Anti-Inflammatory Drugs: NSAIDs, COX-2 Selective Inhibitors, Glucocorticoids and Anti-Cytokine Agents

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Overview

Inflammation is mediated in part by prostaglandins produced by the cyclooxygenase pathway. NSAIDs represent a large class of drugs that inhibit this pathway and serve as combined anti-inflammatory, anti-pyretics, and analgesics. Because NSAIDs are generally nonspecific and exert numerous side effects, more specific therapeutics such as selective COX-2 inhibitors and cytokine therapies are increasingly used.

Prostaglandins: Physiologic and Pathologic Functions

All cells in the body have the capacity to synthesize prostaglandins. In response to inflammatory stimuli arachidonic acid (AA) is separated from plasma phospholipids by phospholipase A_2. Cyclooxygenase metabolizes AA to the cycloendoperoxide prostaglandin H_2 (PGH_2), which itself is converted to either PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2 (prostacyclin) or TXA_2 (thromboxane) by appropriate enzymes (i.e. thromboxane synthesis in platelets, prostacyclin synthase in endothelial cells).

The prostaglandins exert numerous physiologic functions:

- *Physiologic:* temperature homeostasis, bronchial tone, cytoprotection (gastric and renal mucosa), intestinal mobility, myometrial tone, semen viability (some prostaglandins like PGE_1 have anti-inflammatory effects), stimulate renin secretion

The pathologic functions of prostaglandins involve derangements of normal physiology:

- *Pathologic:* fever (aberrant hypothalamic thermoregulation), asthma (airway responsiveness and immune hyperreactivity), ulcers (loss of cytoprotection), diarrhea (intestinal mobility), dysmenorrhea (myometrial tone), **inflammation, bone erosion, pain** (thought to be caused by PGD_2)

Specific functions of prostaglandins in the context of inflammation include:

- PGI_2: inhibits platelet aggregation, vasodilatation, vascular permeability (edema)
- PGE_2: pain, hyperalgesia, heat, vasodilatation, bronchoconstriction, synergistically act with other pro-inflammatory mediators (histamine, complement, LTB_4)
- TXA_2: promotes platelet aggregation, vasoconstriction, bronchoconstriction

Cyclooxygenase

There are two forms of cyclooxygenase (COX) enzymes: COX-1 and COX-2. Though COX-1 and COX-2 catalyze the same reaction, their expression, functions, and properties are markedly different.

	COX-1	COX-2
Expression	Constitutive (activated by physiologic stimuli)	Inducible by pro-inflammatory stimuli (LPS, TNFα, IL-2, IFNγ, etc)
Tissue Localization	Ubiquitous	Inflammatory and neoplastic sites (small amounts in kidney, uterus, ovary, CNS [neocortex, hippocampus])
Role	"**Housekeeping**" and Maintenance	Pro-inflammatory and mitogenic functions (? Neuronal plasticity)

COX-1 produces PGE_2, PGI_2, and TXA_2 in platelets, GI mucosa, vascular endothelium, and the kidney. The ***housekeeping functions*** of these COX-1 produced prostaglandins include maintaining renal and gastrointestinal blood flow (cytoprotection), regulation of vascular homeostasis, renal function, intestinal mucosal proliferation, platelet function, and anti-thrombogenesis.

Pro-inflammatory functions of COX-2 produced prostaglandins include pain, fever, dysregulated proliferation, and inflammation. COX-2 produces prostaglandins at sites of inflammation (in macrophages, in synovial tissue of rheumatoid arthritis joint). Mitogenic functions of COX-2 produced prostaglandin include renal genesis and reproduction.

The goal of pharmacologic anti-inflammatory therapy is therefore to inhibit COX-2 produced prostaglandins! Non-specific inhibition of COX-1 results in side effects!

(Note: There is an entire additional pathway of arachidonic acid metabolic by enzymes called lipoxygenases. 5-lipoxygenase enzyme is not present in all tissues but is limited to neutrophils, eosinophils, monocytes, and certain mast cell populations. Lipoxygenases produce leukotrienes (e.g. LTB_4, LTD_4), which are potent bronchoconstrictors and chemotactic agents. Leukotrienes have important roles in asthma, glomerulonephritis and inflammatory bowel disease. Refer to the Asthma case.)

NSAIDs (Non-steroidal anti-inflammatory drugs)

Most NSAIDs are polycyclic carboxylic acid derivatives with relatively low pKa values. NSAIDs are often classified on the basis of their chemical structure (see Figure 1).

- **Salicylates:** aspirin, diflunisal, 5-aminosalicylate, sodium salicylate, magnesium salicylate, sulfasalazine, olasalzine
- **Acetic acids:** indomethacin, diclofenac, sulindac, etodolac, ketorolac, tolmetin
- **Propionic acids:** ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin
- **Fenamic acids:** meclofenamate, mefenamate
- **Enolic acids (oxicam class):** piroxicam
- **Ketones:** nabumetone (converted to 6-naphthylacetic acid in liver)

NSAID General Pharmacodynamics

All NSAIDs except aspirin act as reversible, competitive cyclooxygenase inhibitors by blocking the hydrophobic channel in cyclooxygenase by which the substrate arachidonic acid accesses the enzyme active site. Aspirin covalently modifies and destroys the cyclooxygenase enzyme.

The ultimate function of the NSAID is to competitively inhibit COX-2, preventing generation of proinflammatory eicosanoids, and thus limiting the extent of inflammation and adverse signs and symptoms.

- Inhibition of COX-1 is an *unintended* side effect that results in many toxicities.
- All NSAIDs have a ratio of inhibition of COX-2 / inhibition of COX-1. The better the ratio, the more specific the therapeutic effect and less side-effects.
  - NSAIDs with high ratio (100:1 to 1000:1) are *COX-2 Selective* (Coxib)
- Despite the benefits of NSAIDs, they only provide symptomatic relief, as the underlying pathophysiology or injury generally is unaffected.

NSAIDs as a broad class of drugs that exhibit three general effects:

- **Analgesia**
- **Anti-pyrexia** (related to decreasing levels of PGE_2 near the hypothalamus)
- **Anti-inflammatory**

NSAIDs are also used in some cases as *anti-thrombotics* and *anti-neoplastics*. As anti-thrombotics NSAIDs impair platelet aggregation, prolong bleeding time, and function as anticoagulants. The COX-2 specific inhibitors do not exert anti-thrombotic effects.

Other functions of NSAIDs include inhibition of the following:

- (Cyclooxygenase inhibition)
- Superoxide generation
- Lysosomal enzyme release
- Neutrophil aggregation / adhesion
- Lymphocyte function
- Cytokine release (IL-6)

Indications for Specific NSAIDs

Please refer to Table 1 to find indications common to each structural class of NSAID. See below for COX-2 selective drugs.

Non-selective NSAIDs are used as analgesics against moderate pain of musculoskeletal and inflammatory origin (headaches, dysmenorrhea, osteoarthritis, rheumatoid arthritis, gout, surgical pain, tendonitis, and bursitis). NSAIDs also function as anti-inflammatory agents in many of these conditions and ulcerative colitis. NSAIDs are commonly used as anti-platelet agents (MI prophylaxis). Acetaminophen (technically not an NSAID) has no anti-inflammatory activity but is widely used as an analgesic and anti-pyretic.

NSAID Pharmacokinetics

The organic acid functionality of NSAIDs confers important pharmacokinetic properties:

- Efficient GI absorption (nearly complete)

- Low first pass hepatic metabolism
- Highly protein bound (95%) (slows the rate at which these drugs can cross the capillary wall and gain access to the tissue)
- Small volumes of distribution
- Accumulation in cells at sites of inflammation (i.e. acidic NSAIDs are preferentially sequestered in inflamed synovial tissues)
- Both efficient enterohepatic and renal excretion
- Variable half lives (the lower the pK_a generally the shorter the half-life)

Plasma Elimination Half Lives: Another method to classify NSAIDs (besides structure)

- Short Half Life (< 6 hours): *more rapid effect* and *clearance*
  Aspirin (0.25-0.33 hrs), Diclofenac (1.1 ± 0.2 hrs), Ketoprofen (1.8 ± 0.4 hrs), Ibuprofen (2.1 ± 0.3 hrs), Indomethacin (4.6 ± 0.7 hrs)
- Long Half Life (> 10 hours): *slower onset of effect* and *slower clearance*
  Naproxen (14 ± 2 hrs), Sulindac (14 ± 8hrs), Namebutone (26 ± 5 hrs), Piroxicam (57 ± 22 hrs) (also COX-2 Selective Inhibitors)

Important Drug Interactions:

- Displace other drugs from plasma protein binding sites:
  - Anti-coagulants (warfarin): GI bleeding risk greatly increased
  - Phenytoin: (increased phenytoin activity, difficulty dosing)
  - Oral Hypoglycemics: (increased phenytoin activity)
  - Methotrexate: (increased phenytoin activity)
- Anti-Hypertensives (diuretics, beta blockers, ACE inhibitors): NSAIDs may blunt the anti-hypertensive effects and cause renal decompensation or renal failure in patients receiving these drugs
- Methotrexate, digoxin, aminoglycosides, lithium: NSAIDs inhibit clearance
- Probenecid: renal clearance of NSAIDs reduced by probenecid
- Antacids: absorption of some NSAIDs inhibited by antacids
- Aspirin: may lower levels of other NSAIDs, but side effects are additive

NSAID Toxicity

NSAIDs affect the gastrointestinal, CNS, hepatic, renal, hematologic, and skin systems. NSAIDs also cause allergic phenomena.

Gastrointestinal Toxicity of NSAIDs

Prostaglandins suppress gastric acid secretion and help maintain gastric mucosal barrier, thus providing gastrointestinal protection. Because of their suppression of prostaglandin synthesis NSAIDs tend to cause gastric irritation, exacerbate peptic ulcer disease, cause mucosal lesions (superficial to penetrating ulcers), and may induce bleeding.

NSAID induced gastropathy typically includes gastritis, gastric bleeding, mucosal and subepithelial damage, and erosions, which may progress to ulcerations and perforations.

- Occult blood loss may occur and massive GI bleeding may also develop.
- Symptoms including pain, dyspepsia, nausea, vomiting are frequent
- Overall, there is poor correlation of these symptoms with endoscopic findings.

- NSAID induced gastric toxicity causes great morbidity, requiring annual care expenditures of $4 billion, and causes 7500 deaths per year.
- FDA estimates that ulcers, bleeding and perforation occur in 1 to 2 % of patients using NSAIDs for three months and 2 to 5% of those using them for one year.
- Specific risk factors for NSAID induced GI toxicity include: higher NSAID doses, older age, concurrent steroid use, history of peptic ulcer disease

Treatment of NSAID Induced GI Toxicity

- Discontinuation / Avoidance of NSAIDs / Use "Gastroprotective" NSAIDs
- Take medication with meal
- Pharmacologic
  - H_2 Receptor Antagonists (high dose)
  - Proton Pump Inhibitors
  - Misoprostol (PGE_1 analog which restores cytoprotective effects)
  - Sucralafate
- COX-2 Specific NSAIDs
  - Reduce risks of ulceration, bleeding, perforation vs. nonselective NSAIDs
  - Reduced endoscopic erosion and ulceration

CNS Toxicity:
CNS toxicity includes headache, confusion, tinnitus (aspirin), dizziness, mood alteration and depression, and aseptic meningitis (particularly in SLE patients). Aspirin is linked to *Reye's Syndrome* (below).

Hepatic Toxicity:
NSAIDs may cause asymptomatic elevations of liver enzyme, or transaminitis (most common with diclofenac. Acute idiosyncratic hepatitis has also been reported. Reye's Syndrome is an often fatal combination of microvesicular steatosis and hepatic encephalopathy thought to be caused by the administration of aspirin to children post febrile viral infection (VZV, influenza B). Out of fear of Reye's Syndrome, aspirin is generally not given to children.

Nephrotoxicity:
In healthy individuals with normal kidneys PGE_2 and PGI_2 play no role in controlling renal function but under certain conditions of localized circulatory stress often associated with elevated levels of angiotensin II and catecholamines, locally produced vasodilating prostaglandins become essential to the maintenance of adequate renal function. Inhibition of these vasodilating prostaglandins by NSAIDs can inhibit renal prostaglandin production, which decreases renal blood flow (RBF) by affecting renal cytoprotection and vascular regulation. Patients at most risk include those with congestive heart failure, volume depletion, chronic renal disease, liver disease and those patients receiving diuretics. Nephrotoxic effects of NSAIDs include edema, high blood pressure, increased creatinine, and potassium imbalances (hyperkalemia). NSAIDs may also result in renal ischemia, nephrotic syndrome, interstitial nephritis (most commonly with fenoprofen), acute renal failure, renal papillary necrosis, and calculi.

Hematologic Effects:
Hematologic effects include the anti-coagulant effects (impaired platelet aggregation and prolonged bleeding time). An effect on platelet aggregation persists for as long as the NSAID is present. NSAIDs should be discontinued for a long enough period before surgery to permit complete excretion of the drug i.e. 4 to 5 times the half-life of the drug. Aspirin must be discontinued 7-10 days prior due to its irreversible effects on platelets.

Blood dyscrasias such as agranulocytosis, thrombocytopenia and aplastic anemia are rarely associated with NSAIDs. Phenylbutazone has the greatest risk of inducing idiosyncratic aplastic anemia (Phenylbutazone was withdrawn from the US market).

Cutaneous and Hypersensitivity Effects:
NSAIDs can cause urticaria, bronchospasm, anaphylaxis, and erythema multiforme. A wide variety of skin reactions most frequently reported with piroxicam and benoxaprofen (withdrawn from market) include photosensitivity reactions, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

NSAID-induced hyperreactivity: NSAID exposure results in ocular and nasal congestion, severe airway obstruction, acute asthmatic attack, and possibly anaphylactic reaction in patients with aspirin allergy.

- Samter's triad: aspirin allergy / hypersensitivity higher in patients with nasal polyps, bronchial asthma, and rhinitis (sinusitis).
- Occurs in 10% of asthmatics

Other Toxicities Unique to Aspirin:
Aspirin can generate *complex acid-base imbalances* because it causes metabolic acidosis and also stimulates the medullary respiratory center, causing respiratory alkalosis.

Salicylism refers to a syndrome of chronic, excessive aspirin dosing characterized by nausea, vomiting, diarrhea, and dehydration, hyperventilation, headache, tinnitus, visual and auditory disturbances, confusion, stupor, and delirium.

COX-2 Selective Inhibitors: The Coxibs

Inhibiting COX-2 is thought to provide a more specifically targeted anti-inflammatory effect while limiting side effects. The coxibs represent a subset of NSAIDs that preferentially block the hydrophobic substrate channel in COX-2 than in COX-1.

Currently approved COX-2 selective inhibitors include celecoxib, rofecoxib, meloxicam, and valdecoxib. These drugs are approved for rheumatoid arthritis, osteoarthritis, pain, primary dysmenorrhea, and familial adenomatous polyposis (decreasing number and size of adenomas in patients with history of FAP).

- The potential therapeutic role of COX-2 inhibitors in Alzheimer's disease is being studied (COX-2 is the predominant isoform in the neocortex and hippocampus).
- COX-2 is induced by LH prior to ovulation and at delivery. COX-2 selective inhibitors may have a role in preventing preterm labor and delivery.

Effects and Toxicities of COX-2 Selective Drugs:
Long-term safety profiles of COX-2 inhibitors are unknown.

COX-2 inhibitors were designed in part to limit the gastrotoxicity associated with NSAIDs. Although the rate of gastropathy induced by COX-2 selective drugs is lower, events still occur and symptoms are similar. However, events are less serious (i.e. less perforation) vs. conventional NSAIDs.

There is some concern that COX-2 inhibitors, in particular rofecoxib, have deleterious effects on the cardiovascular and renal systems by inducing hypertension, edema renal failure, and cardiac failure.

Platelets only express COX-1, so COX-2 has no effect on platelet function or the production of TXA_2. COX-2 may generate thromboembolic complications due to inhibition of endothelial prostaglandin synthesis and lack of effect on platelet thromboxane synthesis; this risk is believed minimal. The implications of this are:

- Patients on MI prophylaxis still need aspirin even if they are on a COX-2 selective inhibitor
- COX-2 inhibitors unlike NSAIDs may be administered safely with warfarin.

COX-2 is present in the kidney and apparently necessary for renal development and function, given knock out models that show inflammation and papillary changes. In addition, the inhibition of COX-2 may generate potential problems with wound healing and angiogenesis.

Glucocorticoids (not covered in lecture)

Glucocorticoids are 21-carbon steroid molecules with a variety of physiologic and metabolic effects. Cortisol (hydrocortisone) is the principal circulating glucocorticoid in humans.

Glucocorticoid activity depends on presence of a hydroxyl group at carbon number 11 in the steroid molecule. Cortisone and prednisone lack glucocorticoid activity until converted to cortisol and prednisolone in the liver (by reducing the C=O at carbon 11 to a hydroxyl). All glucocorticoid preparations marketed for topical use are 11 beta hydroxyl compounds, thus eliminating the need for hepatic transformation.

Commonly used glucocorticoids are characterized short, medium, and long acting on the basis of ACTH suppression after a single dose (of equivalent anti-inflammatory activity to 50 mg of prednisone). The relative potency of the glucocorticoids correlates with their affinity for the glucocorticoid receptor. The observed potency of a glucocorticoid is a measure not only of the intrinsic biological potency but also the duration of action. However, relationships between the circulating half-life and duration of action, and between circulating half-life and glucocorticoid potency are imprecise.

Drug	Plasma Half Life	Biologic Half Life	Glucocorticoid Potency	Equivalent Dose (mg)	Mineralocorticoid Activity
Cortisol	80–115 min	8-12 hrs	1	20	Yes
Prednisone	3.4–3.8 hrs	18-36 hrs	4	5	No
Methylprednisolone	2.3–4.0 hrs	18-36 hrs	5	4	No
Dexamethasone	1.8–4.7 hrs	36-54 hrs	30	0.75	No

It has been suggested that the duration of action of a glucocorticoid is not determined by its presence in the circulation. Steroids pass through the cell membrane and enter the cytoplasm where it binds to a specific cytoplasmic receptor protein. These glucocorticoid receptors are a superfamily of DNA binding proteins that affect gene regulation. Glucocorticoids alter transcriptional regulation of specific cytokine genes. Therefore, the effects of glucocorticoids continue to act within the cell after glucocorticoids have disappeared from the circulation (note disparities in plasma and biologic half lives).

Therapeutic Effects of Glucocorticoids

Glucocorticoids are **anti-inflammatory** and **immunosuppressive** agents.

Glucocorticoids administered at pharmacologic doses inhibit the action of COX-2 by repressing COX-2 expression, repressing expression of cytokines which activate COX-2, blunting the cytokine induced upregulation of COX-2, and limiting the available pool of arachidonic acid substrate by inhibiting phospholipase A_2 (via the lipocortin pathway). These combined actions create a powerful anti-inflammatory effect because virtually all eicosanoid pathways are inhibited. Because of this profound and global suppression, glucocorticoids are indicated for a number of autoimmune and inflammatory conditions.

Effects of Glucocorticoids on Humoral Factors

- Mild decrease in immunoglobulin levels
- Decreased RE clearance
- Decreased synthesis of prostaglandins and leukotrienes

Type of Leukocyte	Effect of Glucocorticoids on Leukocyte: Movement	Function
Lymphocyte	▪ Circulating lymphocytopenia ▪ Depletion of recirculating lymphocytes ▪ Selective depletion of T lymphocytes	▪ Suppression of delayed hypersensitivity skin testing ▪ Suppression of lymphocyte proliferation to antigen ▪ Suppression of mixed lymphocyte reaction ▪ Suppression of natural cytotoxicity
Monocyte	▪ Circulating monocytopenia ▪ Inhibition of accumulation at inflammatory sites	▪ Blockade of Fc receptor binding ▪ Inhibition of IL1 production
Neutrophil	▪ Circulating neutrophils ▪ Accelerated release of	▪ Increase in antibody dependent cellular cytotoxicity

	neutrophils from bone marrow ▪ Blockade of accumulation at inflammatory sites	
Eosinophil	▪ Circulating eosinopenia ▪ Decreased eosinophil migration	

Glucocorticoid Toxicities

Glucocorticoids exhibit a diverse array of toxicities (see Table – memorize these). Recall that a condition of glucocorticoid excess is a *Cushingoid syndrome*.

System	Side Effect of Glucocorticoids
Endocrine	Hyperglycemia, catabolic abnormalities, growth suppression, truncal obesity, hirsutism, impotence, menstrual irregularities
Cardiovascular	HBP, CHF
Musculoskeletal	fatigue, weakness, myopathy, osteoporosis, avascular necrosis
Immunologic	immunosuppression
Ophthalmic	cataracts, glaucoma
Gastrointestinal	PUD, pancreatitis
Neuropsychiatric	pseudotumor cerebri, alterations in mood, psychosis
Dermatologic	fragile skin, ecchymoses, impaired wound healing, acne

Steroid Withdrawal and Glucocorticoid Replacement

Because of suppression of the pituitary-adrenal axis by chronic glucocorticoid therapy, patients that undergo surgical procedures or acute medical illness should receive stress dose steroids generally equivalent to 300 mg of hydrocortisone administered as a split dose over a 24 hour period. Patients may require very slow and low reductions of steroids back to baseline to minimize the symptoms of steroid withdrawal, which include joint and muscle pain, nausea, lethargy, weight loss, and fever.

Anti-Cytokine Agents

Rheumatoid arthritis is a chronic, systemic autoimmune and inflammatory disease that primarily attacks the joints. Autoimmune targeting of normal joint proteins results in inflammation with local release of cytokines, especially **TNFα**, growth factors, and interleukins, all of which induce COX-2 expression. Levels of TNFα, COX-2, and PGE_2 are markedly elevated in the synovial fluid of affected joints. PGE_2 binds to synovial cell receptors on and stimulates release of matrix metalloproteinases (MMPs) which directly damage joint tissue. TNFα also stimulates production of IL-1 and IL-6; these pro-inflammatory mediators along with COX-2 derived prostaglandins activate the surrounding endothelial tissue to recruit inflammatory cells.

The newest therapeutics seek to inhibit the pro-inflammatory effects of the cytokines TNFα and IL-1. By limiting TNF activity, the generation of pro-inflammatory cytokines IL-1 and IL-6 are diminished. Three strategies for inhibiting these molecules have emerged: 1) creating monoclonal Ab to the TNFα and IL-1

proteins, 2) solubilizing forms of the endogenous receptors of TNFα, and 3) making recombinant versions of endogenous receptor antagonist.

Agent	Target	Strategy	Comments	Indications
Etanercept	TNFα	Soluble TNF receptor	Fusion protein: extracellular domain of TNFαR and Fc of human IgG1	Rheumatoid arthritis Juvenile rheumatoid arthritis Psoriatic arthritis
Infliximab	TNFα	mAb	chimeric IgG1 mAb with human Fc and murine Fab	Rheumatoid arthritis (in conjunction with MTX) Crohn's Disease
Adalimumab (D2E7)	TNFα	mAb	Human mAb	Rheumatoid arthritis
Anakinra	IL-1	Block IL-1R	Recombinant IL-1R antagonist	Rheumatoid arthritis

Comparison of Infliximab, Etanercept, and Adalimumab in rheumatoid arthritis:

- Infliximab administered IV (by doctor); etanercept and adalimumab subcutaneously (by patient)
- Infliximab 3 mg/kg loading dose with similar doses at 2 weeks, 6 weeks, and then every 8 weeks thereafter. Etanercept 25 mg twice weekly. Adalimumab 40 mg every other week.
- Infliximab must be administered in combination with methotrexate. Etanercept and adalimumab may be monotherapy or may be combined with methotrexate.
- All reduce signs, symptoms, and *structural damage* (joint erosion on radiograph).

Anti-Cytokine Agent Toxicities:

The anti-cytokine agents blunt the immune response, and thus cause many side effects that result from immunosuppression (infections, and loss of tumor surveillance). The body's response to the foreign protein also poses risk of development of antibodies.

- Injection site reactions
- Hypersensitivity reactions (i.e. to murine protein)
- Opportunistic Infections
  - Tuberculosis
  - Fungi (*Aspergillus*)
    Pneumocystiis carinii
  - *Listeria*
  - Bacterial Sepsis
- Lymphoproliferative Disorders
- Lupus like Syndrome
- Autoantibodies and Antibodies to drug
- Rare aplastic anemia, demyelinating syndrome

Future Applications of Anti-Cytokine Therapies

Because of the broad role of TNFα in disease, application of these drugs to new trials and off label uses is occurring for: ankylosing spondylitis, vasculitis, myositis, GVHD, uveitis, CHF, sarcoidosis, psoriasis, ARDS, Still's disease, Wegener's syndrome, etc.

Figure 1
Structural Classes of NSAIDs

See Dudzinski, D. M. and Serhan, C.N. Eicosanoids: An Update on Biosynthesis, Actions, and Current Pharmacopoeia. *Inflammation* (in press).