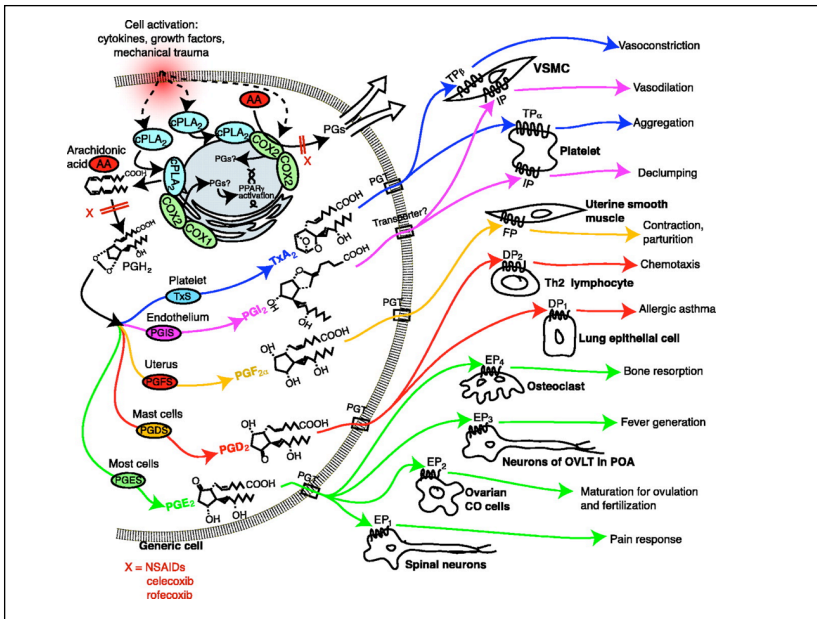


# Ca<sup>2+</sup> binding drives membrane association of phospholipase A2

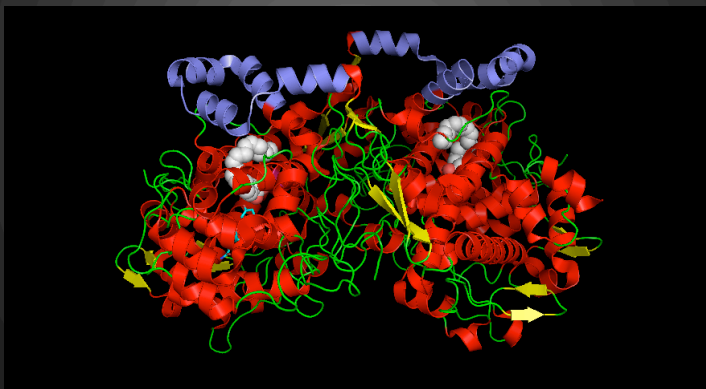


Burke, J. E. et al. J. Lipid Res. 2009;50:S237-S242





## COX isoforms homodimerize



membrane-binding

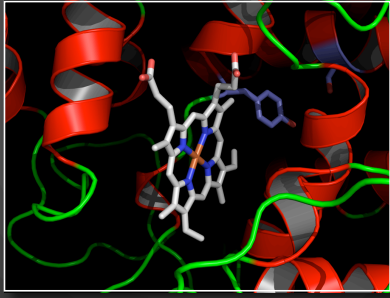
catalytic

epidermal growth factor

## COX isoforms catalyze committed step in prostaglandin, prostacyclin, and thromboxane synthesis

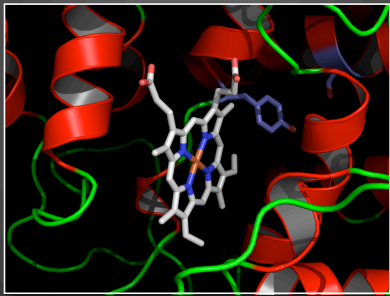
- Both COX1 and COX2 synthesize PGH: it is not clear how or why they function differently downstream
- COX1 homodimer (constitutive) mediates gastric function, renal homeostasis, and platelet aggregation
- COX2 homodimer (inducible) mediates pain, swelling, inflammation and fever.

## COX peroxidase activity

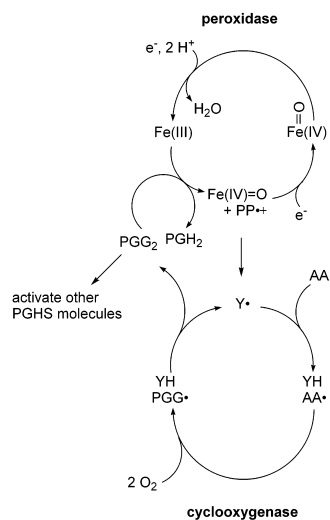


A heme prosthetic group generates the tyrosyl radical

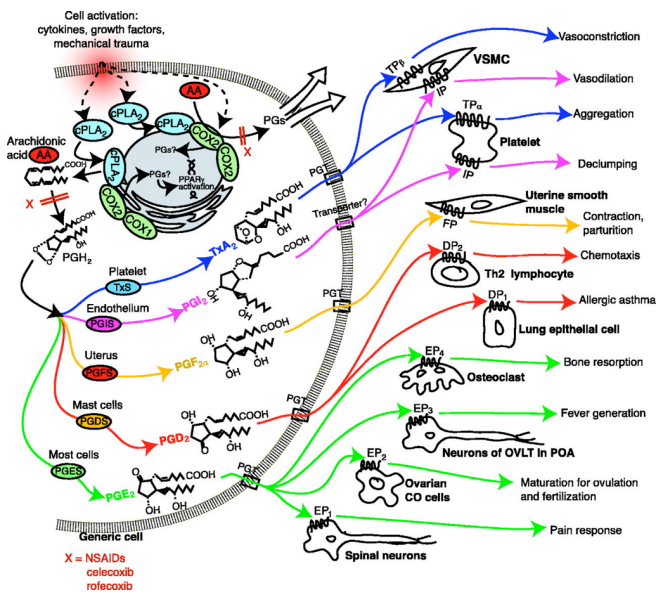
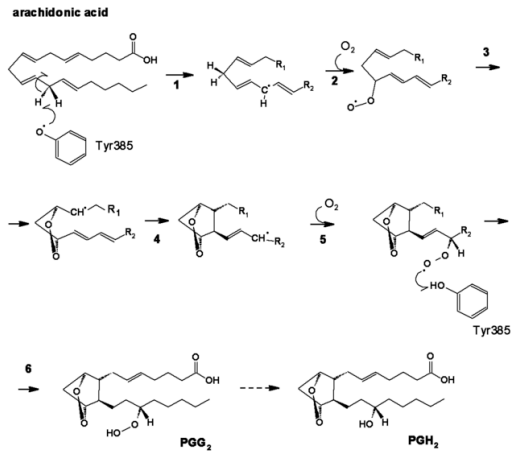
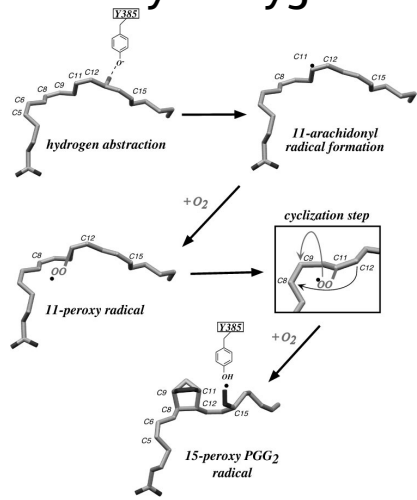
## COX cyclooxygenase activity



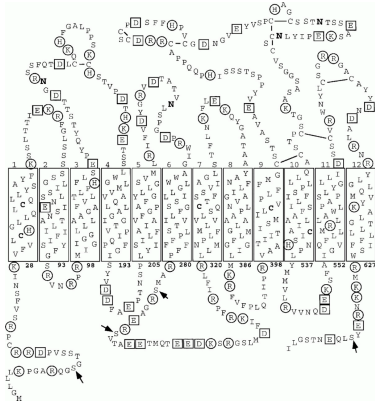
The redox active tyrosine (tyrosyl radical) mediates cyclooxygenation



# cox reaction mechanism includes both peroxidase and cyclooxygenase activities



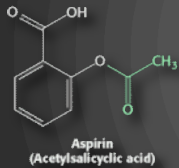
## Eicosanoids are actively transported out of the cell



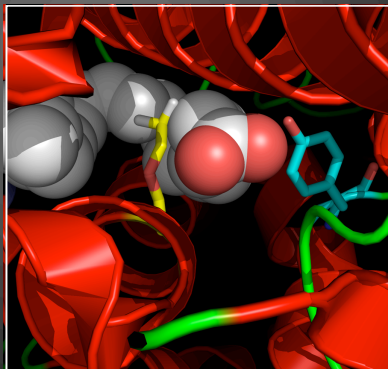
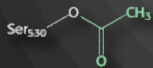
Annu Rev Physiol. 1998;60:221-42

## Aspirin is an irreversible inhibitor of both COX-1 and COX-2

COX-1 Ser530 Arachidonate



Aspirin  
(Acetylsalicylic acid)



- Aspirin is an irreversible inhibitor of both COX-1 and COX-2
- Ibuprofen and naproxen are competitive inhibitors of both COX-1 and (7-fold) COX-2
- Vioxx and Celebrex are highly selective for COX-2 (300-fold)

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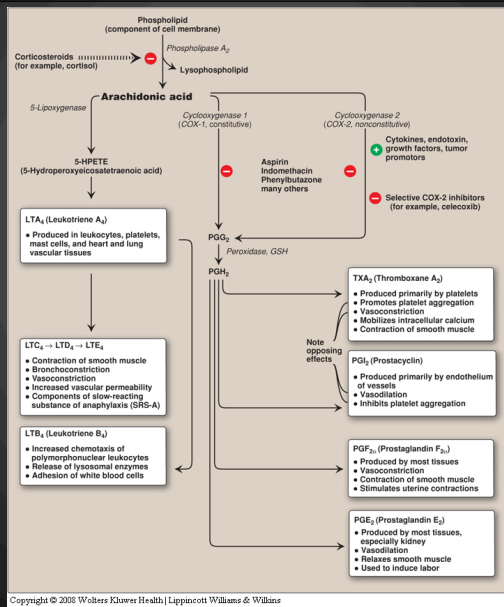
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The Lancet 2007; 370:2138-2151  
 DOI:10.1016/S0140-6736(07)61909-6

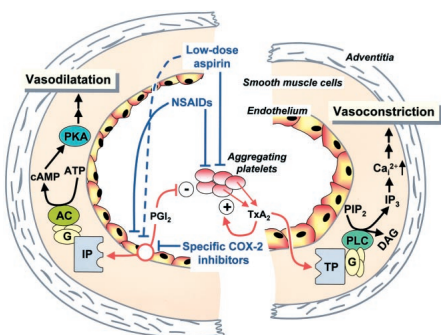
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 Prof Vibeke Strand MD

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## COX-2 inhibitors suppress prostacyclin synthesis without a concomitant suppression of thromboxanes



# They are derived from Arachidonic acid through two main pathways: cox pathway, lipoxygenase pathway

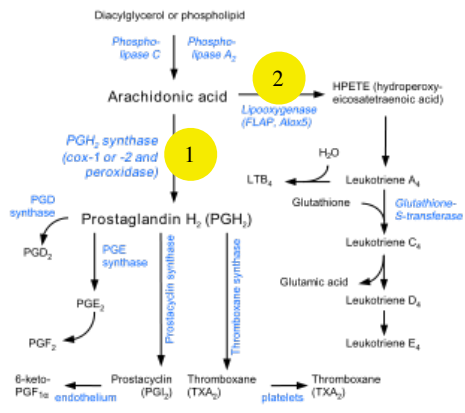


Figure 6 Structure and active site model of LTA4-H

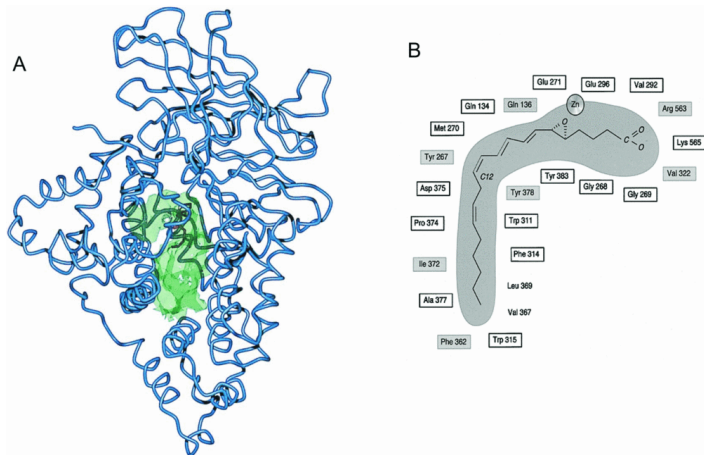


Figure 5 Intracellular organization of the critical enzymes involved in leukotriene biosynthesis

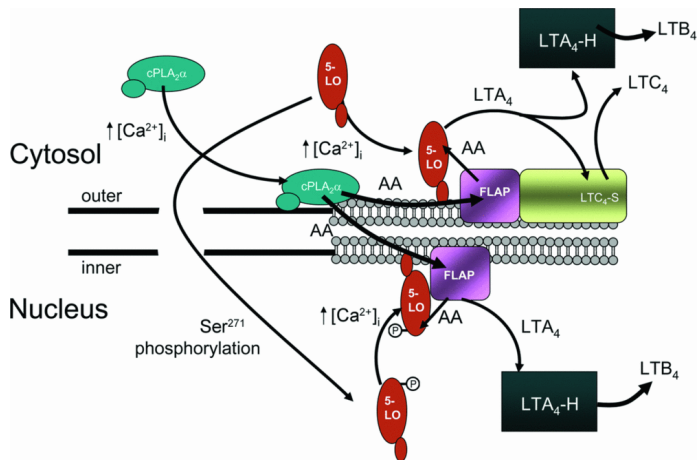


Figure 4 Catalytic cycle of 5-LO

