

# **Clinical pharmacology**

## **(Rheumatoid arthritis & Osteoarthritis)**

5<sup>th</sup> year lecture

4 December 2017

# Rheumatoid arthritis

# Definition

- Chronic multisystem disease of unknown aetiology
- Characterized by synovitis
- Involves peripheral joints
- Not spine (Except C1)
- Symmetrical
- Leads to cartilage damage and bone erosions and subsequent joint damage

# Pathogenesis

- hyperplasia and hypertrophy of the synovial lining cells
- vascular changes:
  - microvascular injury
  - Thrombosis
  - Neovascularization
- Oedema
- infiltration with mononuclear cells

# Cells

- mononuclear cell collections are predominantly T lymphocyte.
- CD4+ T cells > CD8+ T cells
- autoantibodies (RF & CCP) are produced within the synovial tissue lead to the formation of immune complexes
- synovial fibroblasts produce enzymes such as collagenase and cathepsins that degrade components of the articular matrix
- Osteoclasts are also prominent at sites of bone erosion.

# Cytokines

- secreted by activated lymphocytes, macrophages, and fibroblasts.

# **Treatment of RA**

# The goals of therapy are

- (1) relief of pain
- (2) reduction of inflammation
- (3) protection of articular structures
- (4) maintenance of function
- (5) control of systemic involvement



- None of the therapeutic interventions is curative
- The various therapies employed are directed at nonspecific suppression of the inflammatory or immunologic process

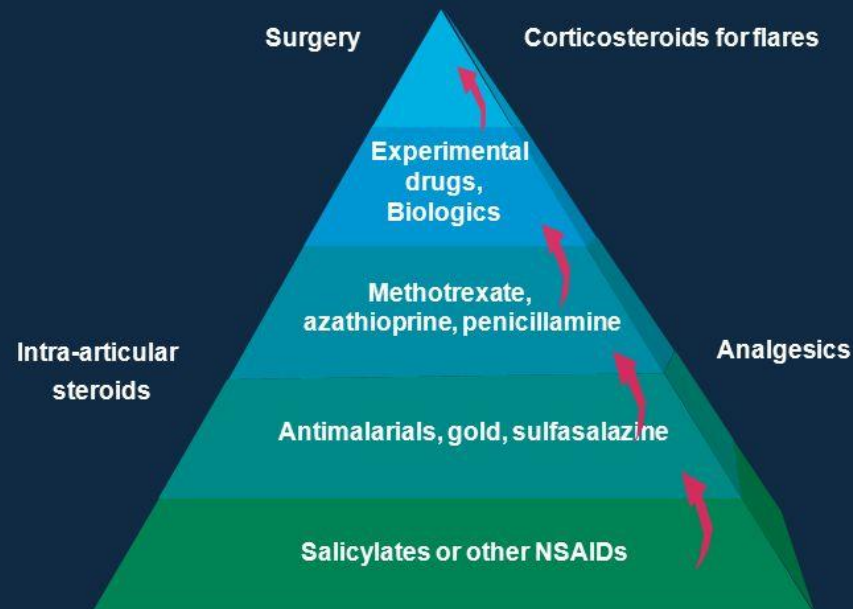
# TREATMENT STRATEGIES

- **There are three general strategies for DMARD treatment of RA:**
  - 1. sequential monotherapy
  - 2. step-up combination therapy
  - 3. initial combination (induction) therapy
- 1<sup>st</sup> approach has been abandoned in light of extensive data showing the superiority of step-up and induction approaches.

- Evidence suggests that “aggressive” treatment to rapidly achieve a low level of disease activity, which often necessitates a combination of agents, has superior efficacy to conservative approaches that involve sequential, low-dose monotherapy

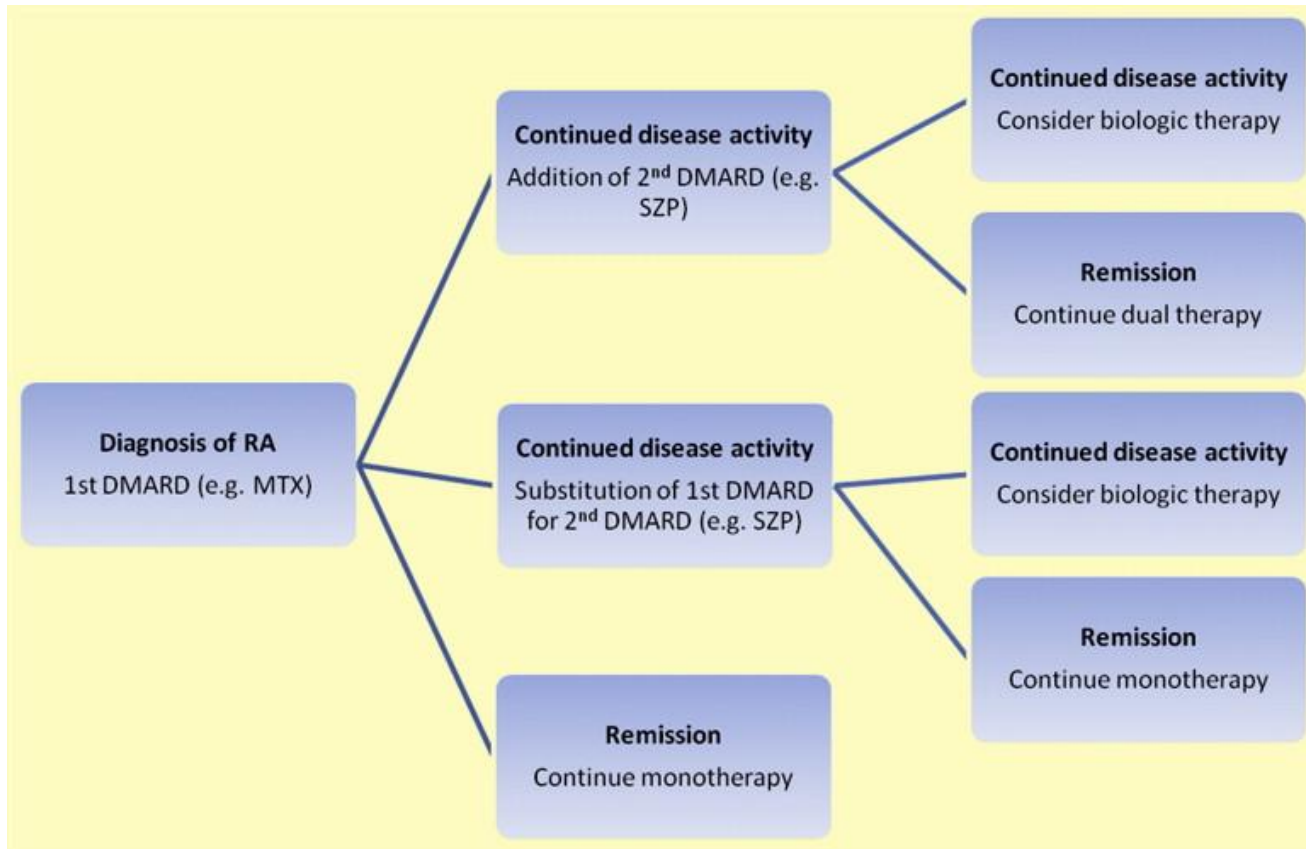
- Given the expense of combination therapy, especially with the biologic DMARDs the step-up combination approach remains the most common in clinical practice

## The Traditional Treatment Pyramid for RA: Sequential Drug Therapy

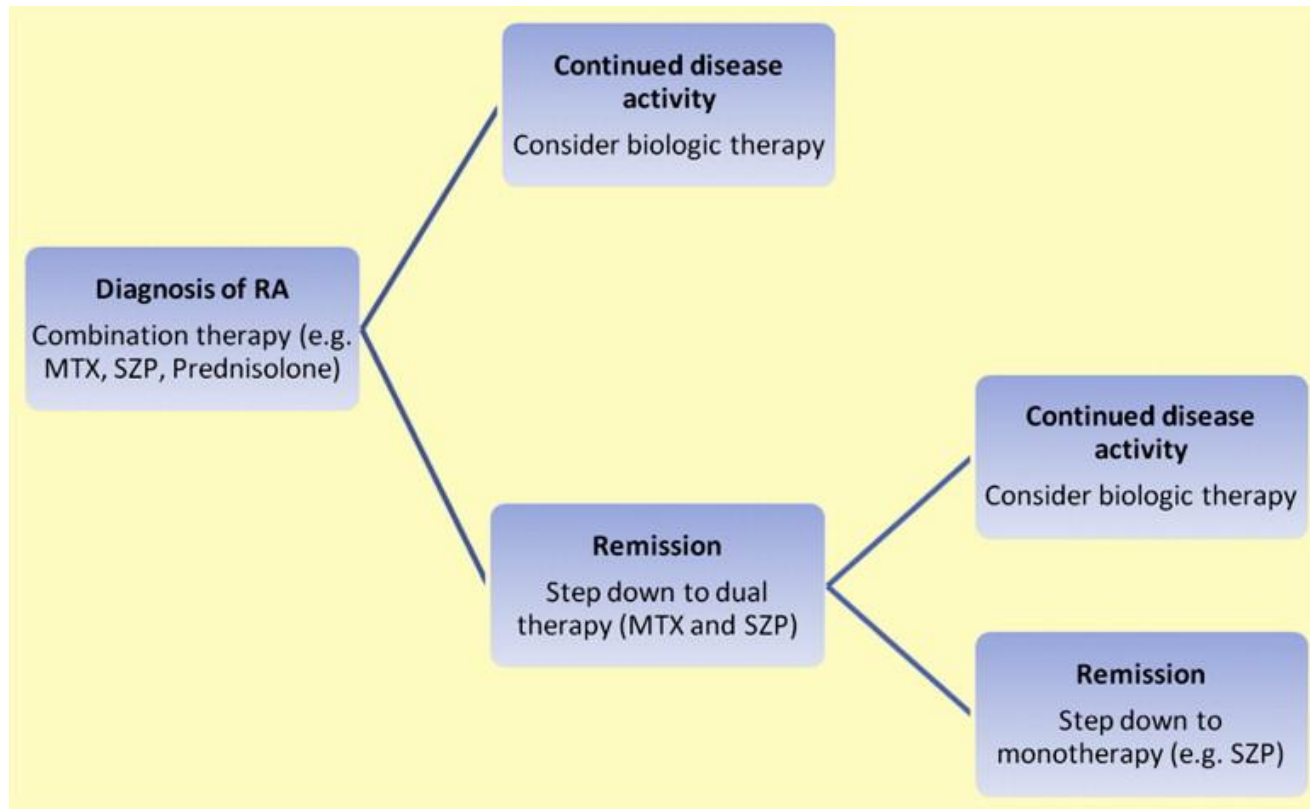


Adapted from *Primer on Rheumatic Diseases*. 10th ed. The Arthritis Foundation; 1993.

# Step-up combination therapy



# Initial combination (induction) therapy



- **Advantage of induction therapy**
  - more rapid control of synovitis and thus accumulation of joint damage
- **Disadvantages of induction approach:**
  - potential overtreatment
  - exposure to unnecessary toxicities in patients in whom disease may have been controlled by a single DMARD
  - difficulty in attribution of an adverse event to a specific drug.



# Conventional DMARDs

**TABLE 94.1 DISEASE-MODIFYING ANTIRHEUMATIC DRUGS**

DMARD	Mechanism of action
<b>Conventional DMARDs</b>	
Methotrexate	Inhibition of purine biosynthesis/cytokine expression. Induction of monocyte apoptosis
Sulfasalazine	Inhibition of cytokine expression/neutrophil migration
Leflunomide	Inhibition of pyrimidine biosynthesis/cytokine expression/neutrophil migration
Hydroxychloroquine	Unknown
Azathioprine	Active metabolite, 6-mercaptopurine, interferes with adenine and guanine biosynthesis
Cyclosporine	Inhibition of T-cell response via calcineurin inhibition
Cyclophosphamide	Lymphocyte cytotoxicity

# Biologic DMARDs

Biologic DMARDs	
Etanercept	Soluble 75kDa TNF receptor: inhibits biologic effects of TNF- $\alpha$
Infliximab	Chimeric anti-TNF- $\alpha$ antibody: inhibits biologic effects of TNF- $\alpha$ . Cell lysis of TNF- $\alpha$ expressing cells
Adalimumab	Human anti-TNF- $\alpha$ antibody: inhibits biologic effects of TNF- $\alpha$
Anakinra	Recombinant IL-1 receptor agonist: inhibits biologic effects of IL-1
Rituximab	Anti-CD20 monoclonal antibody: depletes B cells
Abatacept (CTLA4Ig)	Inhibits T-cell co-stimulation

# Disease monitoring

- **When assessing how active the disease is the doctor will take four factors into account:**
  1. Number of tender joints
  2. Number of swollen joints
  3. PGA: How active you think your disease is on a scale of one to ten
  4. ESR or CRP



09:57

das28

ESR

## DAS28 Calculator

Tender joint count:

2

Swollen joint count:

2

Erythrocyte Sediment. Rate(mm/hr):

9

Patient Global Health(mm):

20

Reset

Calculate DAS28

3.01

Low activity

About..

[www.tantorsystems.com](http://www.tantorsystems.com)

# DAS-28 interpretation

< 2.6 → remission

2.6 - 3.2 → low disease activity

3.2 - 5.1 → moderate disease activity

> 5.1 → high disease activity.

# Initial DMARD

- Methotrexate is the first-line DMARD of choice
- Aggressive dose escalation of methotrexate
- Start 10 mg/wk & ↑ by 5 mg every 4 wk
- Because of the slow onset of action of MTX, an interval of 4 to 6 weeks is required to determine whether a patient has responded to a dose increase
- an interval of 3 months is recommended to evaluate the initial response to methotrexate

- patients who have had an inadequate response to 20 to 25/week of oral methotrexate → change to SC or IM methotrexate may be more efficacious

# Alternative initial therapy

- Leflunomide
- Sulfasalazine
- Hydroxychloroquine



- Leflunomide & sulfasalazine have equivalent efficacy to MTX
- Sulfasalazine given to patients with contraindications to MTX

- Hydroxychloroquine:
  - low toxicity profile
  - low cost
  - safe in pregnancy
- less potent than other DMARDs, especially in its ability to slow radiographic progression.

# Screening prior to starting DMARDs

- All need LFT, KFT, CBC
- MTX: CXR
- Biologics: CXR, hepatitis B & C, PPD
- HCQ: ophthalmology

# Treatment monitoring

- NSAIDs: regular KFT
- Steroids: annual DEXA
- DMARDs: CBC, KFT, LFT
  - After 2 weeks
  - 1 month
  - 3 monthly

The drugs

# NSAIDs

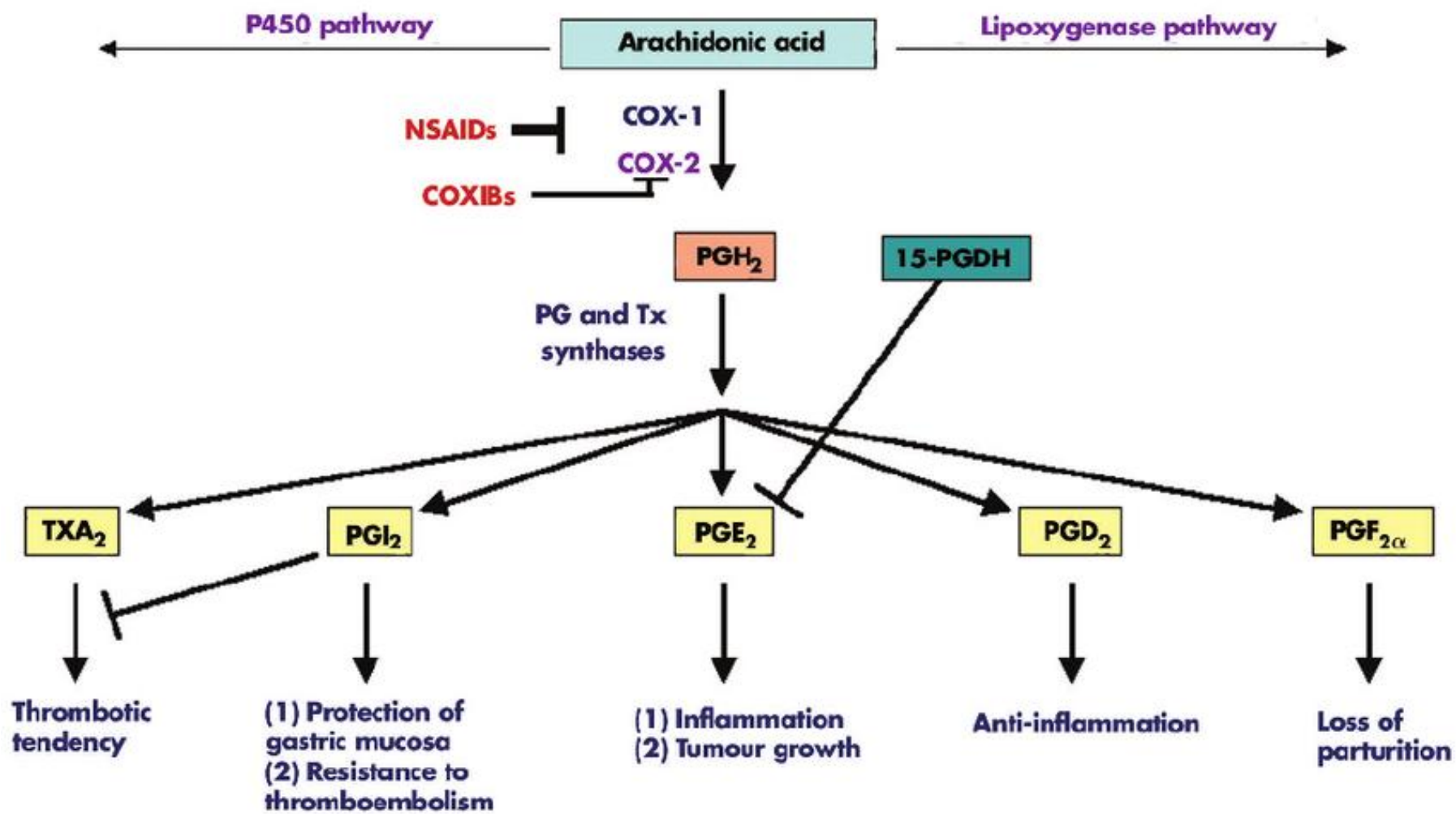
- Chemically heterogeneous group of compounds that provide symptomatic relief of pain and inflammation
  - Analgesic
  - anti-inflammatory
  - antipyretic
- not disease modifying, so their use as monotherapy for a prolonged period of time should be avoided.

# MECHANISM OF ACTION

- Inhibition of the cyclo-oxygenase (COX)
- prostanooids reproduce the main signs and symptoms of the inflammatory response
  - PGE2 and PGI2 cause erythema, an increase in local blood flow,
  - PGE2 can produce fever.

- PG-synthase is found in two isoforms
  - COX-1, which is expressed constitutively in all cells but is inducible under appropriate conditions
  - COX-2, which is inducible in response to inflammatory, mitogenic or hemodynamic stimuli



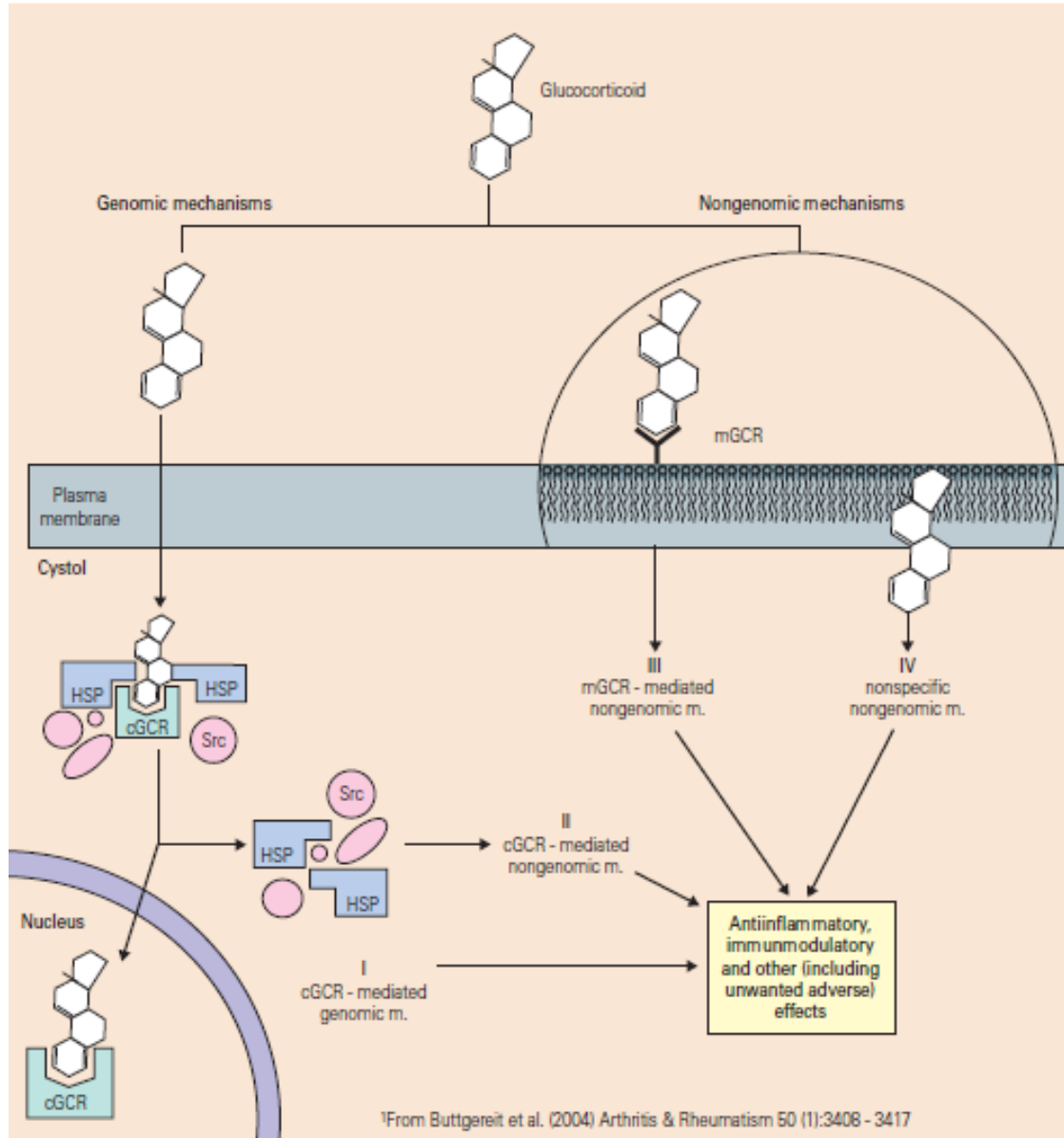


# Side effects of NSAIDs

- GI: erosions, ulcers, GI haemorrhage
- Renal: salt & water retention, ARF
- Hypersensitivity
- Ductus arteriosus
- Liver: raised LFTs
- Skin: EM, TEN, urticaria

# Corticosteroids

## MECHANISMS OF THE CELLULAR ACTIONS OF GLUCOCORTICOIDS



# Corticosteroids

- The glucocorticoid/glucocorticoid receptor complex inhibits transcription factors NF- $\kappa$ B and AP-1.
- result in the decreased synthesis of proinflammatory cytokines such as IL-1, IL-2, IL-2 receptor, IFN- $\alpha$ , IL-6, and TNF- $\alpha$ .

# **Efficacy of steroids in rheumatoid arthritis**

- Short- to moderate-term glucocorticoid studies reveal improved disease activity and functional status
- low dose glucocorticoids prevent radiographic joint destruction in RA.

# Route of administration

- Oral
- IM
- IV
- Intra-articular

# Adverse effects

- long-term, relatively low-dose glucocorticoid use is a significant cause of numerous potentially serious adverse



# Adverse effects

- Bone and muscle
- Cardiovascular
- Gastrointestinal
- Infections
- Metabolic and endocrine
- Dermatologic
- Neuropsychiatric
- Ophthalmologic

# Muscle and bone

- Osteoporosis leading to fracture.
  - cumulative dose
- Osteonecrosis of bone
- Myopathy
  - peak dose of glucocorticoid rather than cumulative dose

# Cardiovascular

- Hypertension
- Hyperlipidaemia
- atherosclerotic vascular disease.

# Dermatologic

- skin thinning
- Ecchymoses
- cushingoid appearance
- Acne
- Hirsutism
- impaired wound healing

# GI

- Gastritis
- Ulcers
- GI bleeding.
- Pancreatitis

# Endocrine & metabolic

- Hyperglycemia
- adrenal suppression

# Neuropsychiatric

- Insomnia
- depression
- Memory impairment

# Ophthalmologic

- Cataracts
- Glaucoma

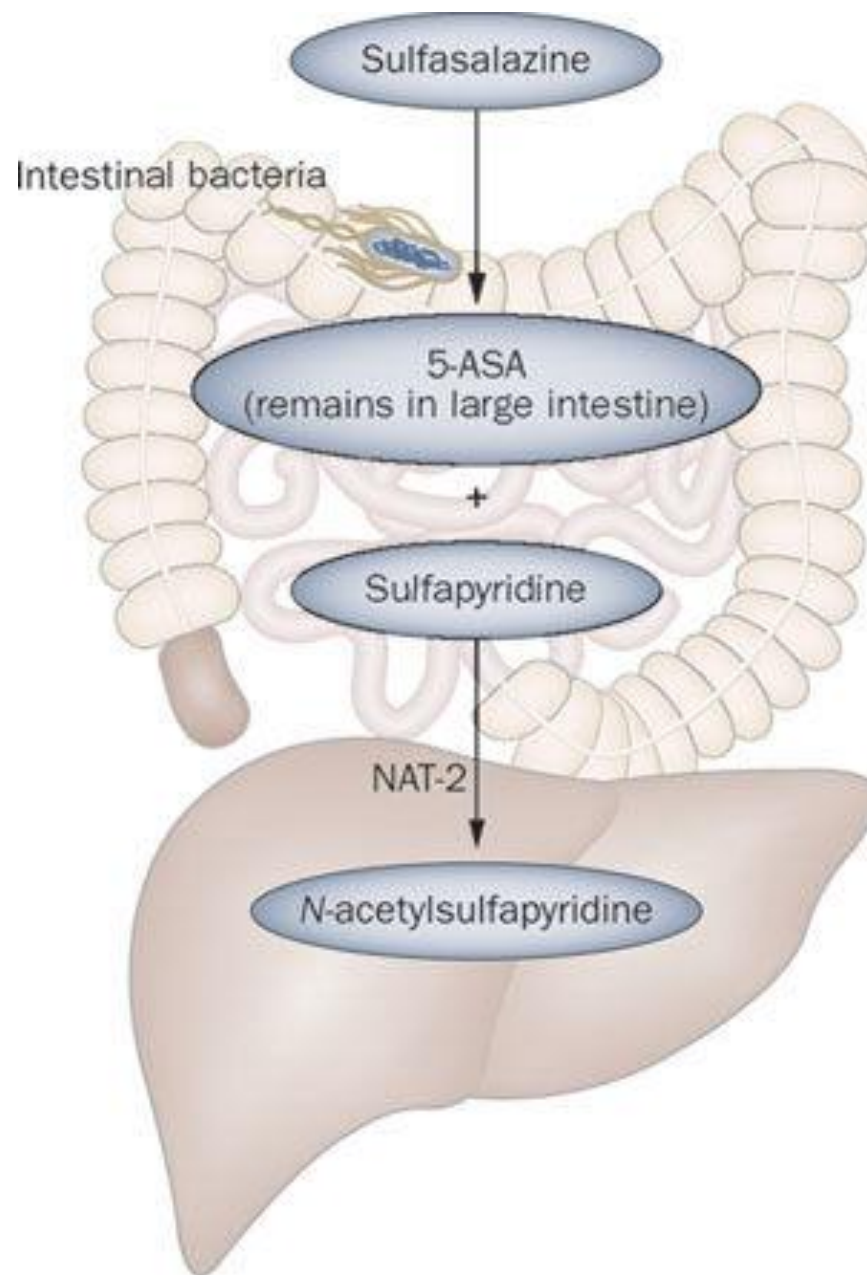


# Hydroxychloroquine

- limited efficacy when used alone
- more effective when used in combination with MTX or sulfasalazine
- Retinopathy
  - can lead to blindness
  - extremely rare
  - Depends on cumulative dose (max 5 mg/kg)

# Sulfasalazine (SSP)

- Sulfapyridine + 5-ASA
- After ingestion it is split in the large intestine by bacterial enzymes into sulfapyridine (SP), which is then absorbed, and 5-ASA, which is excreted
- decreases the progression of radiologic damage



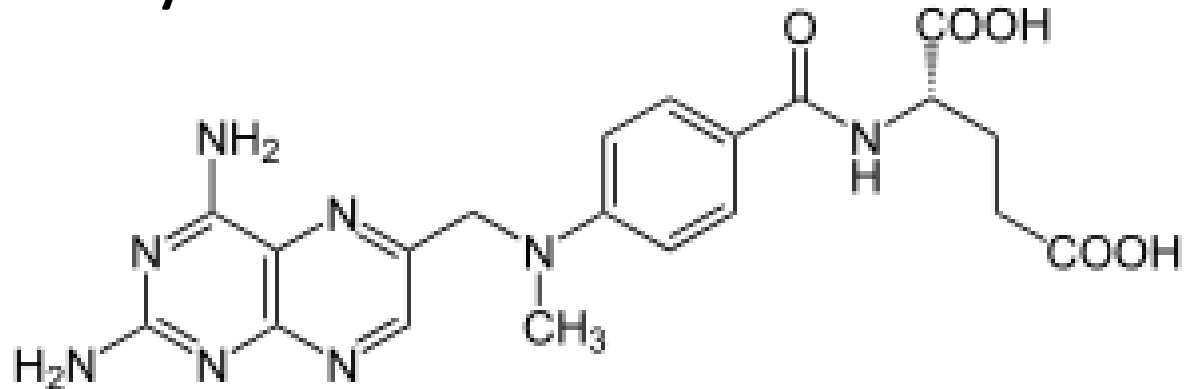
# Adverse effects of SSP

- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Leucopenia
- Rashes
- Hepatotoxicity

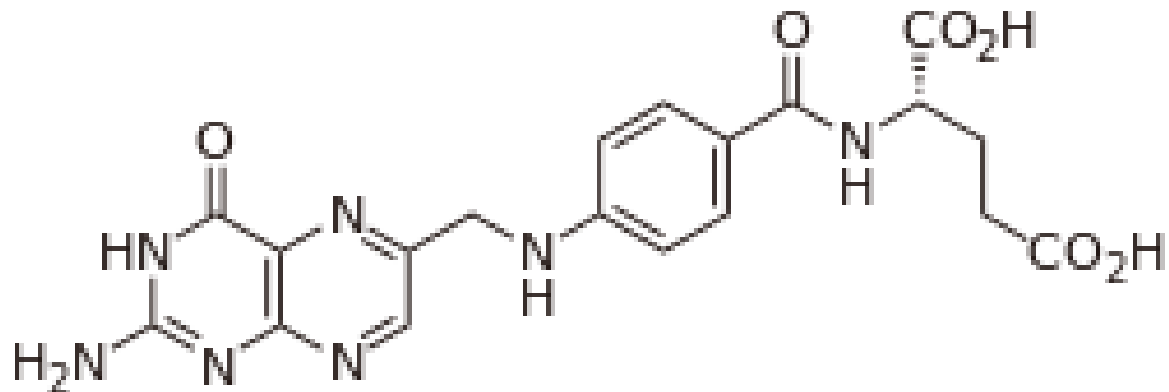
# Methotrexate (MTX)

- first-line agent in the treatment of RA
- structurally similar to folic acid

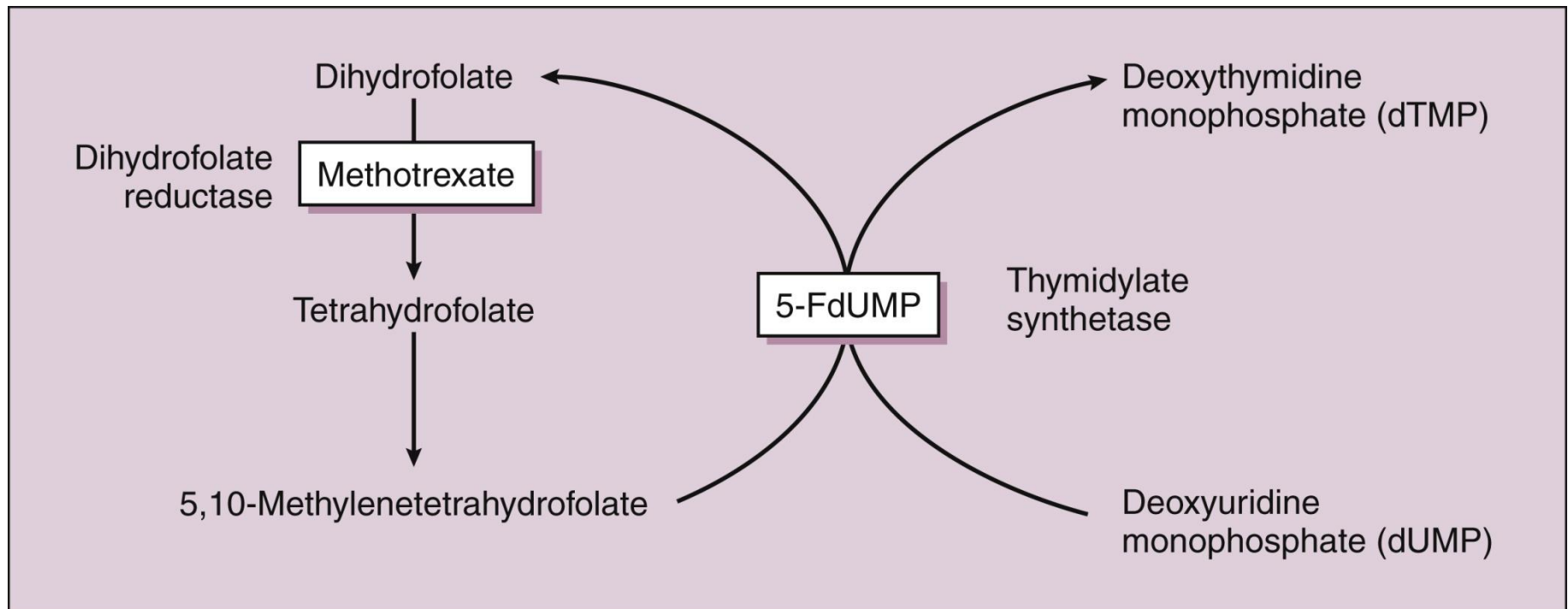
MTX



Folic acid



- Inhibits dihydrofolate reductase (DHFR) thereby deprives the cell of tetrahydrofolate
- slows radiographic progression of RA.



- monitoring of methotrexate therapy is required
- Serious liver disease and idiosyncratic pulmonary hypersensitivity are rare potential adverse effects.
- Methotrexate is a known teratogen and effective contraception should be considered in women with the potential for pregnancy.
- Men also

# Adverse effects of MTX

- most common:
  - anorexia
  - Nausea
  - Vomiting
  - diarrhea
- Hematologic abnormalities:
  - leukopenia (most common)
  - Anemia
  - thrombocytopenia.



- hepatic toxicity
- lung toxicity:
  - acute interstitial pneumonitis
  - Pulmonary fibrosis
- To prevent adverse effects of MTX, folic acid or folinic acid (leucovorin) is given concomitantly.

# MTX

- Small rheumatoid nodules may increase in size at start of MTX therapy
- Hepatic fibrosis & cirrhosis is rare with MTX & occurs in  $< 0.1\%$  of patients
- Pulmonary toxicity may present as an unexplained cough or may present with fever, hypoxia, eosinophilia & interstitial infiltrates
- Avoid concomittant use of other antifolate drugs such as trimethoprim

# Contraindications to MTX

- active liver disease (including chronic hepatitis B and C infection)
- alcohol abuse
- pregnancy
- breastfeeding.

# Leflunomide

- Leflunomide inhibits pyrimidine synthesis, resulting in blockade of T-cell proliferation
- as effective as methotrexate and sulfasalazine
- provides additional benefit in patients partially responsive to methotrexate.
- The most common side effects are gastrointestinal symptoms and hepatotoxicity.
- Combination of leflunomide with methotrexate results in a significant increase in liver enzyme abnormalities.
- Leflunomide is teratogenic and is therefore contraindicated in women who may become pregnant.

# Leflunomide

- Has a long half life & should be stopped at least 4 months before attempting pregnancy
- If elimination of leflunomide is desired (toxicity or pregnancy) cholstyramine 8 g TDS should be given for 11 days

# Azathioprine

- pro-drug (active metabolite 6-mercaptopurine)
- Purine analogue. inhibits purine synthesis  
→ ↓ T&B cell proliferation
- azathioprine use in RA is generally reserved for those patients who are intolerant of other agents

# Biologic DMARDs

# Anti-TNF

- BIOLOGIC EFFECTS OF TNF- $\alpha$ 
  - Adhesion molecule expression (E selectin, ICAM-1)
  - Synthesis of other proinflammatory cytokines (IL-1, IL-6, GM-CSF)
  - Synthesis of chemokines (e.g., RANTES, IL-8, MIP-1)
  - Activation of numerous cell types (T cells, B cells, macrophages)
  - Inhibition of regulatory T cells
  - Matrix metalloproteinase induction
  - Upregulation of RANK ligand expression
  - Induction of apoptosis
  - Antiviral and antitumor effects



# Anti-TNF

- TNF- $\alpha$  primarily mediates inflammation by promoting cellular activation and trafficking of leukocytes to inflammatory sites.

# Anti-TNF

- Infliximab
- adalimumab
- Golimumab
- certolizumab
- etanercept

### **BOX 61.3** RELATIVE CONTRAINDICATIONS TO THE USE OF TUMOR NECROSIS FACTOR INHIBITORS

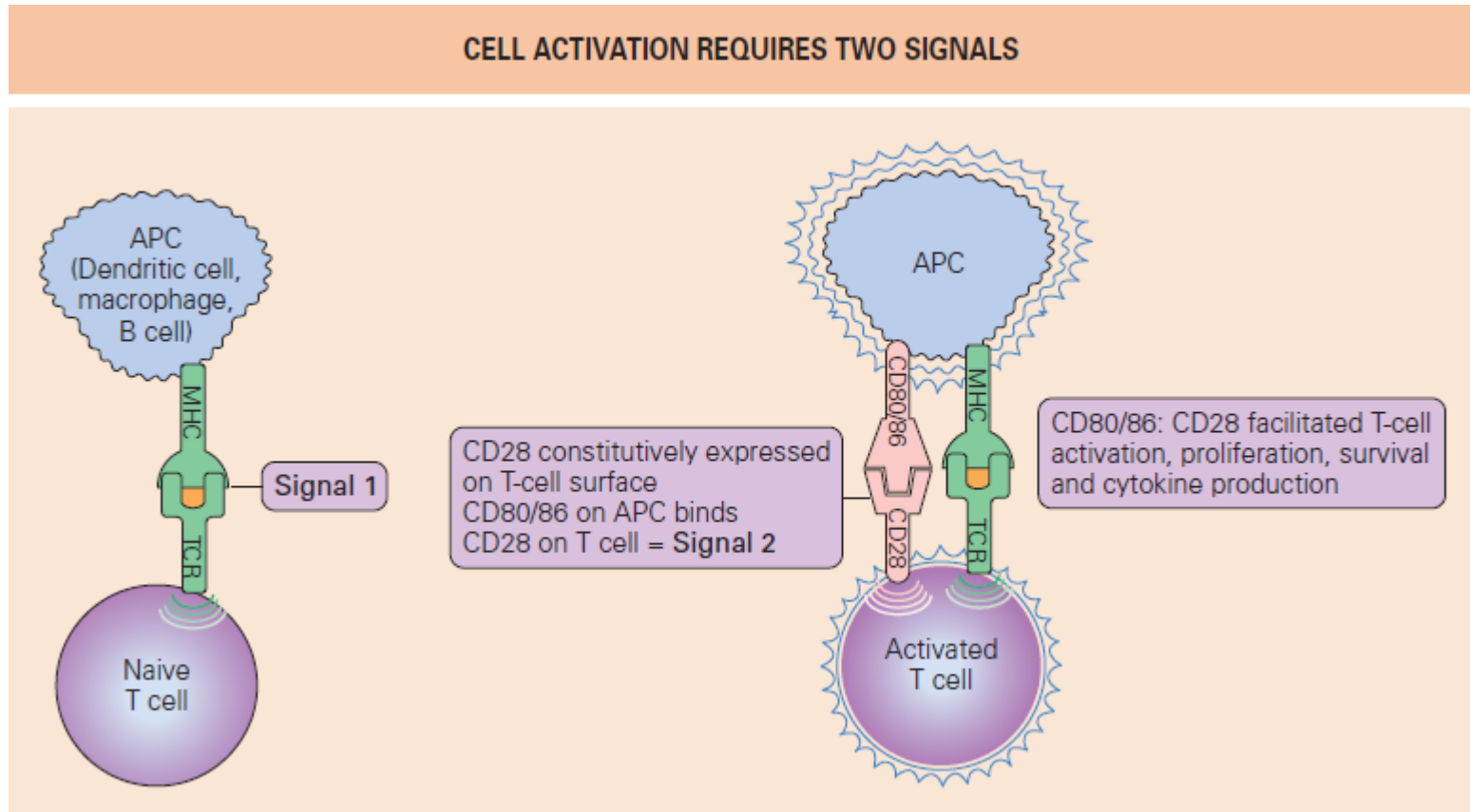
- Systemic lupus erythematosus, lupus overlap syndrome
- Multiple sclerosis, optic neuritis, demyelinating disorders
- Current, active, serious infections
- Recurrent or chronic infections
- Untreated latent or active mycobacterial infection
- Hepatitis B infection
- Congestive heart failure
- Pregnancy

# T-cell co-stimulation

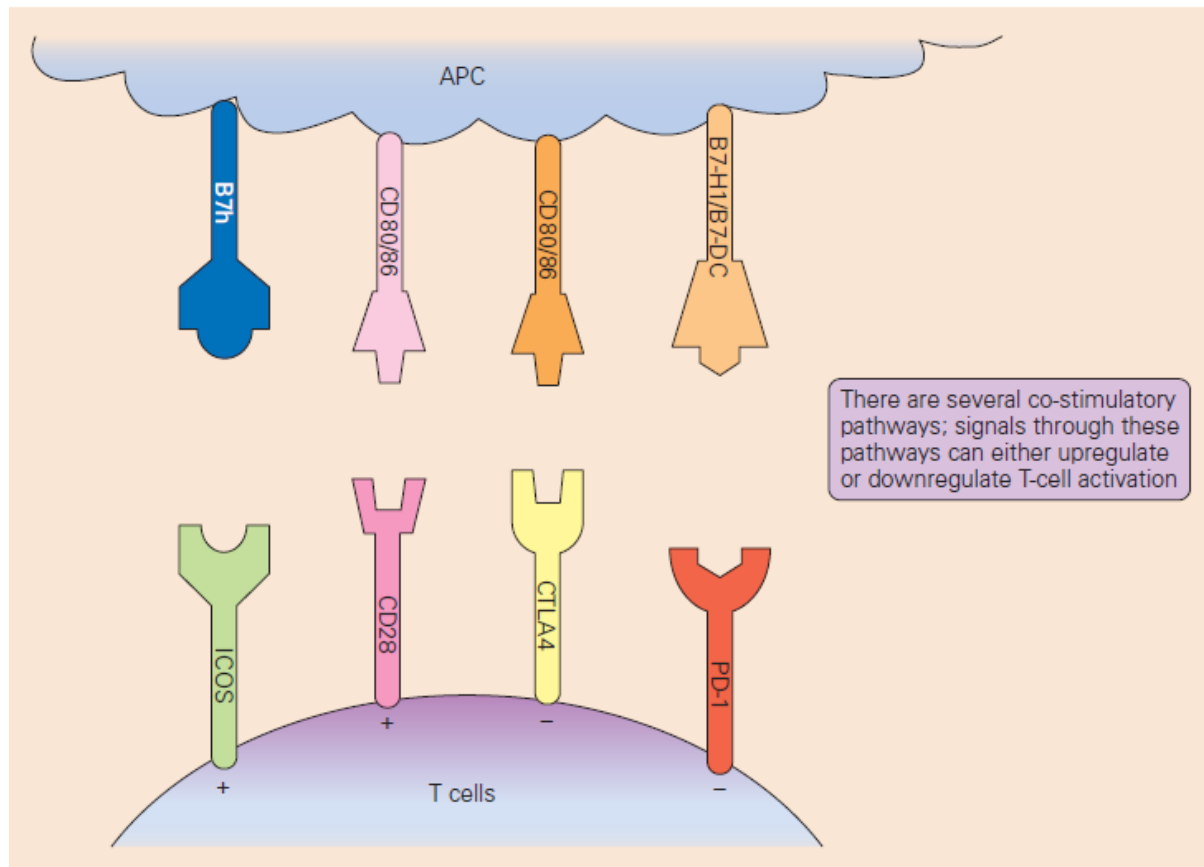
## T-cell activation requires two signals:

First signal: engagement of the TCR with the MHC antigen complex

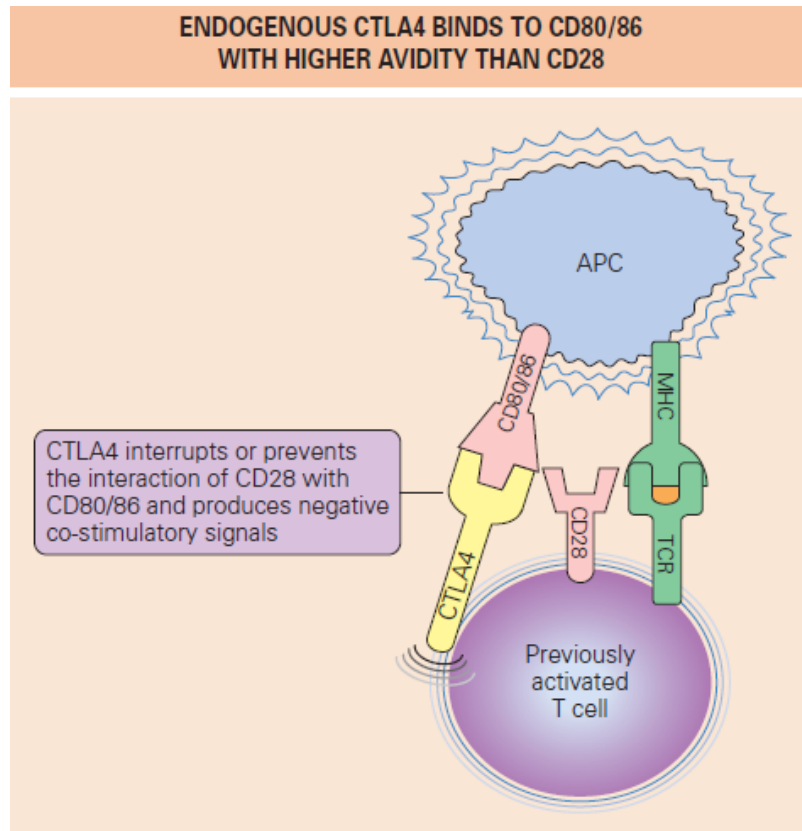
Second signal: transmitted by CD28 that interacts with either CD80 and CD86 ligands on APCs, leading to T-cell activation and proliferation



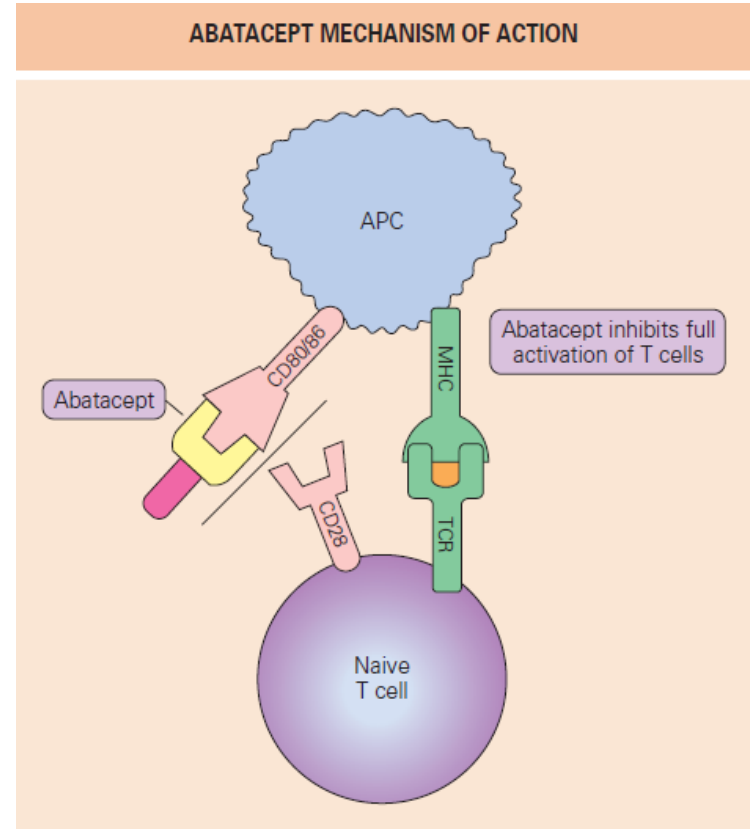
## CO-STIMULATION IS REQUIRED FOR FULL T-CELL ACTIVATION



CTLA4 binds to CD80/86 with higher avidity than CD28



Abatacept binds to CD80/86 and inhibits T-cell co-stimulation



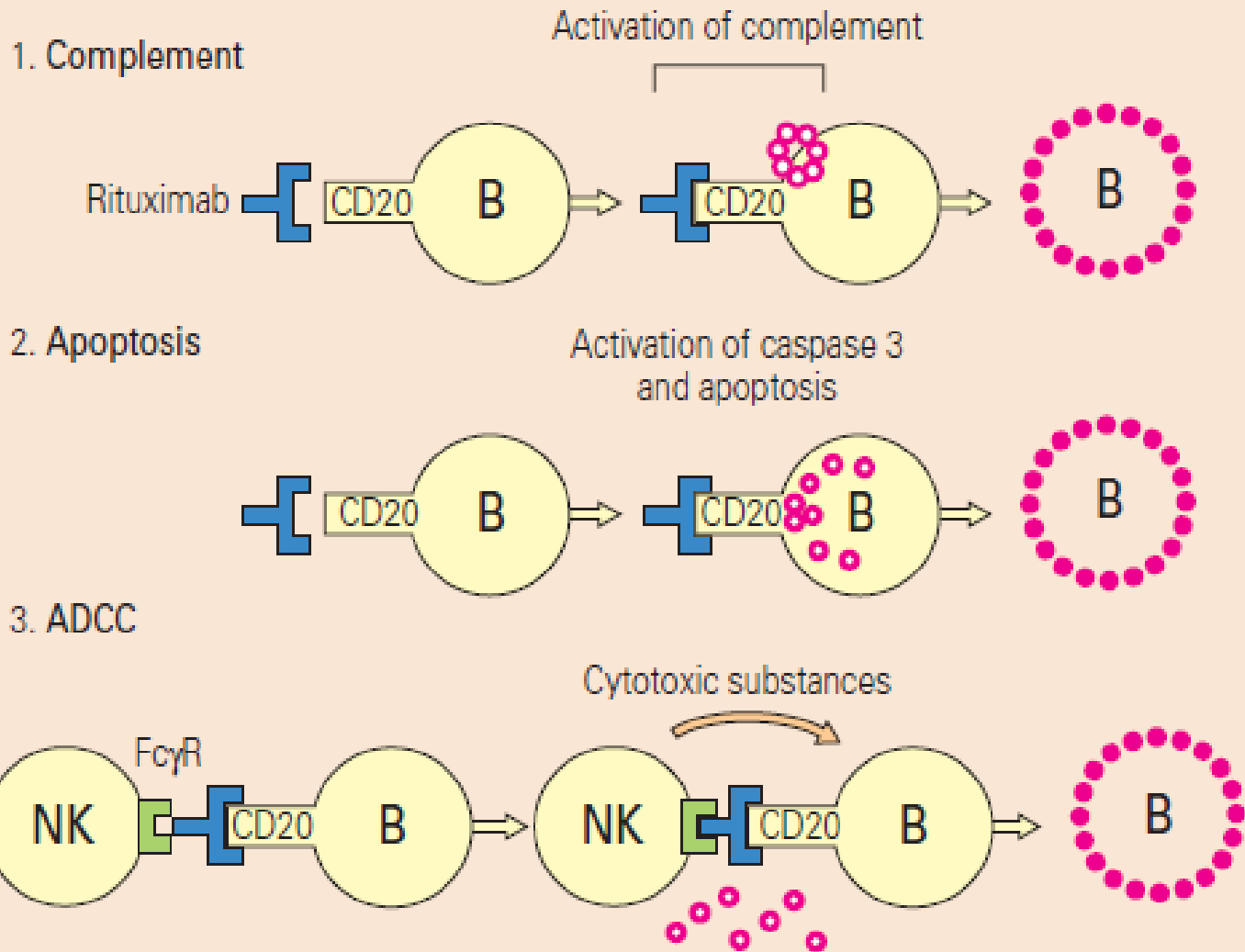
# Anti-B Cell (Rituximab)

- CD20 is expressed on mature naïve B cells that have exited the bone marrow to enter blood
- it is not expressed on stem cells or on plasma cells
- Rituximab is a high-affinity chimeric monoclonal antibody specific to CD20



- Rituximab causes B-cell depletion by:
  1. antibody-dependent, cell-mediated cytotoxicity
  2. complement-dependent cytotoxicity
  3. apoptosis

## MECHANISMS OF B-CELL KILLING BY RITUXIMAB



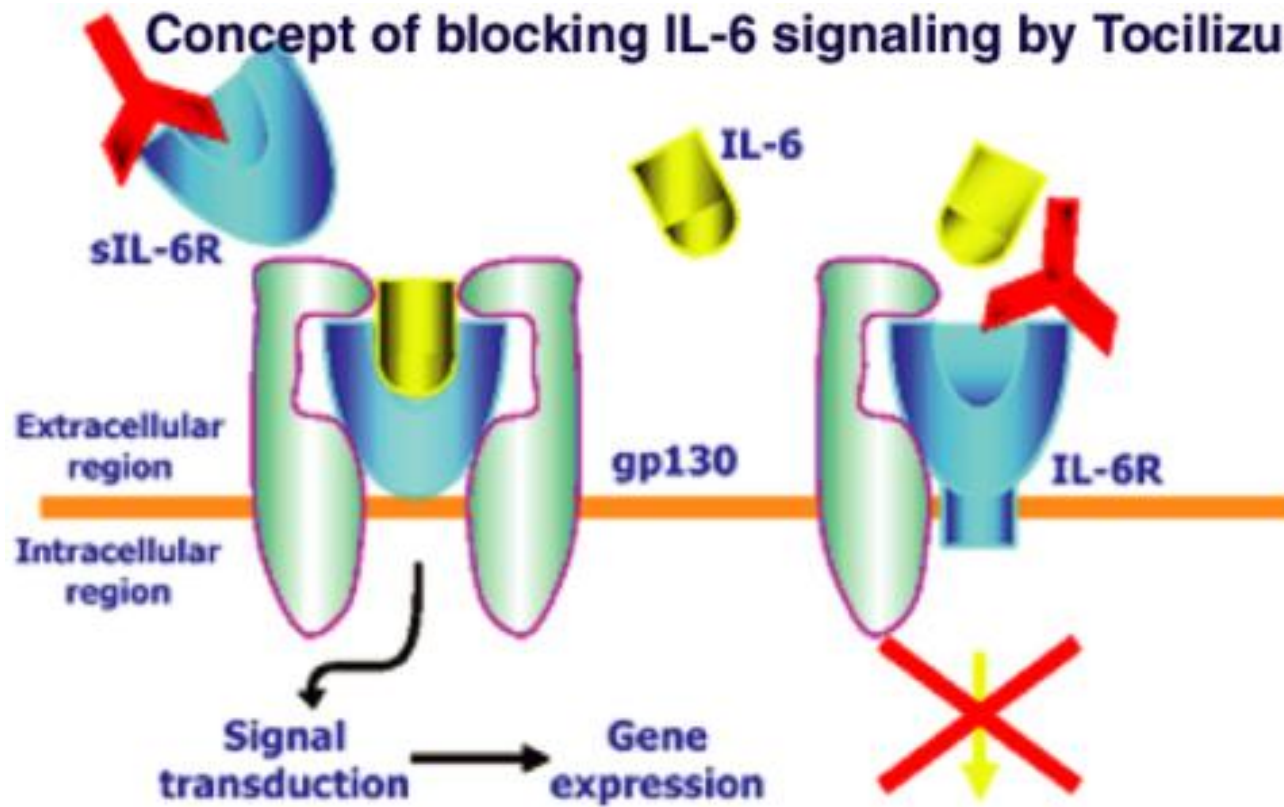
- Rituximab is given intravenously

# IL-6

- Actions interleukin-6 (IL-6) include:
  - stimulation of B cell proliferation
  - immunoglobulin production
  - initiation of the acute-phase response.

- Tocilizumab is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R).

## Concept of blocking IL-6 signaling by Tocilizumab



# Osteoarthritis

- Osteoarthritis (OA) is the most common form of arthritis
- pain is the most common symptom.
- aims of treatment:
  - to reduce pain
  - improve function and quality of life.
- management requires a combination of non-pharmacologic and pharmacologic modalities



# Non-pharmacologic therapies

- Patient education
- Self-management
- Aerobic exercise
- Strengthening exercise
- Water-based exercise
- Weight loss
- Insoles
- Braces
- Cane/stick
- Local heat/ice
- Acupuncture
- Transcutaneous electrical nerve stimulation
- Yoga
- Ultrasound

# Pharmacologic therapies

- paracetamol
- Non-steroidal anti-inflammatory drugs
- COX-2 selective inhibitors
- Topical NSAIDs
- Topical capsaicin
- Opioid analgesics
- Glucosamine sulfate
- Chondroitin sulfate
- Intra-articular corticosteroids
- Intra-articular hyaluronic acid preparations

# Surgical intervention

- Joint lavage
- Arthroscopic debridement
- Osteotomy
- Joint replacement
- Joint fusion

**Thank you**