Selected Topics in Clinical Immunology - Biologics-

Biomedical Sciences

April 6, 2017

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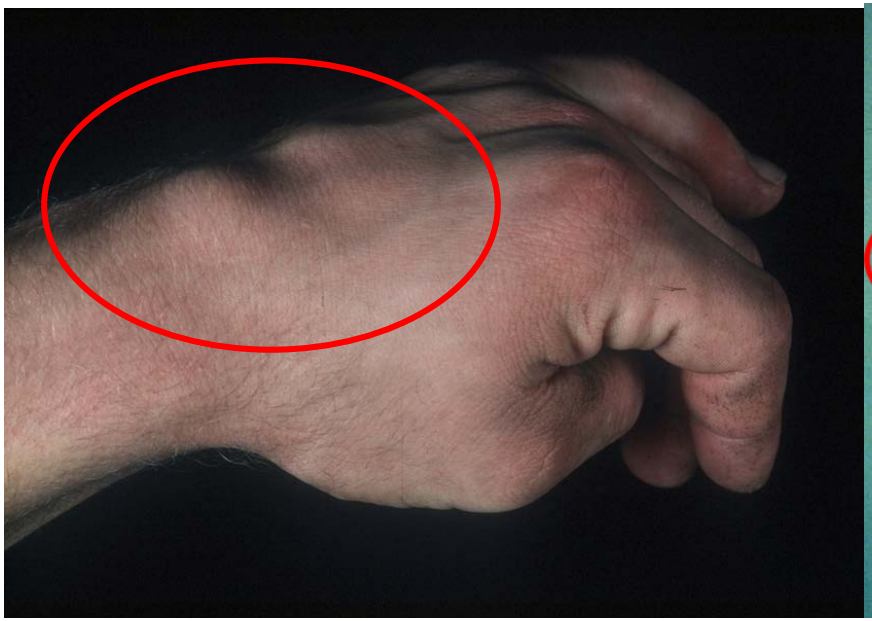
today´s menu

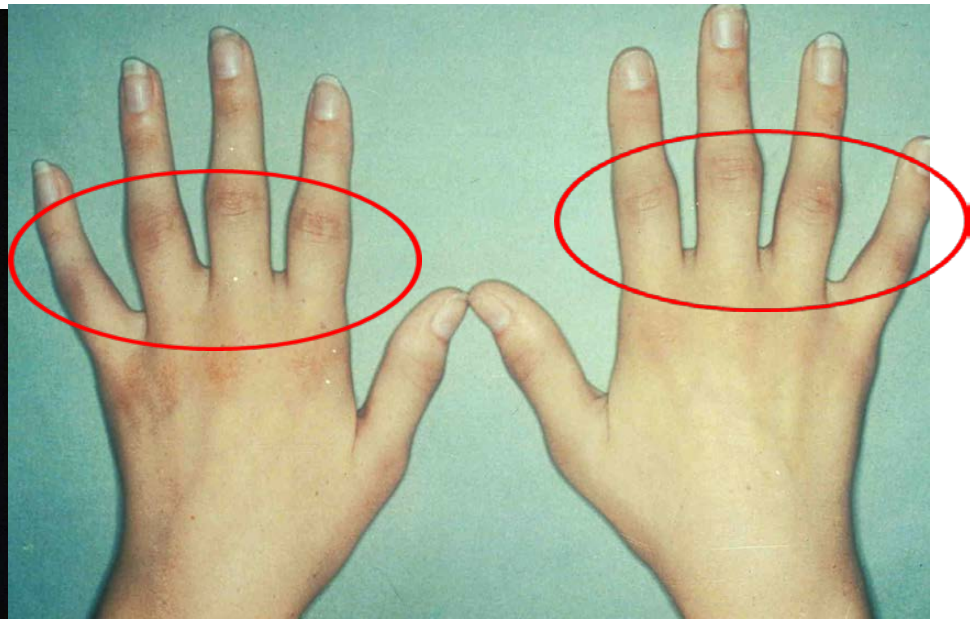
- lessons regarding pathogenesis
- cytokines
- cytokine inhibitors / cytokine antagonists
- therapeutic antibodies beyond anti-cytokines
- immunoreconstitution

what are we talking about

pathogenesis of inflammatory diseases

- rheumatoid arthritis, early

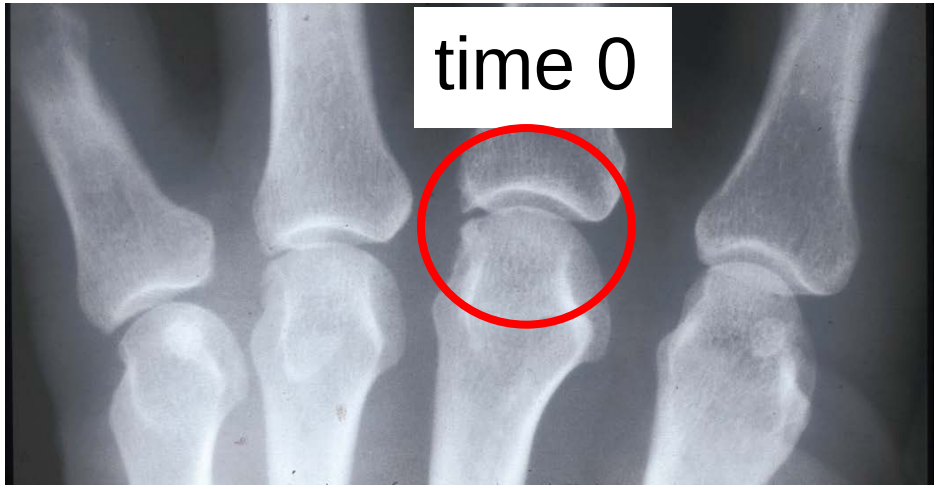


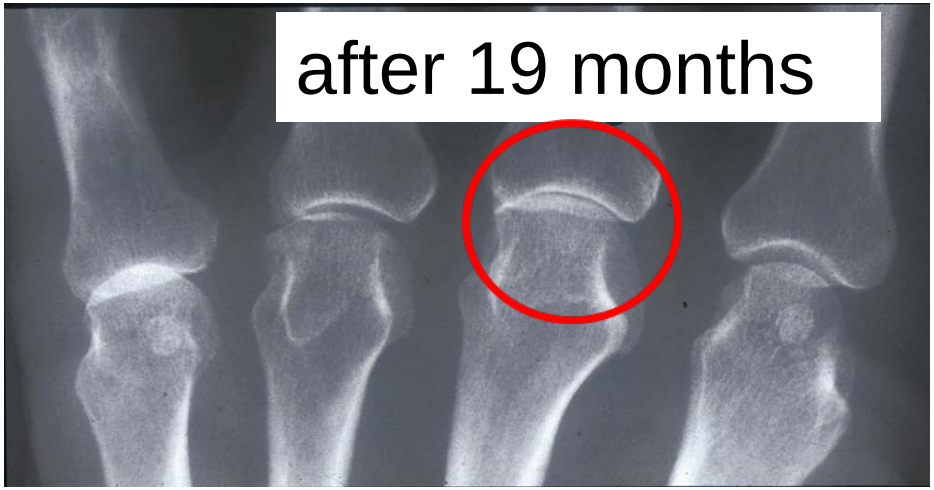


what are we talking about

pathogenesis of inflammatory diseases

- rheumatoid arthritis
- joint space narrowing

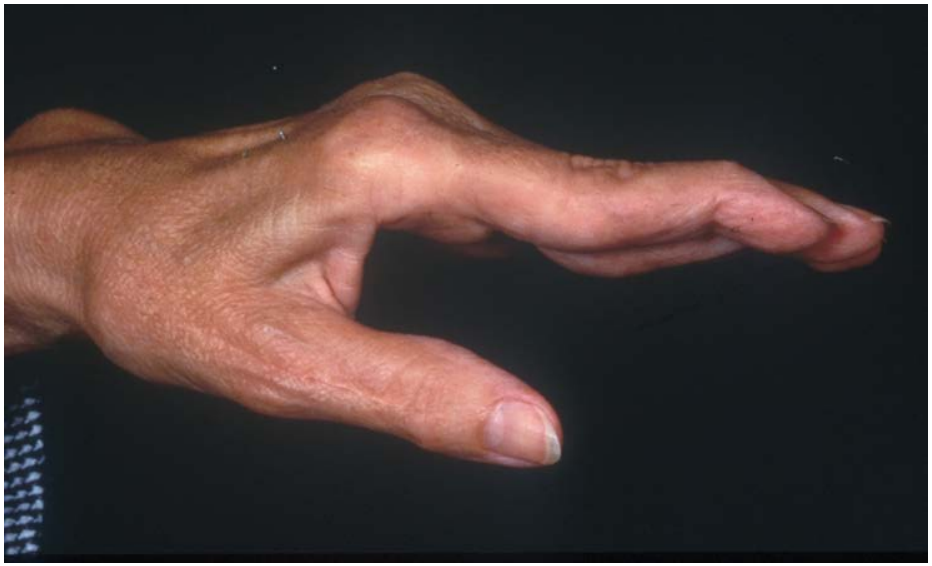


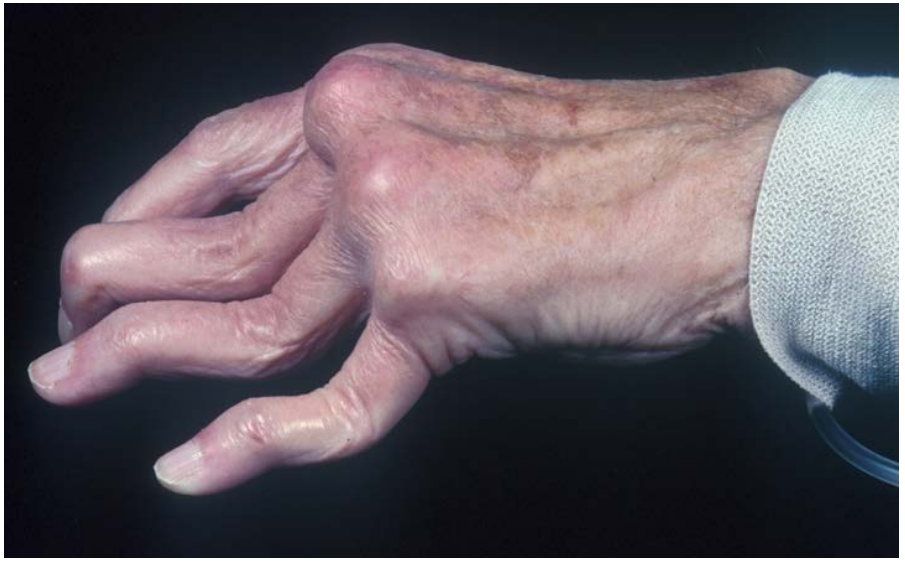


what are we talking about

pathogenesis of inflammatory diseases

- rheumatoid arthritis, late





Clinical example

Rheumatoid Arthritis (RA)

joint inflammation

tendons and bursae

systemic inflammation

ESR, CrP

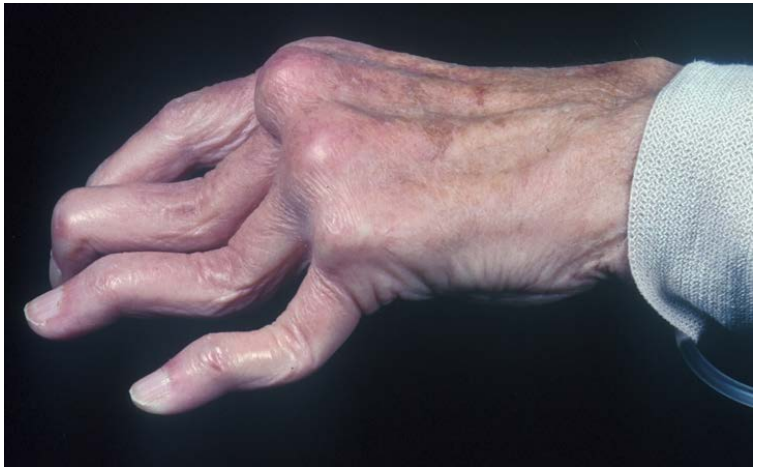
anemia, thrombocytosis

rheumatoid factor

CCP-antibodies

pathogenesis of inflammation

- molecular mechanisms rheumatoid arthritis



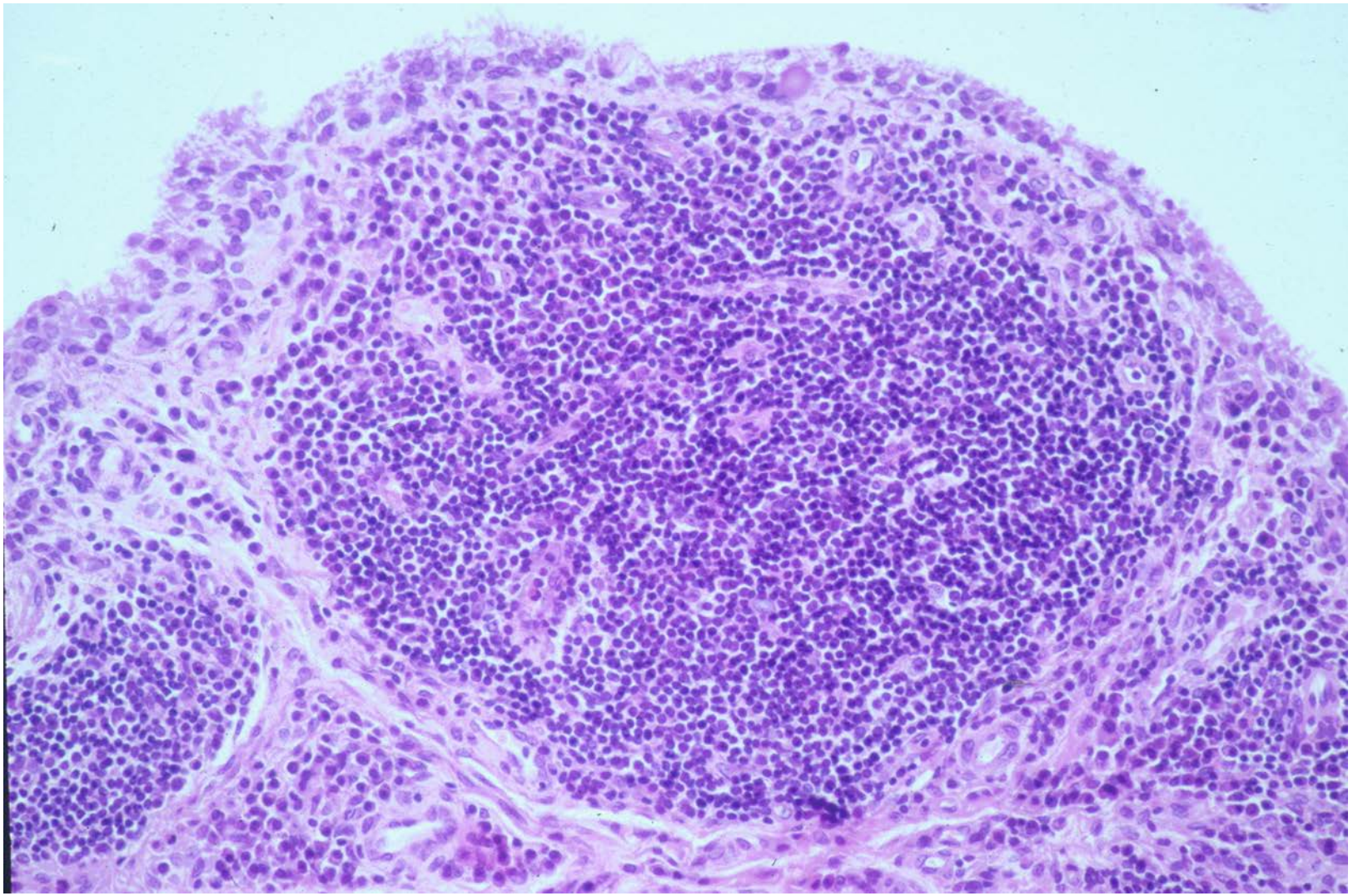
cytokine production

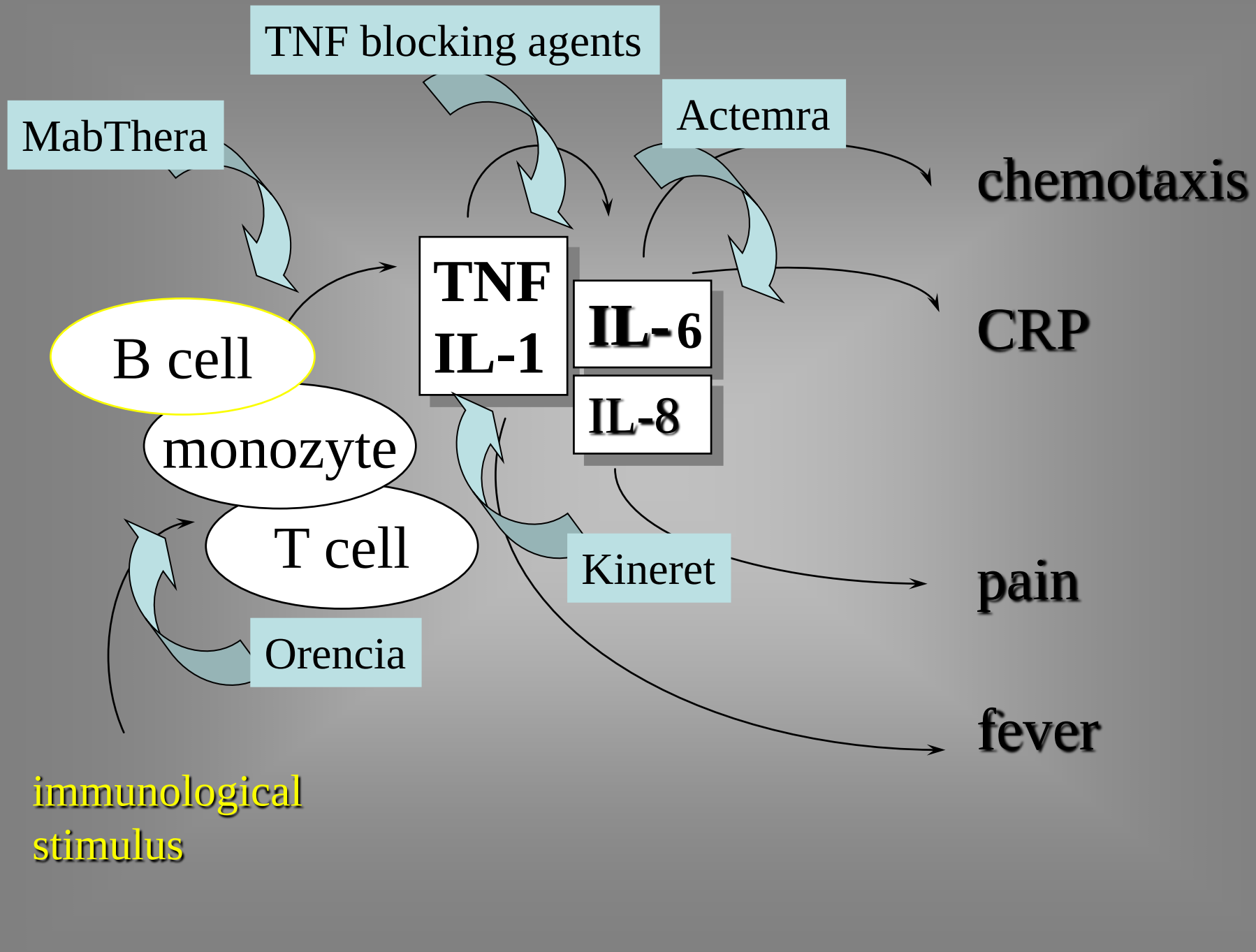
TNF, IL-6

- ESR, CrP, anemia…

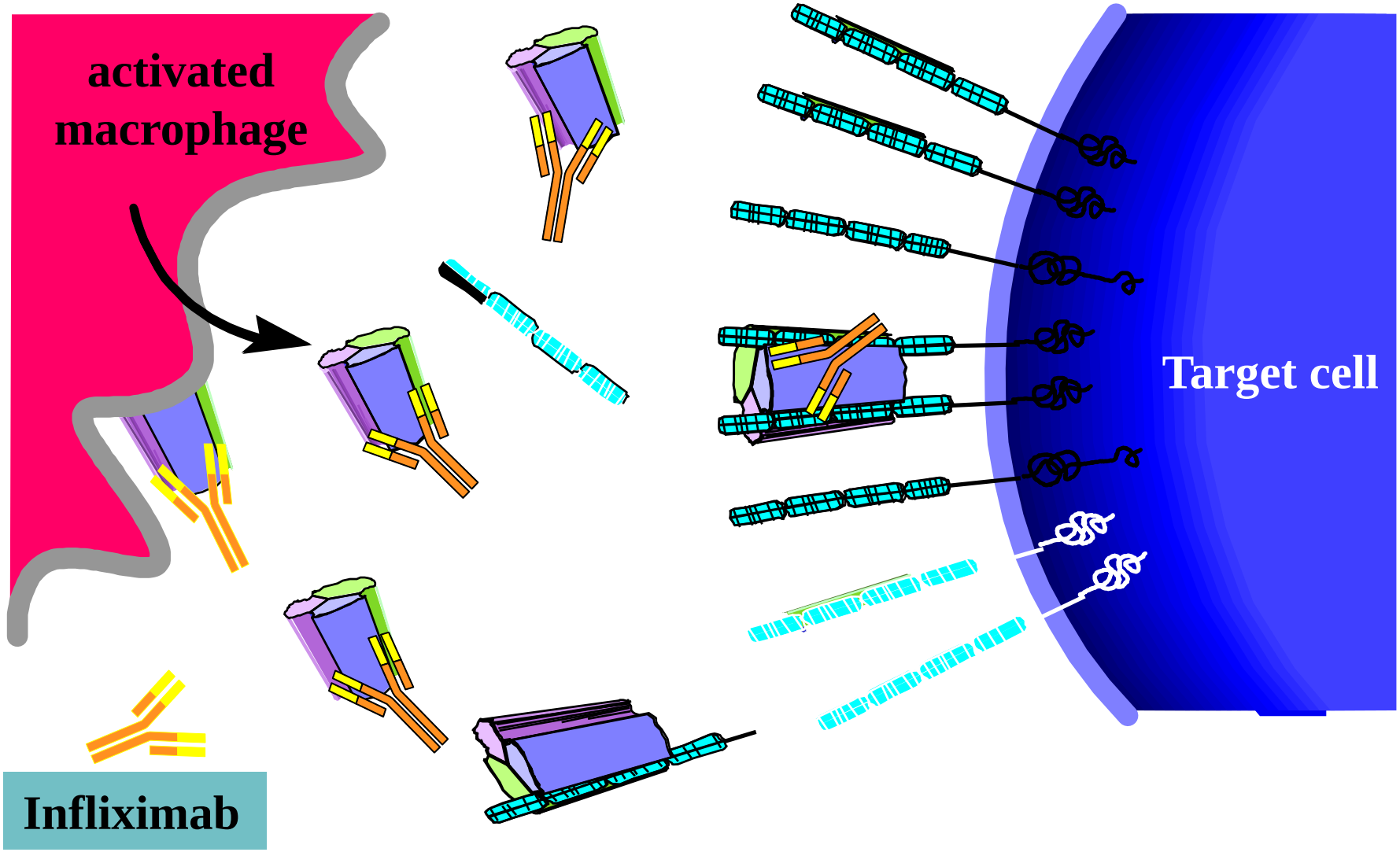
lymphotoxin

- inflammation and joint damage in RA
- lymphoid structures in the synovium



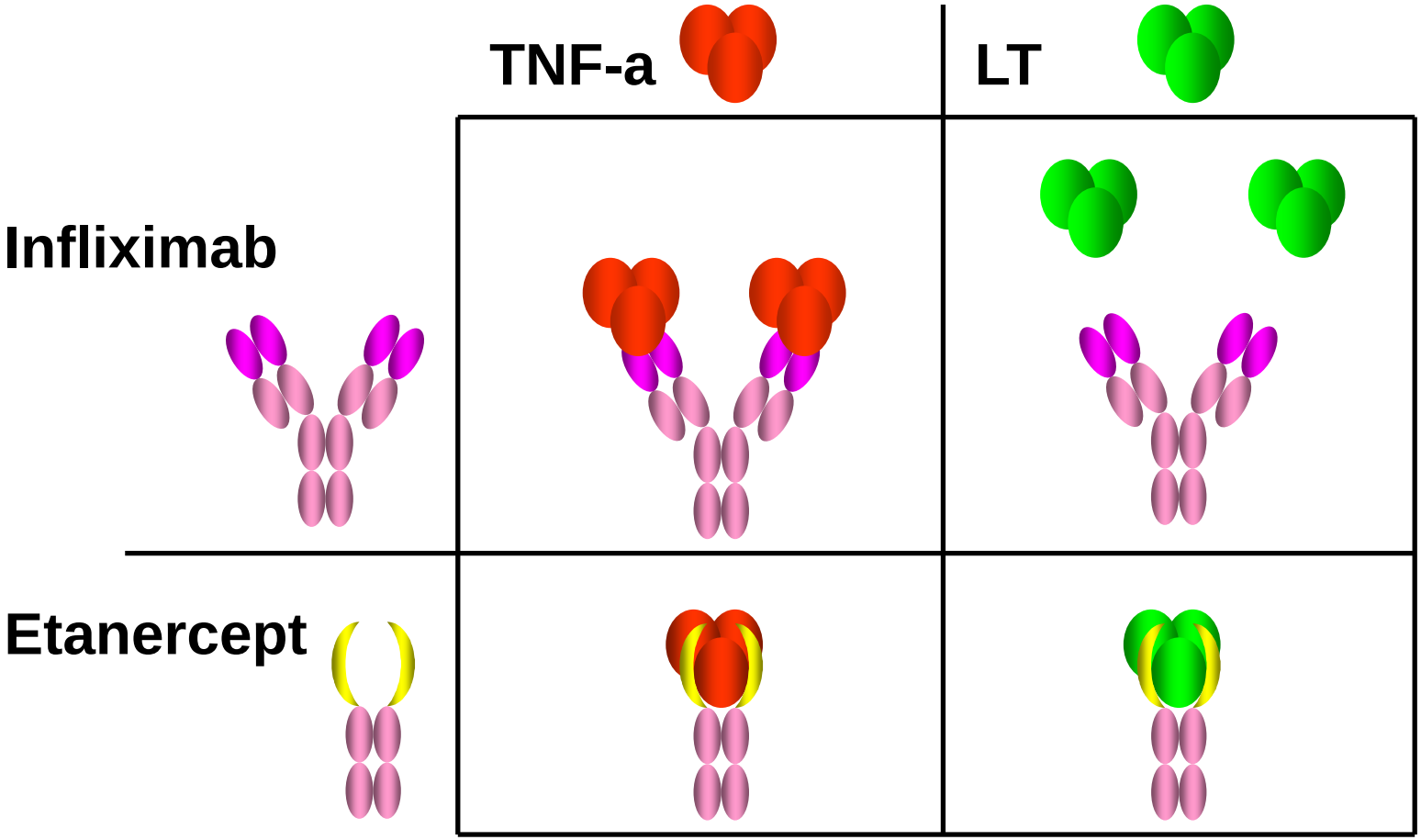

TNF blocking agents
MabThera
Actemra
chemotaxis
TNF
IL-1
IL-6
IL-8
CRP
B cell
monozyte
T cell
Kineret
pain
Orencia
fever
immunological
stimulus

TNF-blockade by Infliximab



specificity of monoclonal antibody versus fusion protein

TNFa and lymphotoxin binding



mechanisms of inhibition

neutralizing antibody 1

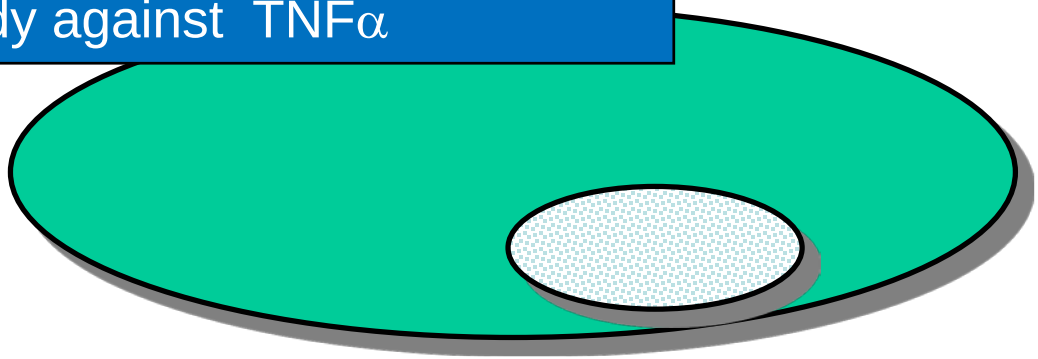
Etanercept (Enbrel®)

fusionprotein (IgG1 + TNFα -receptor)

3 **soluble receptor**

Infliximab (Remicade®)
chimeric antibody against TNFα

Adalimumab (Humira®)
humanised antibody against TNFα



cytokine

cytokine receptor

treatment goals

- reduction of disease activity
- prevention of joint destruction
- long-lasting remission
- minimalized side effects

treatment goals

how to measure...

- reduction of disease activity («**D**isease**A**ctivity**S**core»)

  number of tender joints

  number of swollen joints

  ESR/ CrP

- prevention of joint destruction / disease damage

  ultrasound

  X-rays

  MRI (magnetic resonance imaging)

summary anti-cytokine strategies

- ***neutralization of***
  - TNF
  - IL-1
  - IL-6
  - IL-17
- ***competitive blocking of receptor***
  - IL-1 receptor antagonist (IL-1ra)
- ***use of soluble receptor***
  - TNF R
  - abatacept

beyond anti-cytokine antibodies

pathogenesis of RA

B-cells as important factors

- abundance of B-cells in the synovium of affected joints
  organized into lymphoid structures

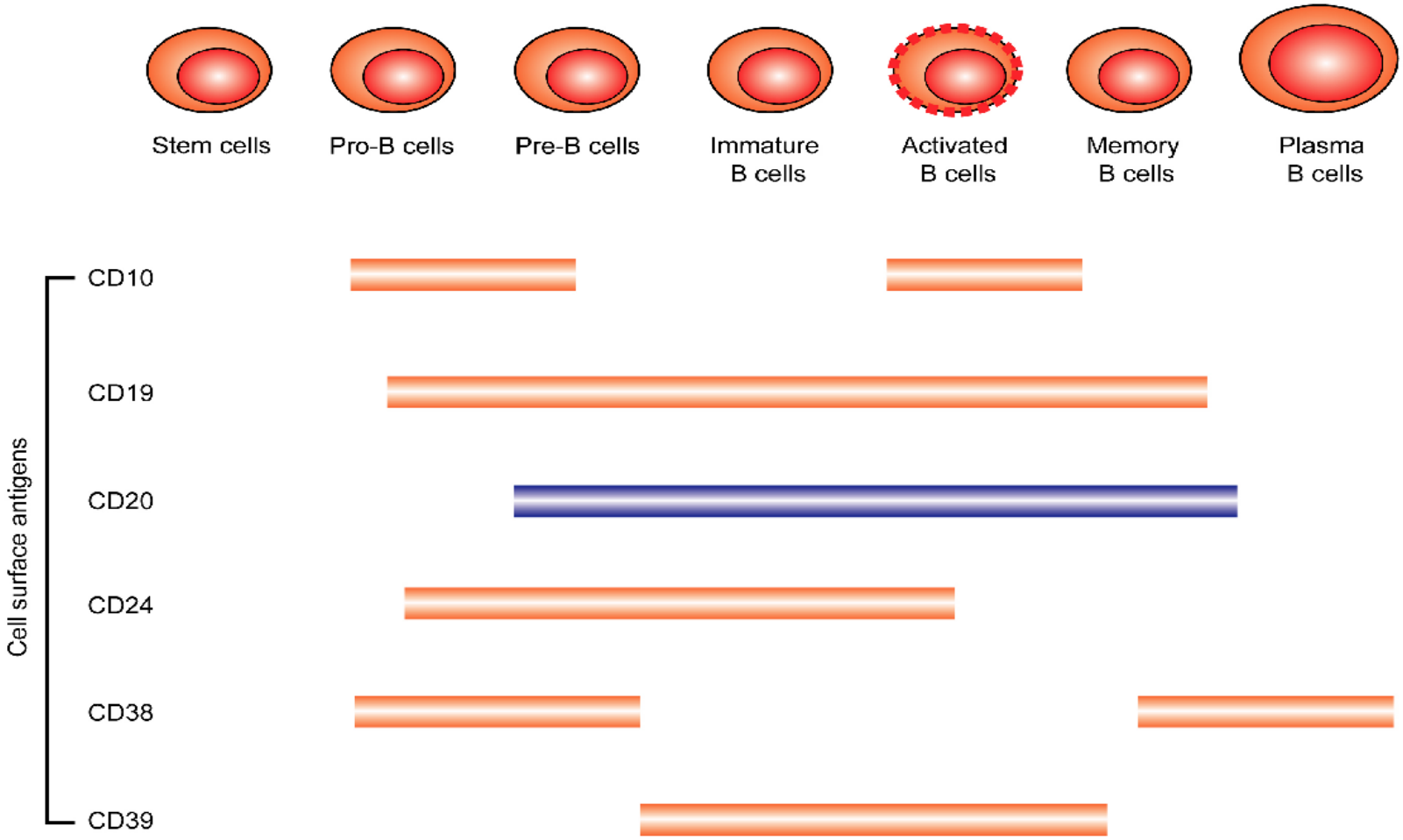
- 3 critical roles of B-cells
  antigen presentation and T-cell activation
  autoantibody production
  cytokine production

autoantibody production

autoreactive B cells

- produce autoantibodies including RF
- => formation of immune complexes
- => production of pro-inflammatory cytokines

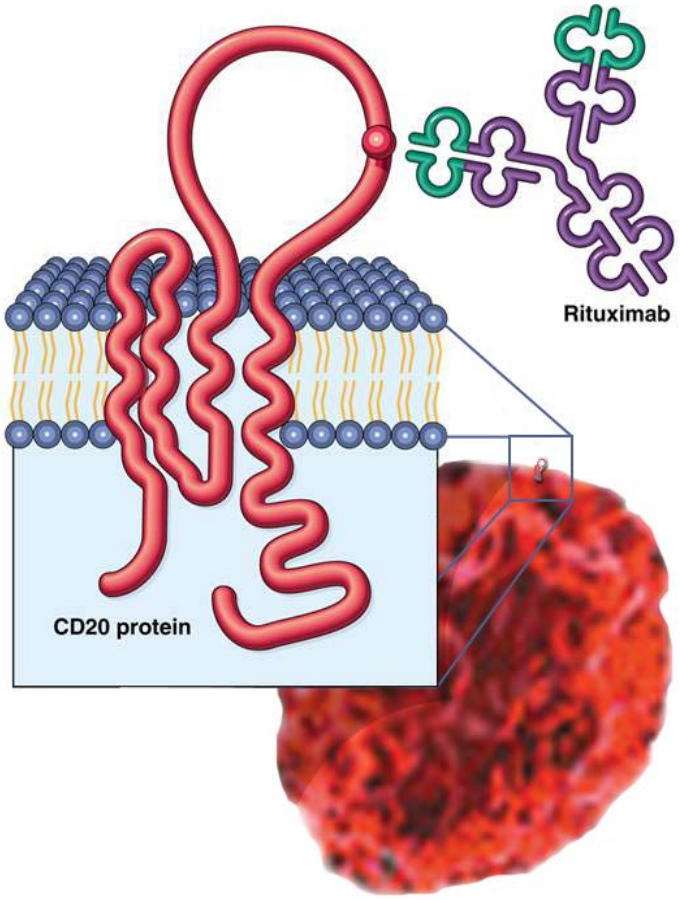
Steps in the maturation of B cells



Rituximab (MabThera®/Rituxan®)

Rituximab

- novel
- genetically engineered
- anti-CD20 therapeutic monoclonal antibody
- *selective* depletion of CD20+ B-cells



CD20: an ideal B cell target

CD20

- 297-amino acid phosphoprotein
- highly expressed on B cells but not on stem, dendritic or plasma cells
- no known natural ligands for CD20

complement-dependent cytotoxicity

Rituximab bound to CD20

- interacts with C1q
- triggers activation of the complement system
- leads to B cell lysis via formation of pores in the membrane

pachymeninigitis in a patient with RA

summary cell-targeted strategies

- depletion of B lymphocytes
- depletion of CD+ lymphocytes

- classical immunosuppressive agents

  ciclosporine

  => inhibit function / activity of T-lymphocytes

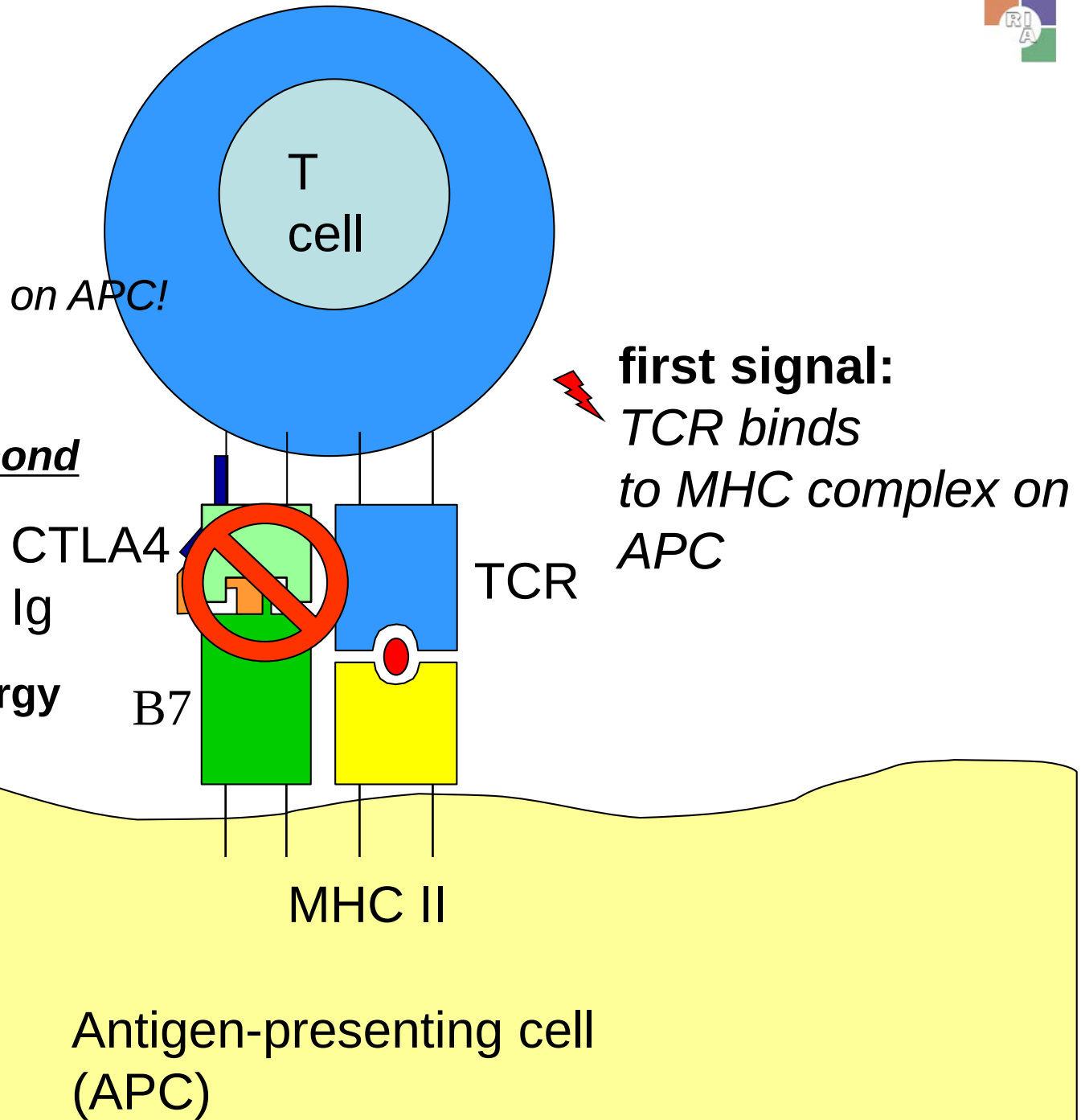
  => used in organ transplantation

CTLA4:
Cytotoxic
Tcell
Leukocyte
Antigen **4**

***CTLA4** binds to B7 on APC!*

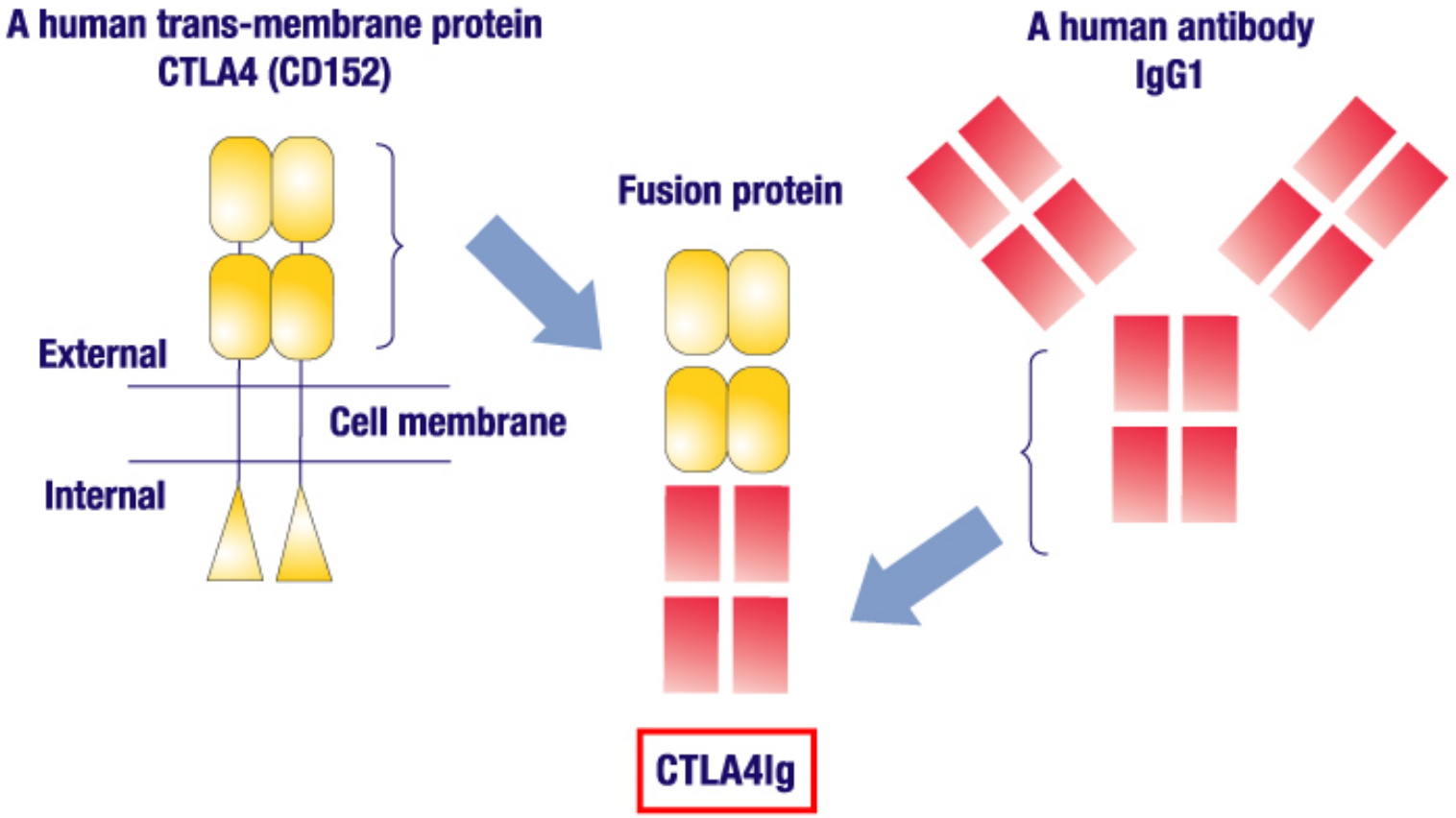
T cell receives no second signal from B7!

T cell apoptosis/ anergy



first signal:
TCR binds to MHC complex on APC

blockade of the CD28 pathway



Anti-TNF antibodies and the risk of malignancies *JAMA 2006, 295 (19): 2275*

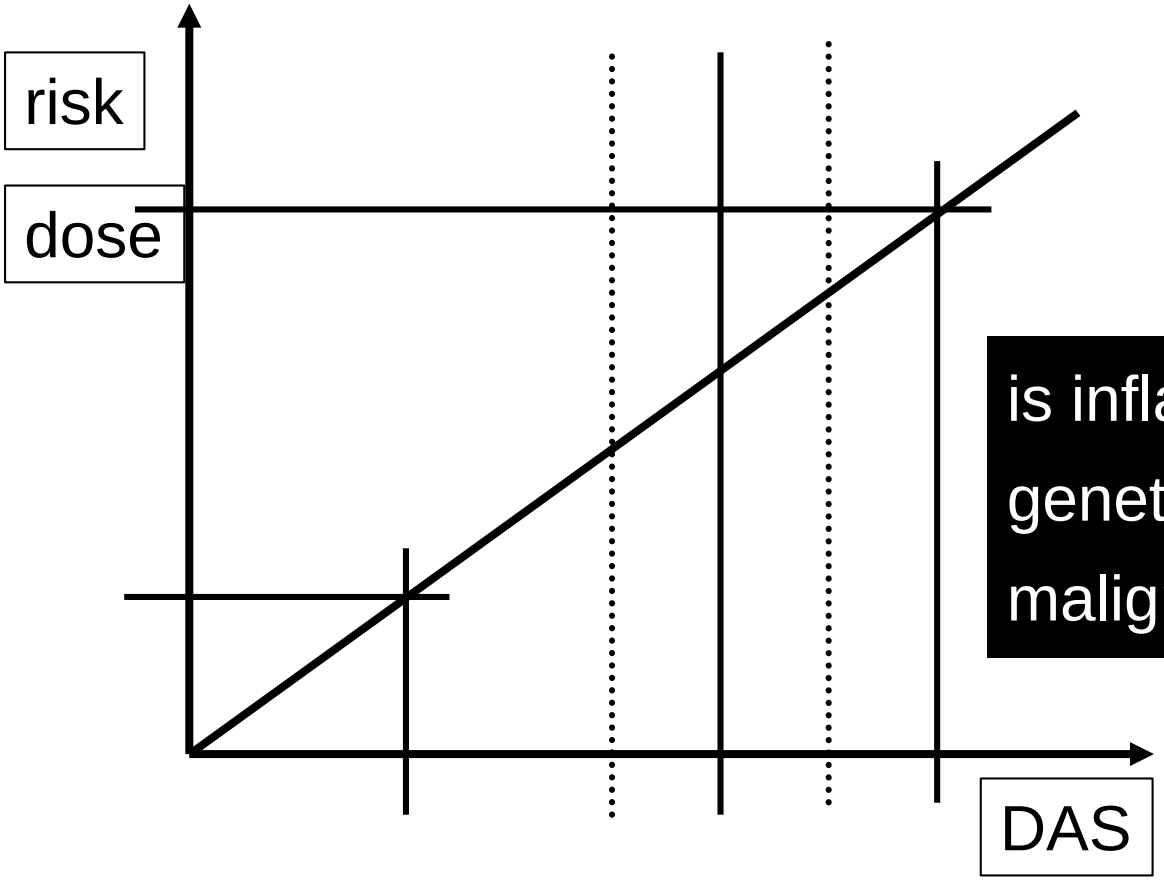
- systematic review and meta-analysis in randomized controlled trials
- 144 trials, 9 suitable for analysis
- Etanercept excluded (why?)
- RA patients only
- 3493 patients, 1512 controls
- Infliximab up to 10mg/kg, every 4 wk
- Adalimumab up to 40mg per wk
- Duration of therapy until diagnosis of malignancy: 2 -114 weeks (!!)

Anti-TNF antibodies and the risk of malignancies *JAMA 2006, 295 (19): 2275*

results

- 29 malignancies in verum, 3 in placebo
- **OR 3.3 (1.2 – 9.1)**
- however:
  - Low dose: OR 1.4 (0.3 – 5.7)
  - High dose: OR 4.3 (1.6 – 11.8)
- number needed to harm (NNH): **154** (91 - 500)

relation:
risk of malignoma / disease activity



is inflammation itself (or are genetic factors) propagating malignancies ?

case control study showing an increased lymphoma risk of up to 25 (BMJ 1988)

after review of the existing literature and thorough discussion:

- screening for Tbc and latent Tbc infection should be performed in all patients prior to any anti- TNF-a therapy

- screening should be based on history, chest X-ray and an IGRA test.
  - history: detailed history of exposure to or prior treatment for Tbc, considering the risk associated with birthplace or country of origin
  - chest X-ray: for detecting past or present Tbc
  - IGRA test