# Biologics in Rheumatology

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100 mg
Remicade
100 mg


Medication
Guide
HUMIRA PEN
(adalimumab)
HUMIRA®
(adalimumab)


RoActemra®
20 mg/ml
concentrate for solution
for infusion
Tocilizumab
400 mg / 20 ml
For intravenous
infusion after dilution
Roche
1 vial of 20 ml


Enbrel MyClic autoinjektor


ALWAYS DISPENSE WITH
MEDICATION GUIDE
NDC 0069-1001-01
Pfizer
Xeljanz®
(tofacitinib) tablets
5 mg*
60 Tablets
Rx only
Exp.
Lot


AMGEN
Kineret
(anakinra)
100 mg
Single Use 1 mL Prefilled Glass Syringes
with 27 Gauge Needles
100 mg/0.67 mL
Rx Only

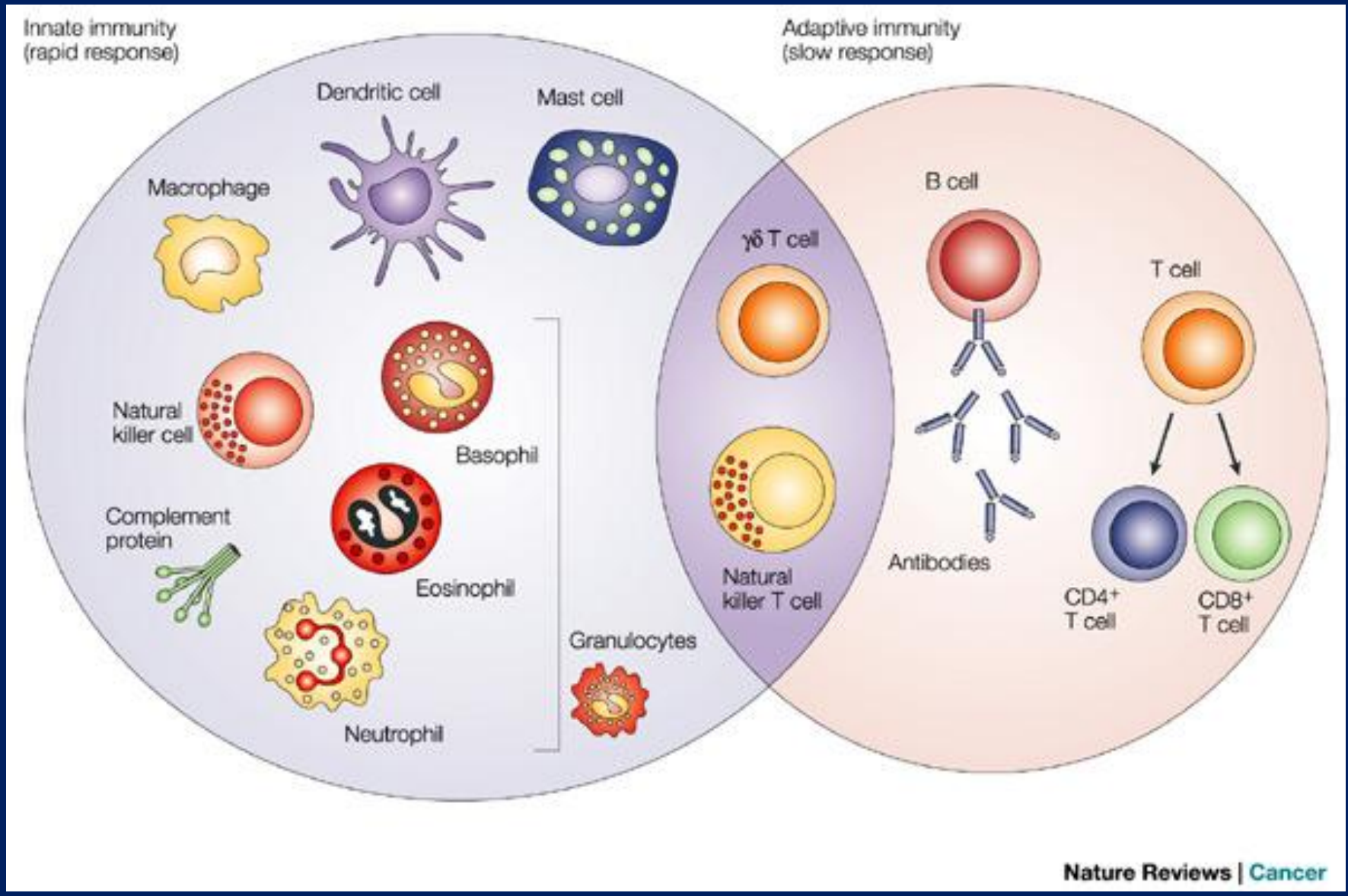

ORENCIA
(abatacept)
250 mg/vial

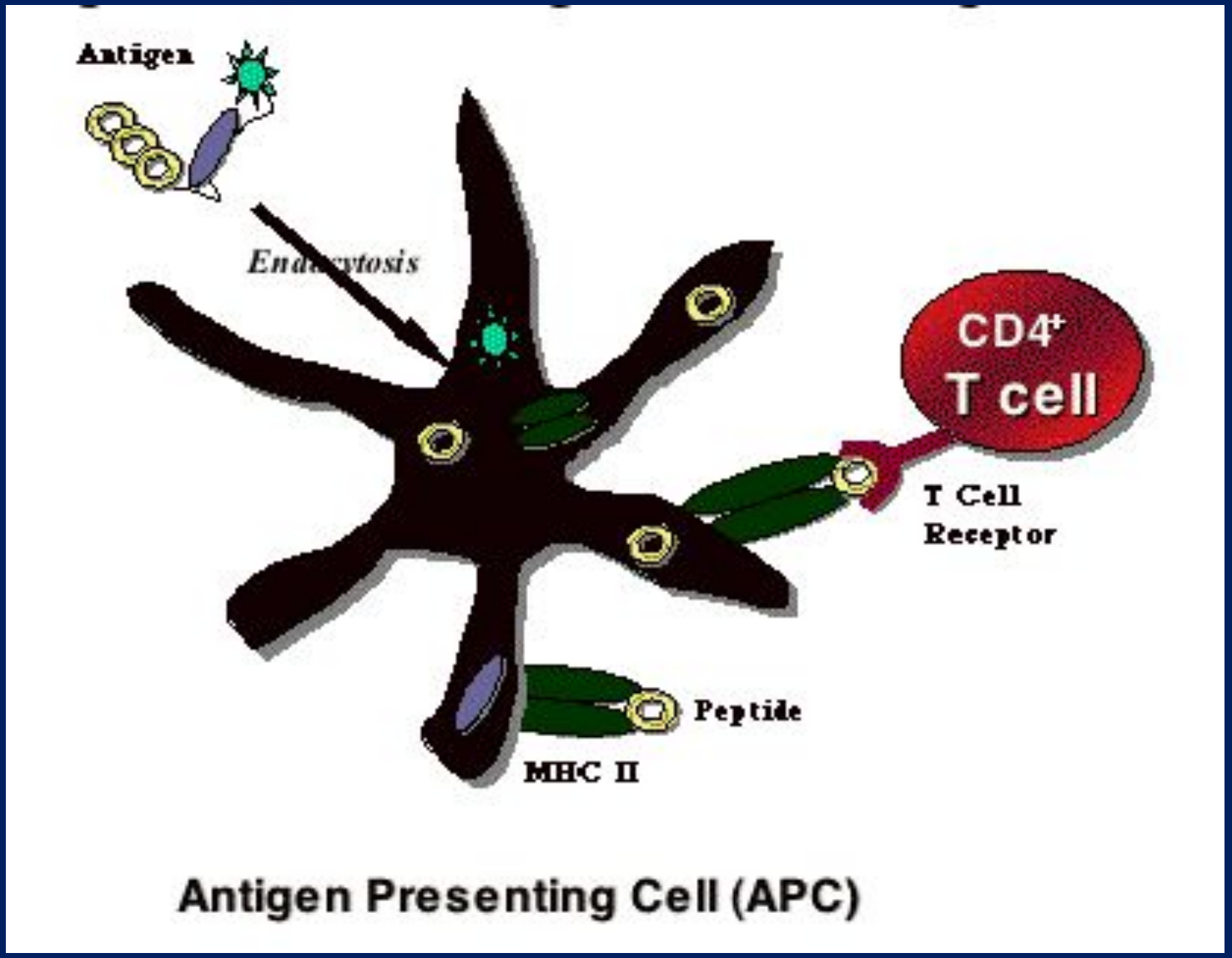

Benlysta
(belimumab)
For Injection
400 mg/vial
Benlysta
(belimumab)
For Injection
400 mg/vial


MabThera® 500 mg
Concentraat voor oplossing voor infusie
Solution à diluer pour perfusion
Konzentrat zur Herstellung einer Infusionslösung
Rituximab
500
Roche
MabThera
500 mg/50 ml
MABTHERA
A CELL THERAPY LASTING SUCCESS

# List of diseases treated with biologic drugs

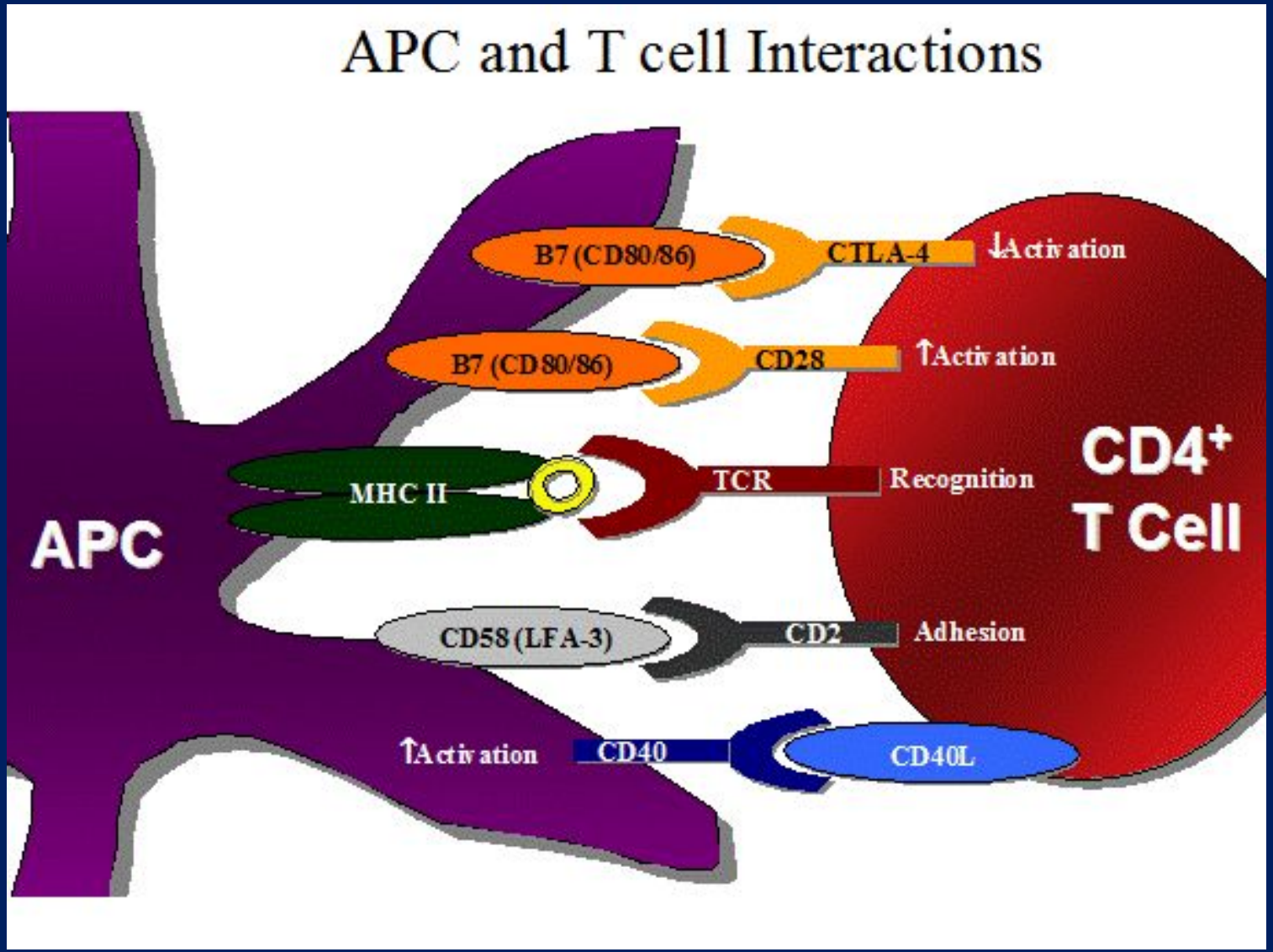
- Rheumatoid arthritis
- Juvenile arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Psoriasis
- Crohn's d-se
- Ulcerative colitis
- Systemic Lupus Erythematosus
- APLAS
- Anterior uveitis
- Osteoporosis
- ANCA-associated granulomatous vasculitis
- Giant cell arteritis
- Takayasu arteritis
- Behcet s-me
- Adult onset Still d-se
- Periodic fevers
- Pyoderma gangrenosum
- Hidradenitis suppurativa
- Gout
- B-cell Lymphoma
- Familial Mediterranean Fever


Innate immunity
(rapid response)
Adaptive immunity
(slow response)
Dendritic cell
Mast cell
Macrophage
B cell
γδ T cell
T cell
Natural
killer cell
Basophil
Complement
protein
Eosinophil
Natural
killer T cell
Antibodies
CD4+
T cell
CD8+
T cell
Granulocytes
Neutrophil
Nature Reviews | Cancer




Antigen Presenting Cell (APC)

Primer: Immunology and Autoimmunity
Stephanie C. Eisenbarth and Dirk Homann

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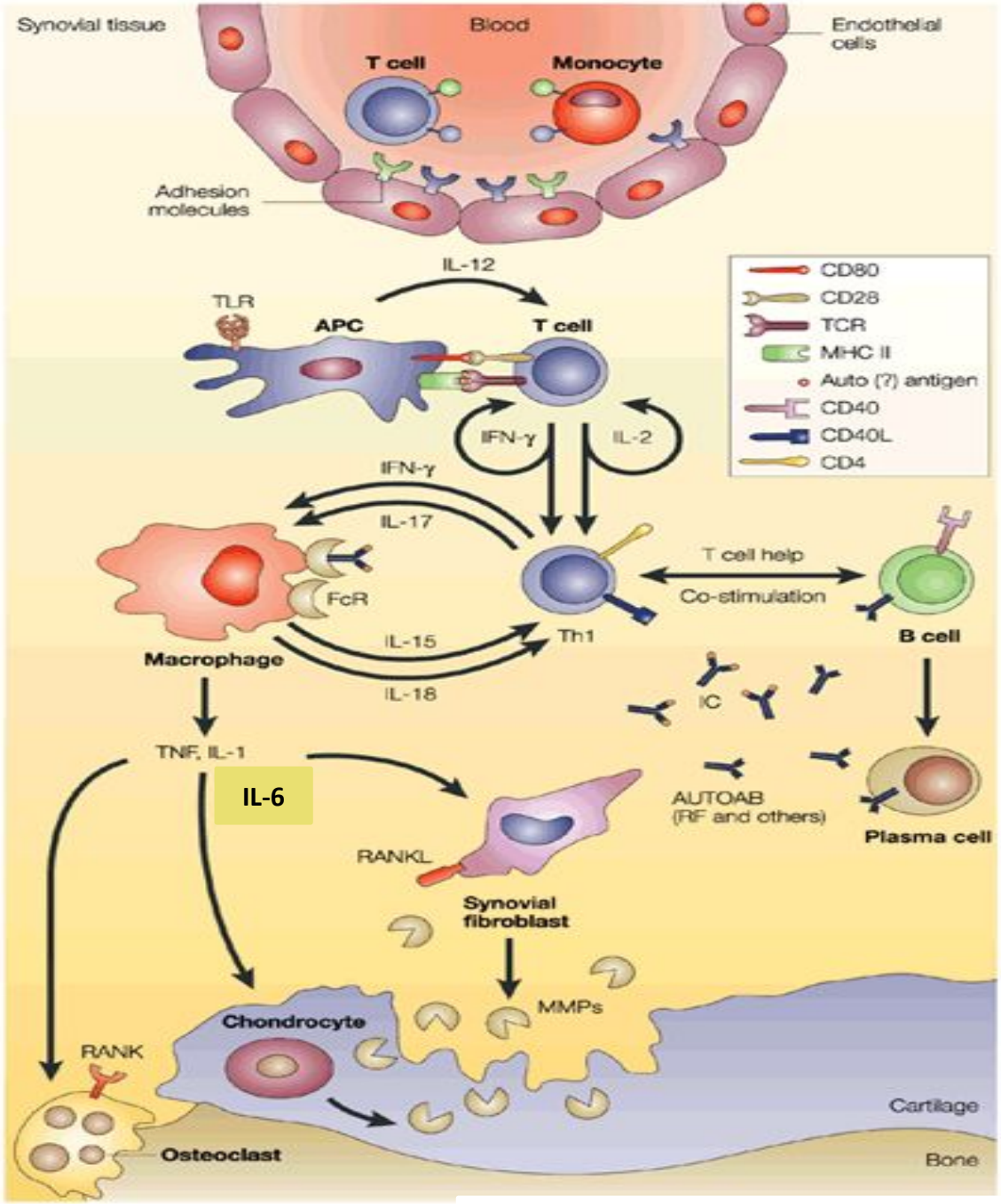
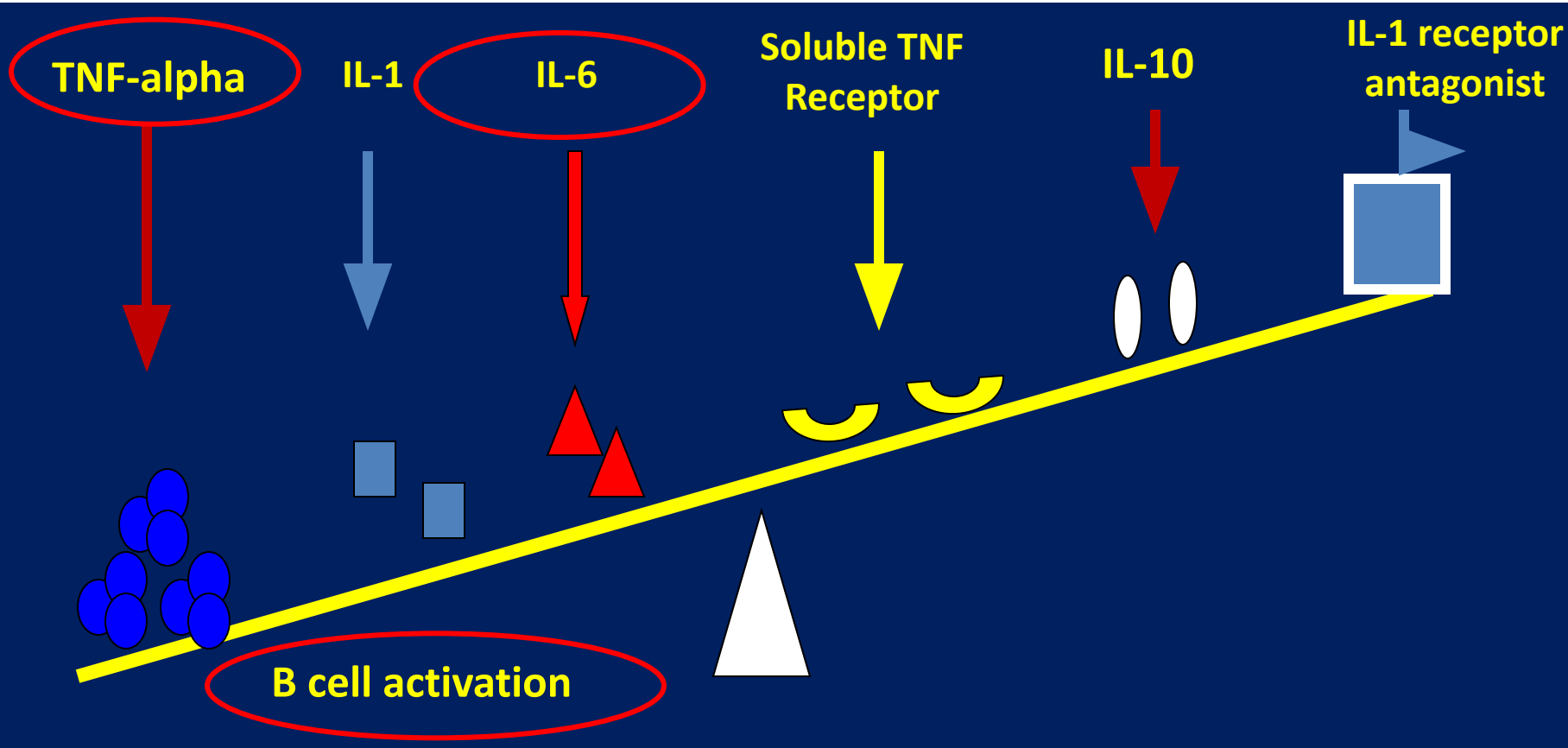


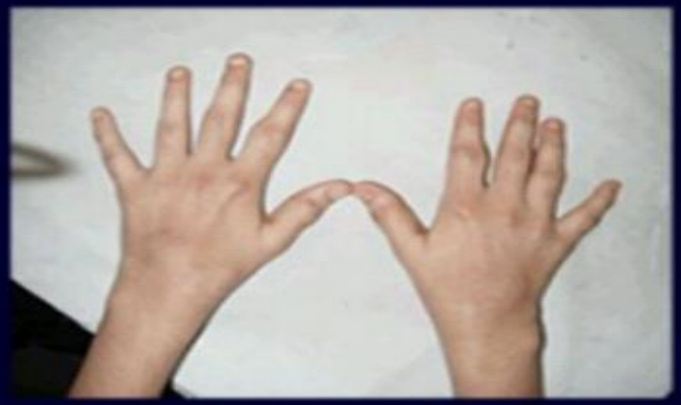

Smolen&Steiner .Nature Rev Drug Disc

# Cytokines disequilibrium in joints of patients with RA




Feldman M et al, Rheumatoid arthritis, cell 1996; 85:307-10

# HISTORY OF RHEUMATOID ARTHRITIS



| | |
|---|---|
| 4500 BC | 1st evidence of RA seen in skeletons |
| 123 AD | Description in ancient Indian texts |
| 1800 | Description by Dr Augustin Jacob Landré-Beauvais |
| 1859 | The term Rheumatoid Arthritis coined by Sir Alfred Garrod |
| 1899 | Aspirin |
| 1929 | Gold |
| 1938 | Sulphasalazine |
| 1949 | Corticosteroids |
| 1951 | Methotrxate |
| 1952 | Hydroxychloroquine (Plaquenil) |
| 1991 | Leflunomide (Arava) |
| 2001 | Infliximab (Remicade), Etanercpet (Enbrel) |
| 2003 | Adalimumab (Humira) |
| 2005 | Abatacept (Orencia) |
| 2006 | Rituximab (Mabthera) |
| 2009 | Tocilizumab (Actemra) |
| 2012 | Tofacitinib (Xeljanz) |

The era of NSAIDs & Steroids

The era of DMARDs

The Era of Biologics, DMARDs & strategies to achieve Remission

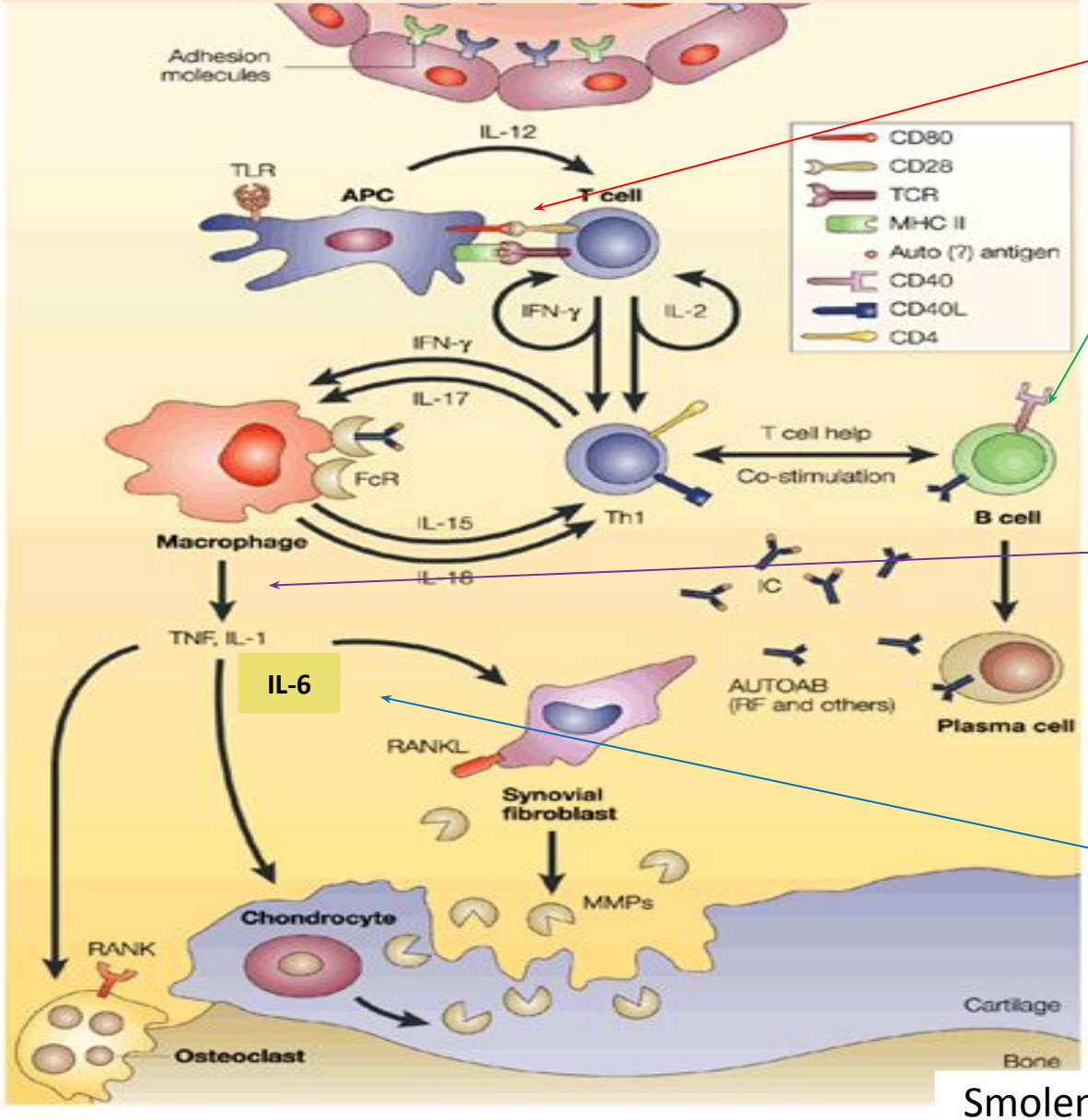
COBRA study- landmark study that showed 'combination DMARDs works better than single DMARD' 1997----->

TICORA study
Intensive management better results than routine management 2004----->

Treat to Target recommendations published

'Drug free remission' in a subgroup shown in multiple studies 2010 2011 ----->

# Carrent Biological Targets in RA




CTLA-4Ig / Abatacept

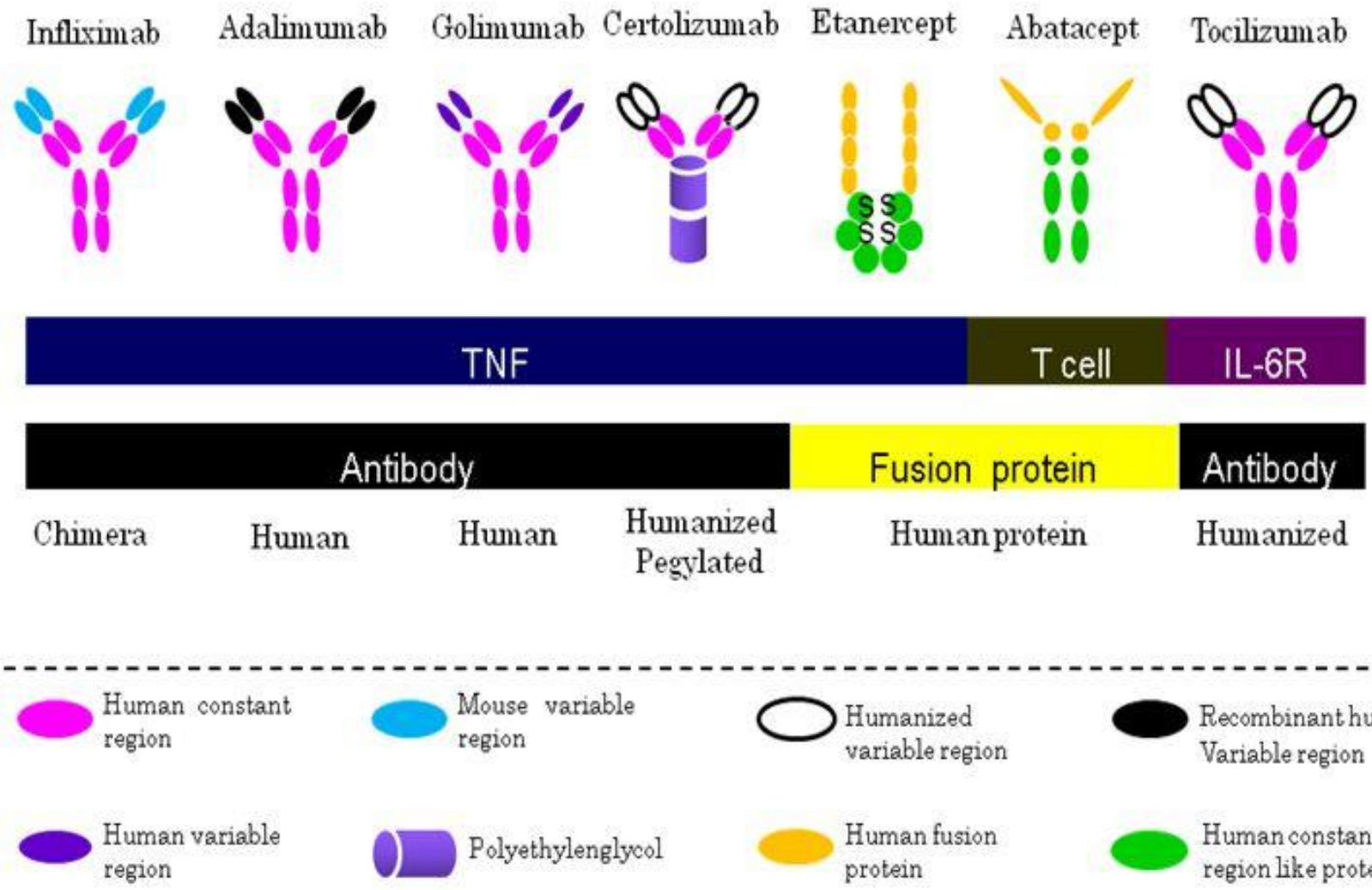
Anti-CD20 / Rituximab

Pro- inflammatory cytokines targeted hitherto:
-TNF / INF, ETN, ADA, GOL
- IL-1 / Anakinra

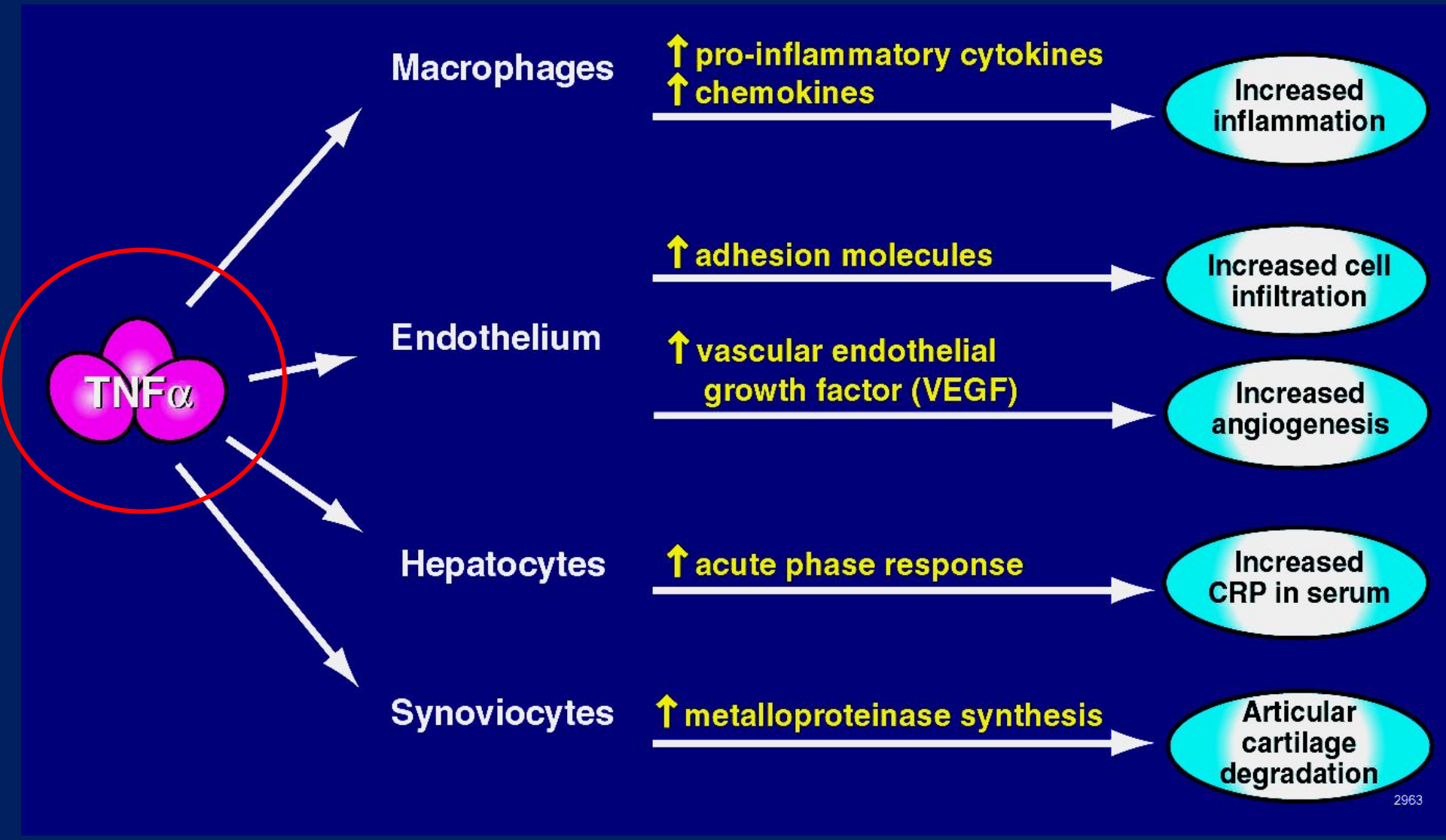
IL-6 / Tocilizumab

Small molecule
Tofacitinib

Smolen&Steiner .Nature Rev Drug Disc


Infliximab
Adalimumab
Golimumab
Certolizumab
Etanercept
Abatacept
Tocilizumab
S S
S S
TNF
T cell
IL-6R
Antibody
Fusion protein
Antibody
Chimera
Human
Human
Humanized
Pegylated
Human protein
Humanized
Human constant region
Mouse variable region
Humanized variable region
Recombinant human Variable region
Human variable region
Polyethylenglycol
Human fusion protein
Human constant region like protein

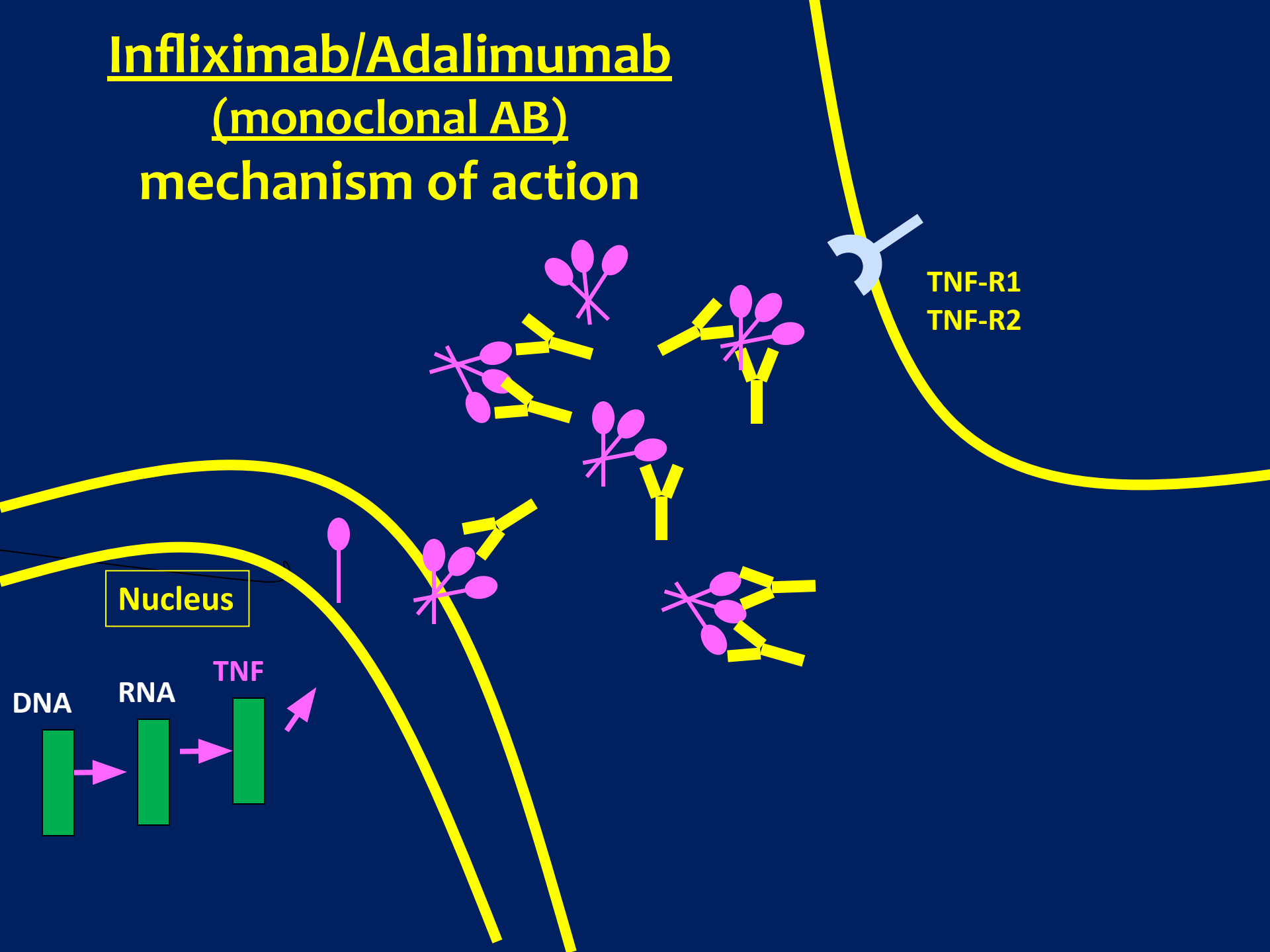
# Key Actions Attributed to TNFa



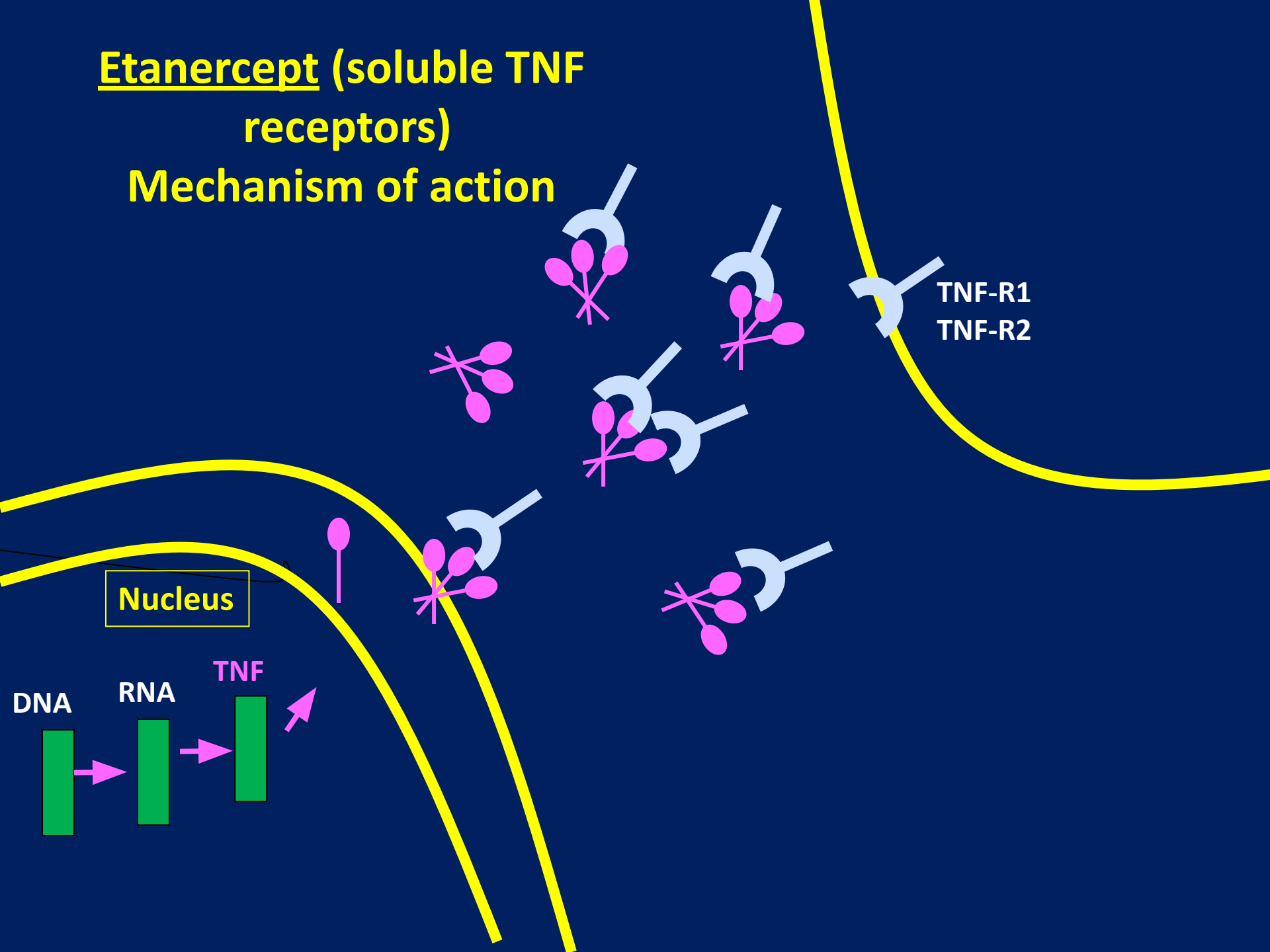
# Infliximab/Adalimumab

## (monoclonal AB)

## mechanism of action



# Etanercept (soluble TNF receptors) Mechanism of action



# Anti TNF side effects

**Anaphylaxis**

**Local site irritation**

**Rash**

**Chest pain**

**Shortness of breath**

**Infections- All+TB, histoplasmosis**

(Less with etanercept)

**Secondary malignancy? Lymphomas**

**Anti chimeric and other Ab's** (no etanercept)

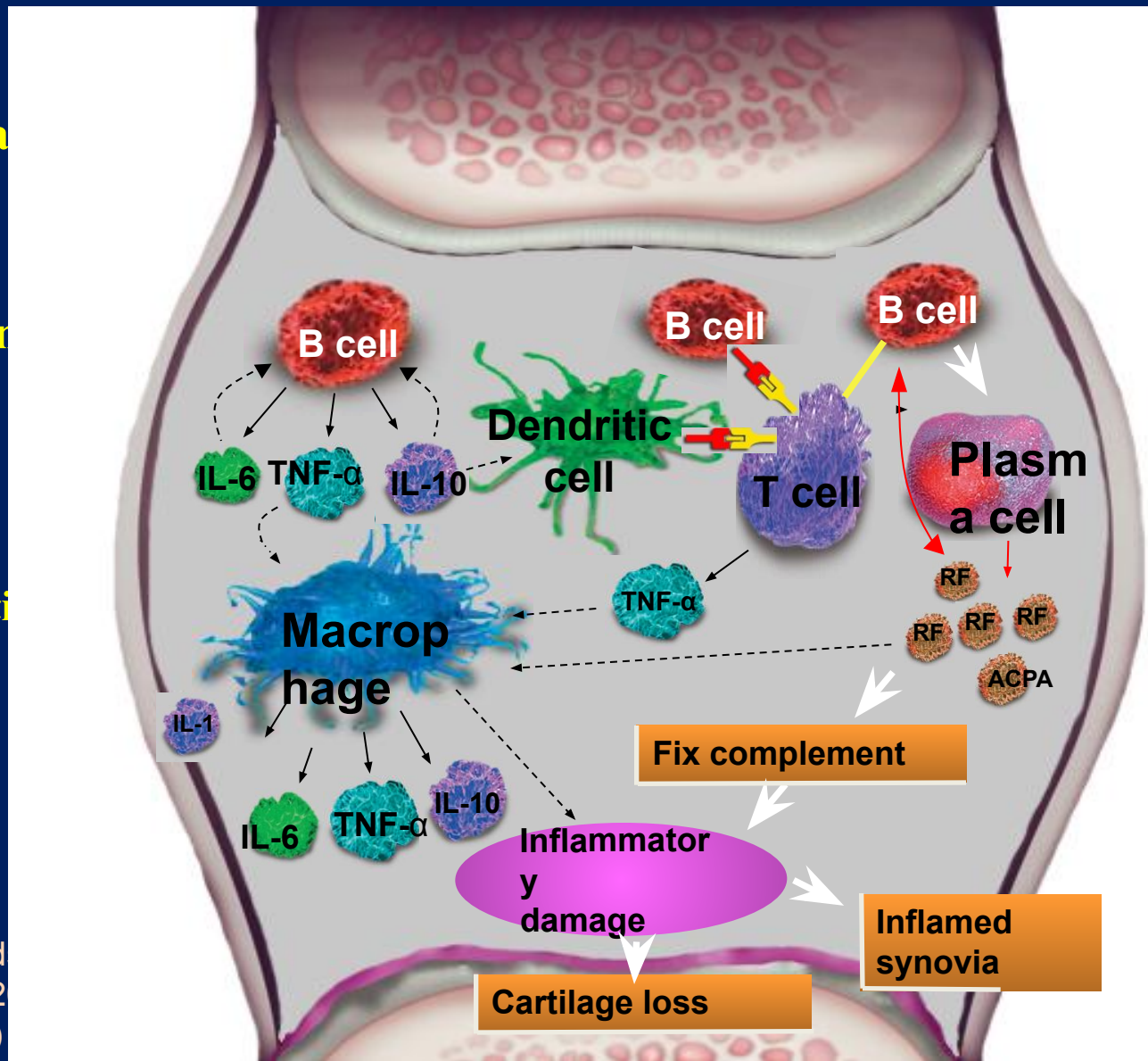
**Demyelinating disease**

# Relative contraindications to the use of TNF inhibitors

- SLE, Lupus overlap s-me
- Multiple sclerosis, optic neuritis, demyelinating disorders
- Current, active, serious infections
- Recurrent or chronic infections
- Untreated latent or active mycobacterial infections
- Hepatitis B infection
- CHF
- Pregnancy

# Potential Roles of B Cells in the Immunopathogenesis of RA

- **Secretion of proinfla cytokines**
- **Antigen presentatio**
- **T-cell activation**
- **Autoantibody producti and self-perpetuation**



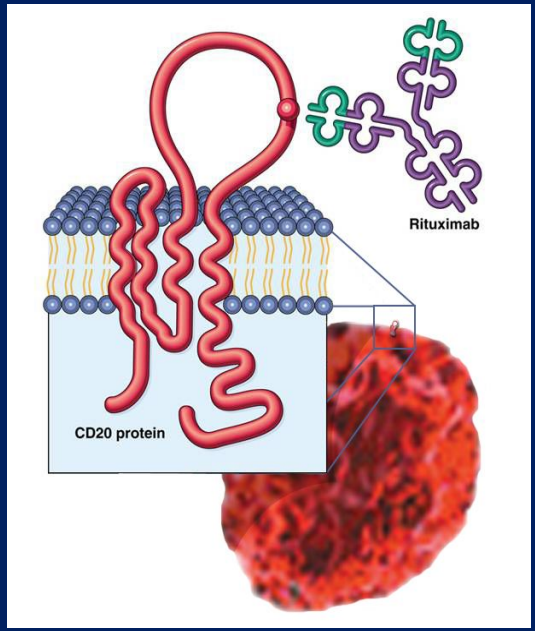

(Dörner & Burmester, 2003; Edward Gause & Berek, 2001; Shaw et al, 2 et al, 2001; Zhang & Bridges, 1986)

# Steps in the Maturation of B Cells

| Cell surface antigens | Stem | Pro B | Pre B | Immature | Activated | Memory | Plasma |
|---|---|---|---|---|---|---|---|
| CD10 | | | | | | | |
| CD19 | | | | | | | |
| CD20 | | | | | | | |
| CD24 | | | | | | | |
| CD38 | | | | | | | |
| CD39 | | | | | | | |

# Rituximab

- **Rituximab is a genetically engineered anti-CD20 therapeutic monoclonal antibody that *selectively* depletes CD20+ B cells**

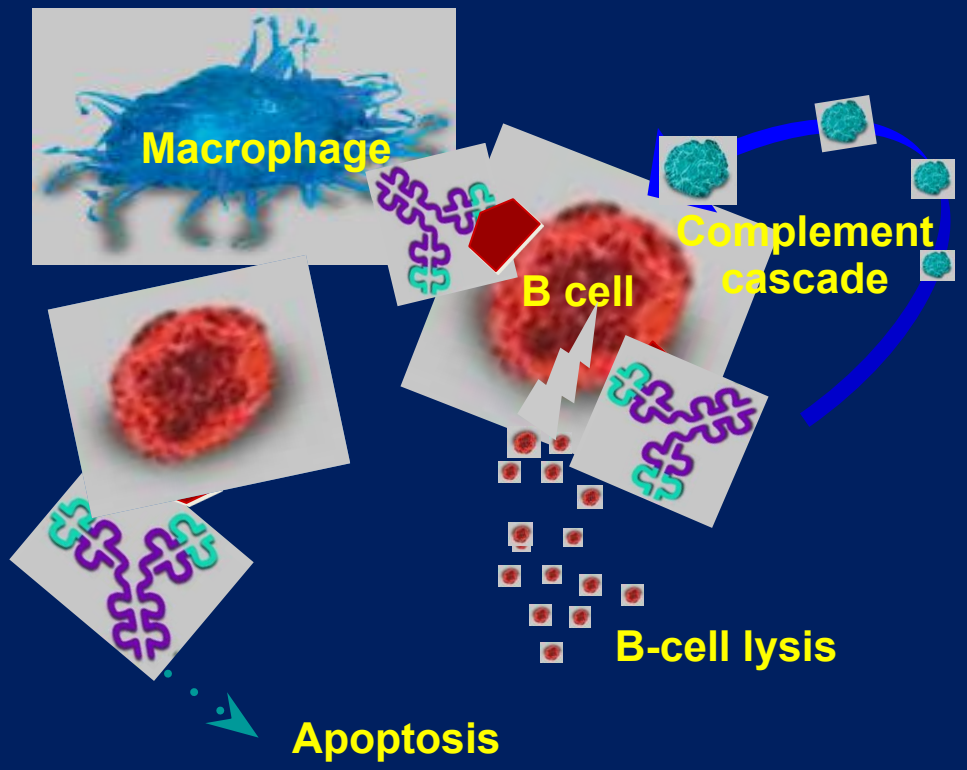


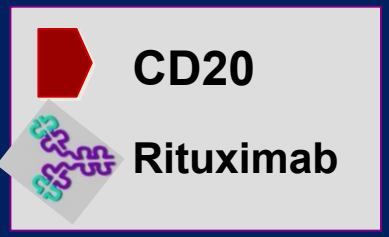

- **CD20 is a 297 amino acid phosphoprotein (33–35 kD) found on the surface of B cells**
- **CD20 is highly expressed on B cells but not expressed on stem, dendritic or plasma cells**
- **There are no known natural ligands for CD20**

(Shaw et al, 2003; Silverman & Weisman, 2003)

# Rituximab: Mechanism of Action

- **Rituximab initiates complement-mediated B-cell lysis**
- **Rituximab initiates cell-mediated cytotoxicity via macrophages and natural killer cells**
- **Rituximab induces B-cells apoptosis**




(Clynes et al, 2000; Reff et al, 1994)

# Rituximab, side effects

- Mild to moderate infusion reactions
- Increased risk of infections
- Hepatitis B reactivation
- Progressive multifocal leukoencephalopathy (PML)- very low in patients with RA

It is possible to treat:
- Patients with solid tumors in past
- Patients with latent TB

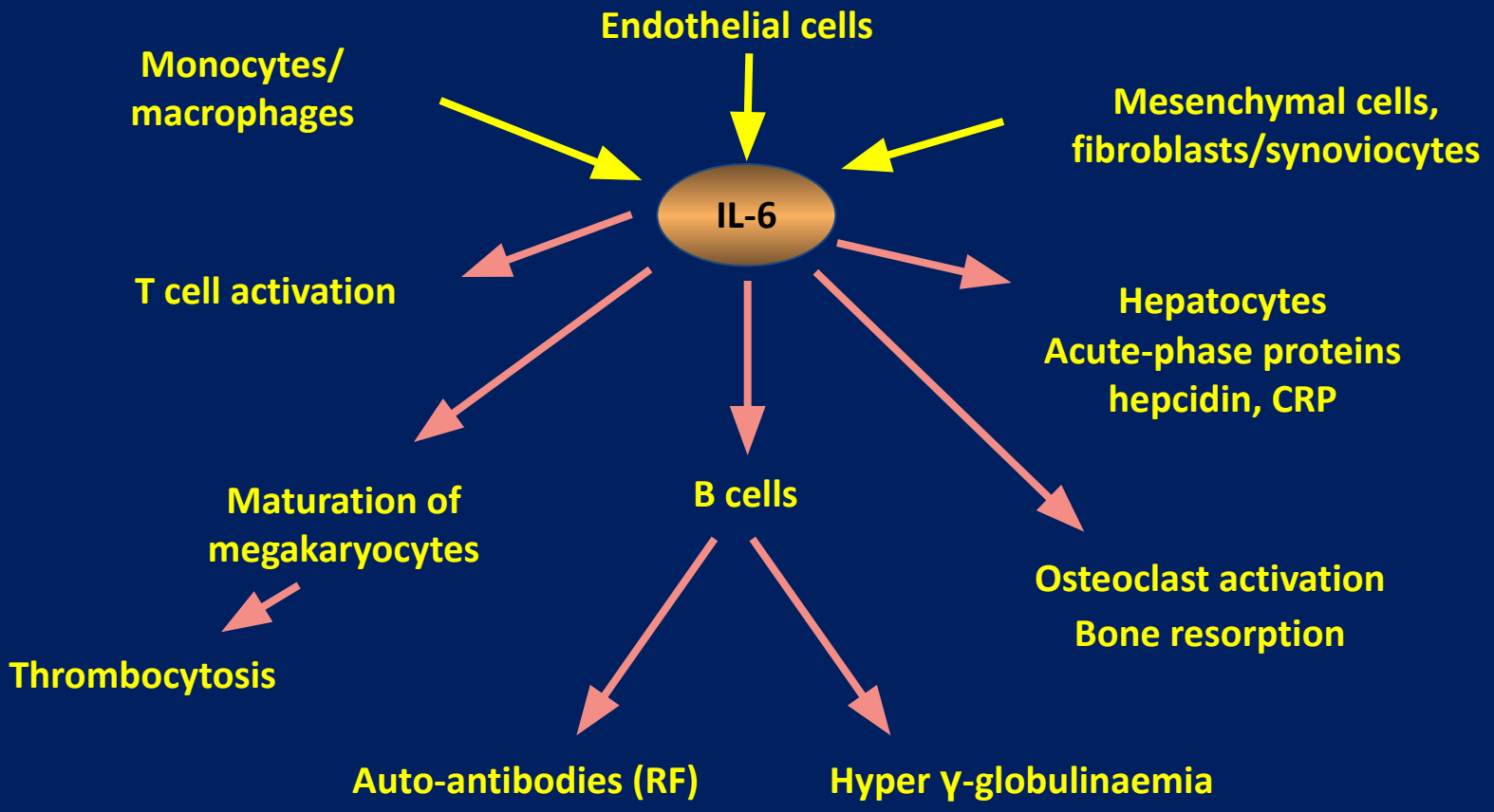
# Most Frequently Reported Adverse Events (up to Week 48)

| | MTX (n=40) | Rituximab (n=40) | Rituximab + CTX (n=41) | Rituximab + MTX (n=40) |
|---|---|---|---|---|
| All events* | 85 | 88 | 85 | 85 |
| RA exacerbation | 55 | 40 | 37 | 18 |
| Hypotension** | 18 | 30 | 29 | 18 |
| Hypertension** | 15 | 18 | 7 | 25 |
| Nasopharyngitis | 15 | 10 | 7 | 15 |
| Arthralgia | 8 | 8 | 5 | 13 |
| Back pain | 8 | 13 | 7 | 3 |
| Hyperglycaemia | 10 | 5 | 7 | 8 |
| Cough | — | 15 | 5 | 8 |
| Flushing | 8 | 13 | 5 | 3 |
| Headache | 5 | 5 | 7 | 8 |

Lymphocyte depletion, In some reduced Ig, non TB infections
Infusion related reactions

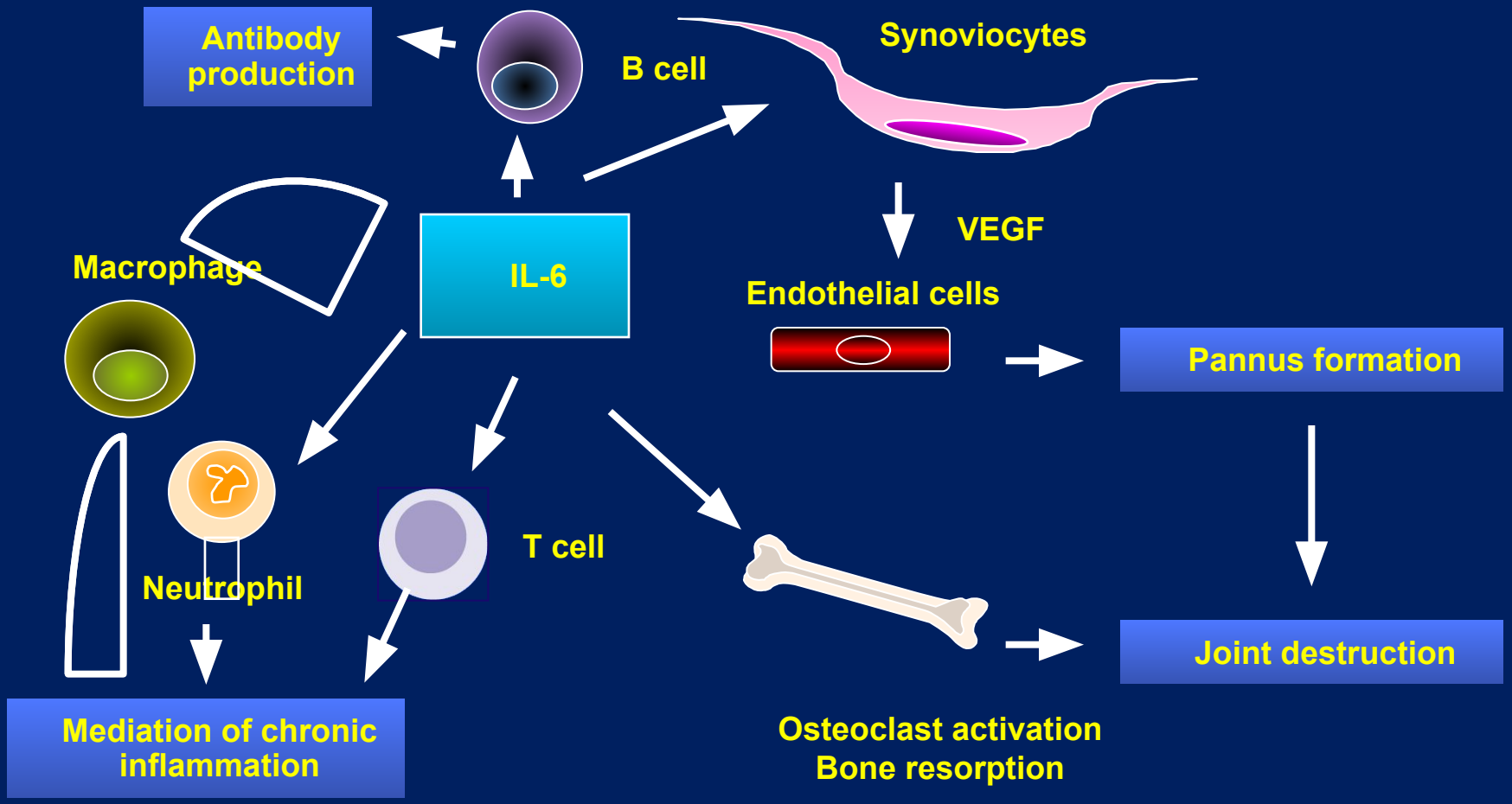
*% of patients reporting an event
**Hypo/hypertension defined as >30 mmHg change in diastolic or systolic blood pressure

# IL-6: Fundamental role in the inflammation that drives RA



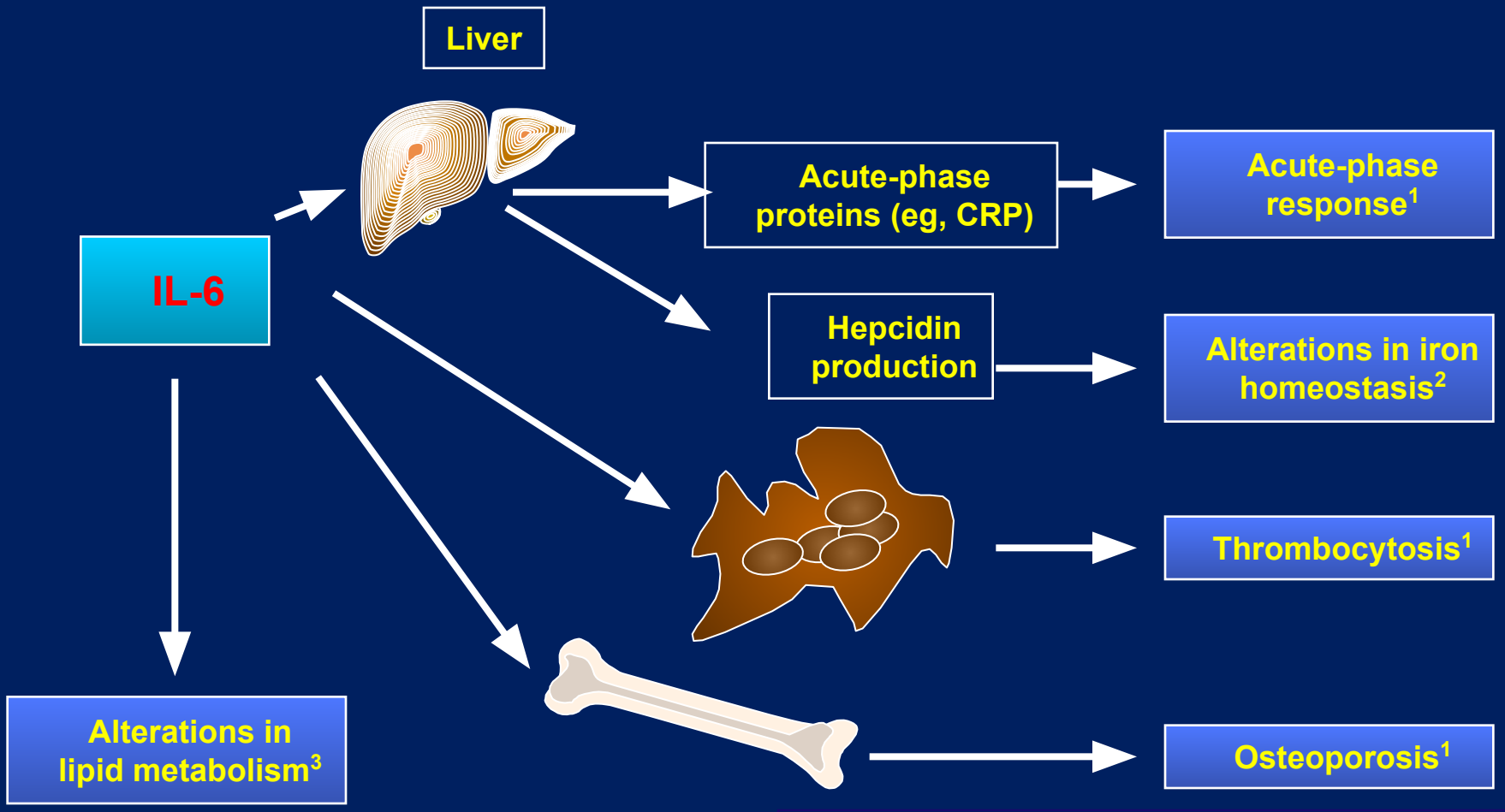

Firestein GS. *Nature* 2003;423:356–361; Smolen JS and Steiner G. *Nat Rev Drug Disc* 2003;2:473–488

# Articular effects of IL-6 in RA[1,2]




1. Adapted from Choy E. *Rheum Dis Clin North Am*. 2004;30:405−415;
2. Gabay C. *Arthritis Res Ther.* 2006;8(suppl 2):S3.

# Systemic effects of IL-6 in RA

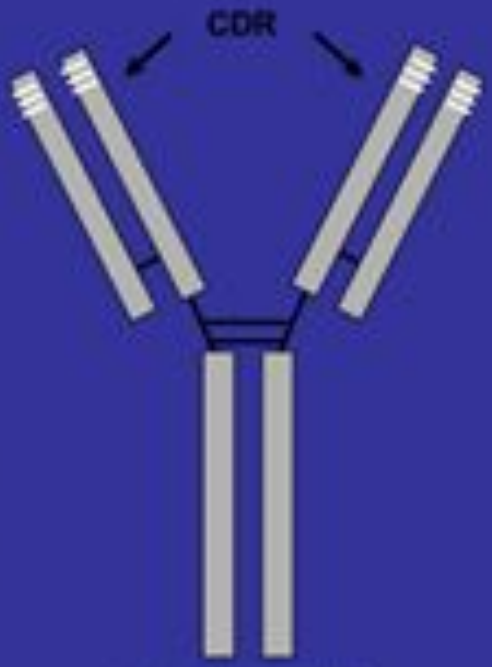




1. Choy E. *Rheum Dis Clin North Am*. 2004;30:405–415;
2. McGrath H *et al*. *Rheumatology*. 2004; 43:1323–1325;
3. Al-Khalili L *et al*. *Mol Endocrinol*. 2006; 20:3364–3375.

# Tocilizumab

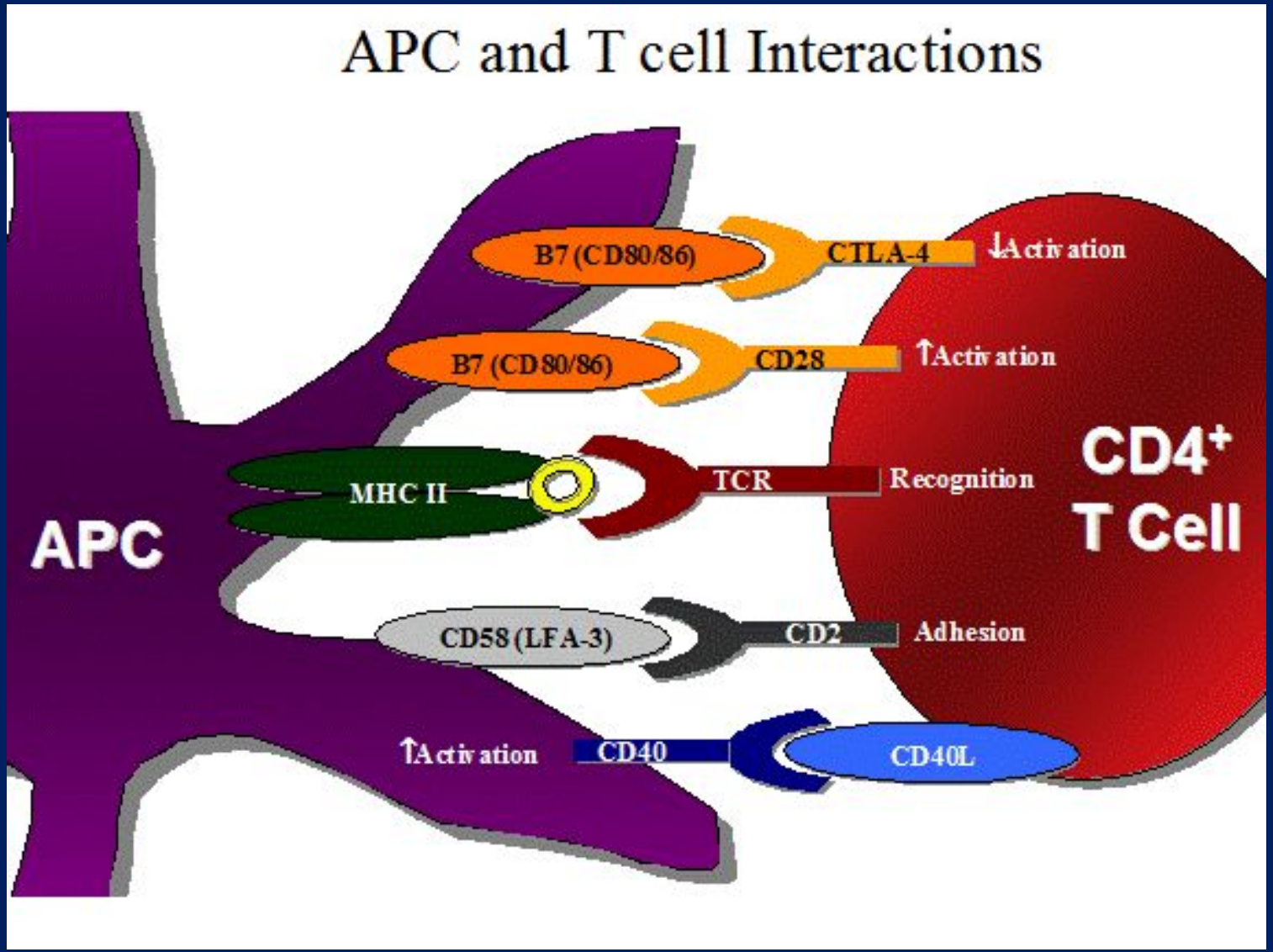
- Humanized monoclonal antibody[1]
- Binds to membrane-expressed and soluble forms of IL-6R[1]
- Blocks IL-6 binding to its receptor[1]
- Inhibits IL-6R mediated signaling[1]




Tocilizumab[2]

CDR, complementarity-determining region.

1. Smolen JS et al. *Arthritis Res Ther.* 2006;8(suppl 2):S5.
2. Roche-generated image. P-MOA-NO-061.




Primer: Immunology and Autoimmunity
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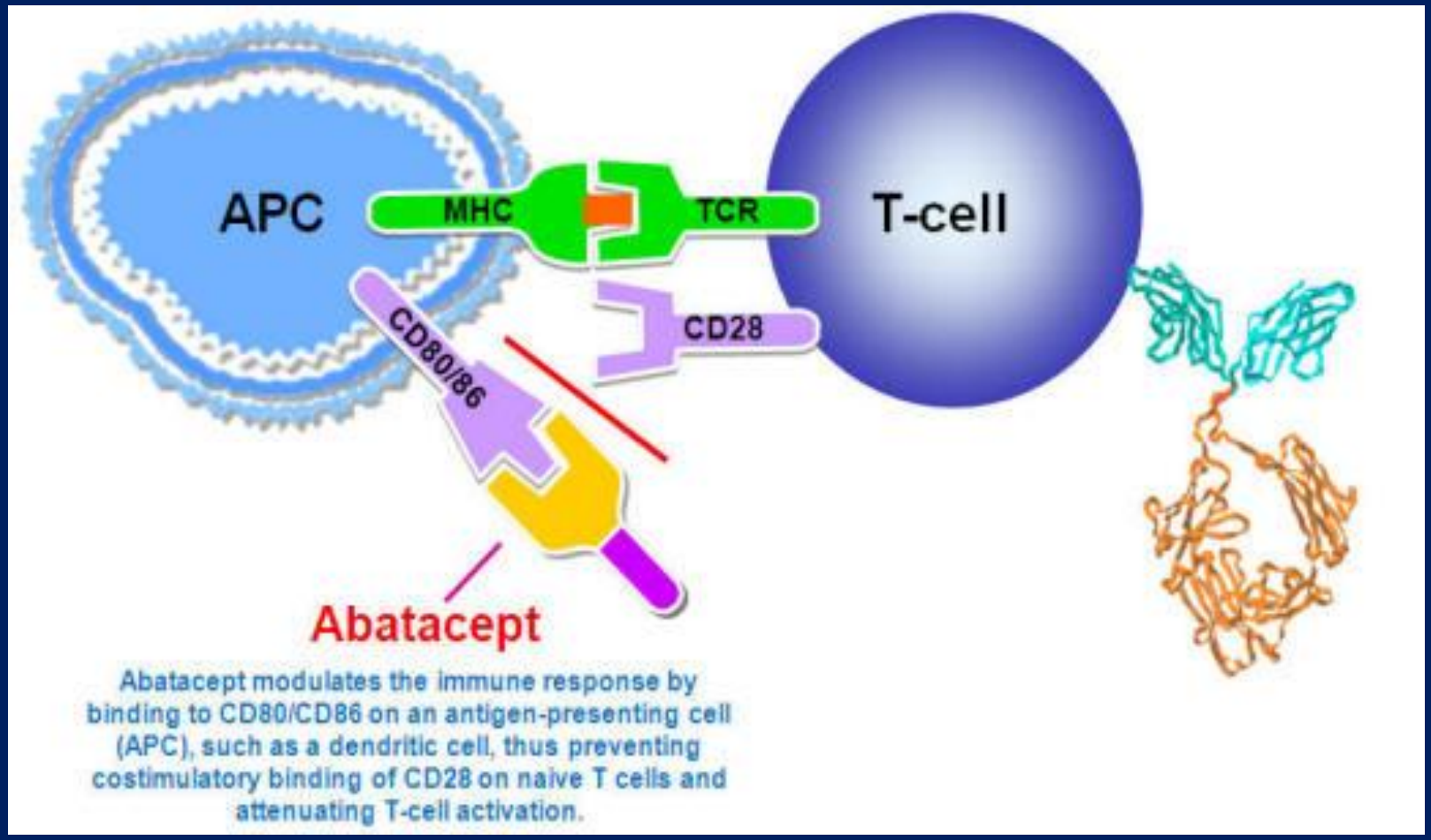
# ABATACEPT / ORENCIA
# Costimulation blockade in RA



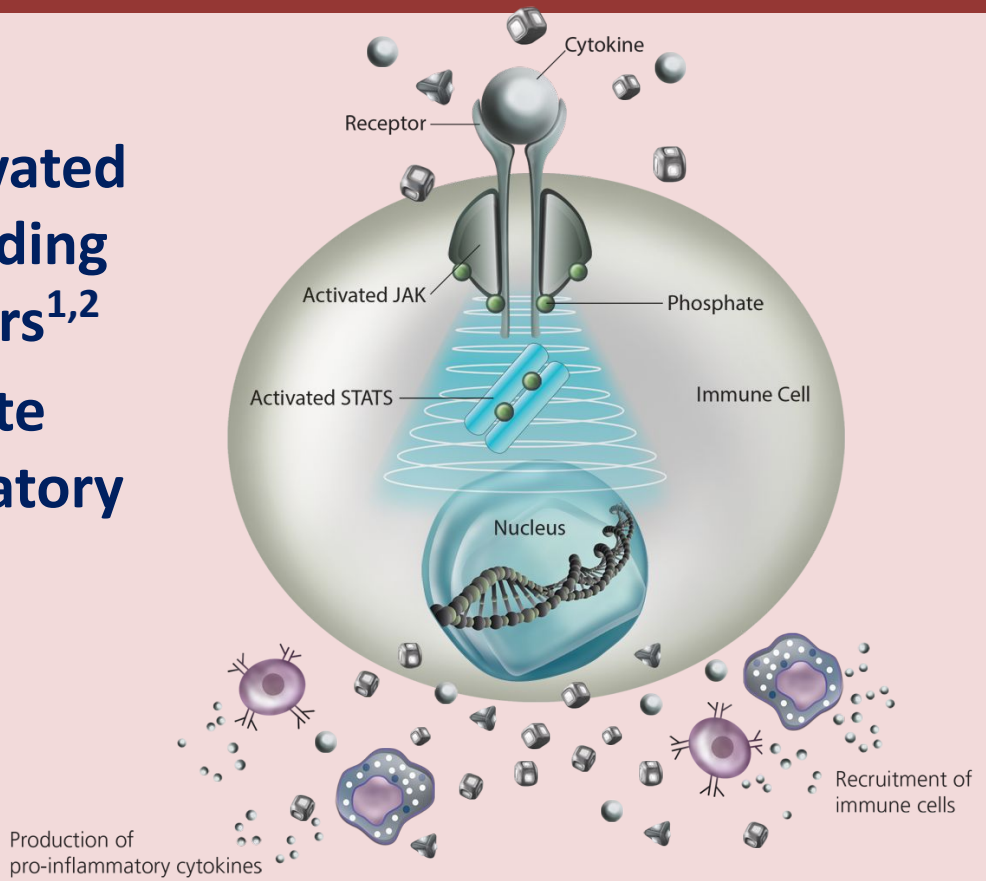

http://www.rheumatologysa.com/biologics.html

# XELJANZ (Tofacitinib): a new class of oral RA therapy that targets inflammation from inside the cell

- First Oral Agent To Compete with Biologics
- A novel nonbiologic medicine for rheumatoid arthritis (RA)
- It is the first Janus kinase (JAK) inhibitor for this disease

# Janus kinases (JAKs)

- **JAKs are intracellular enzymes that are activated by cytokines upon binding to cell surface receptors[1,2]**
- **Activated JAKs generate immune and inflammatory responses[1]**



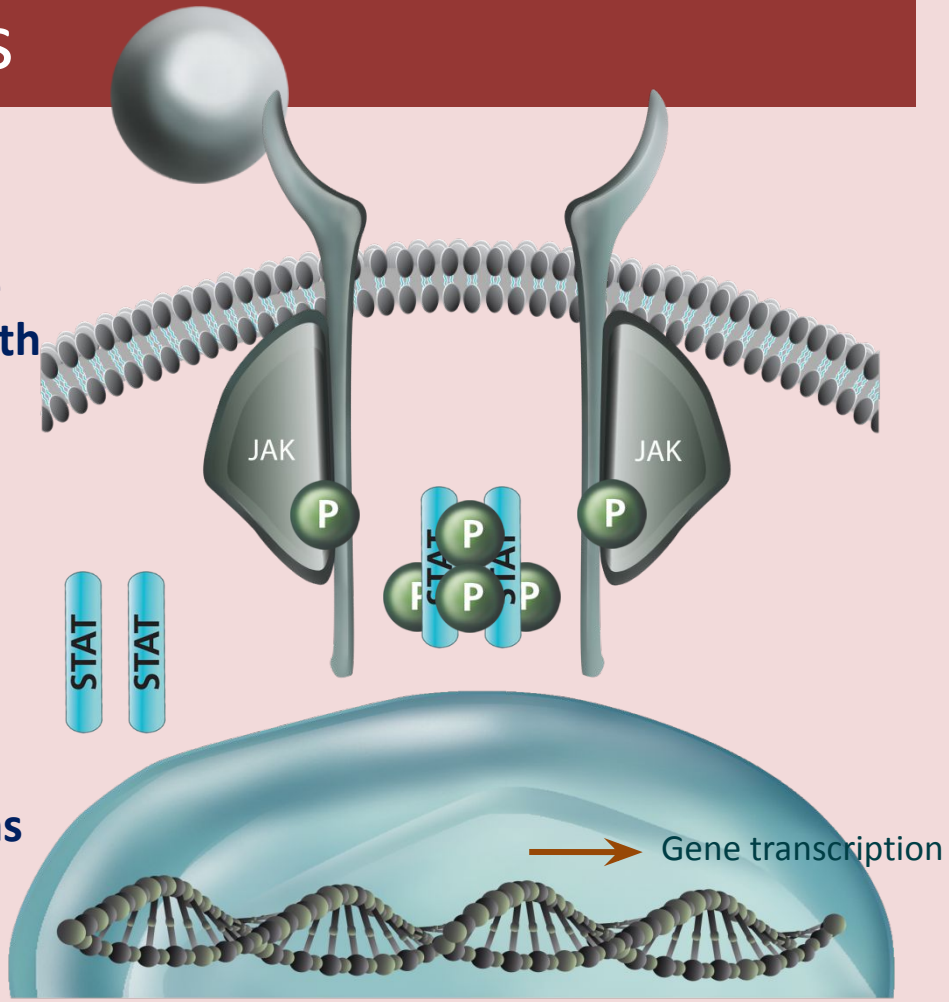

**JAKs play a central role in immune and inflammatory responses**


1. Ghoreschi K et al. *J Immunol* 2011;186:4234–4243.
2. O'Sullivan LA et al. *Mol Immunol* 2007;44:2497–2506.


JAK, Janus kinase; P, phosphate;
STAT, signal transducer and activator of transcription.

# Binding of cytokine receptors activates JAK signalling pathways

- **Rapid membrane to nucleus signalling:**
  - **Cytokines bind trans-membrane receptors that are associated with JAKs**
  - **Binding activates JAKs**
  - **JAKs phosphorylate receptors**
  - **STATs bind to receptors**
  - **JAKs phosphorylate STATs**
  - **STAT translocate to the nucleus**
  - **STATs bind DNA and activate transcription to produce proteins that mediate immune responses/inflammation**




**JAKs activate STATs, which then act as transcription factors**



1. Shuai K, et al. *Nat Rev Immunol* 2003;3:900–911.

JAK, Janus kinase; P, phosphate;
STAT, signal transducer and activator of transcription.

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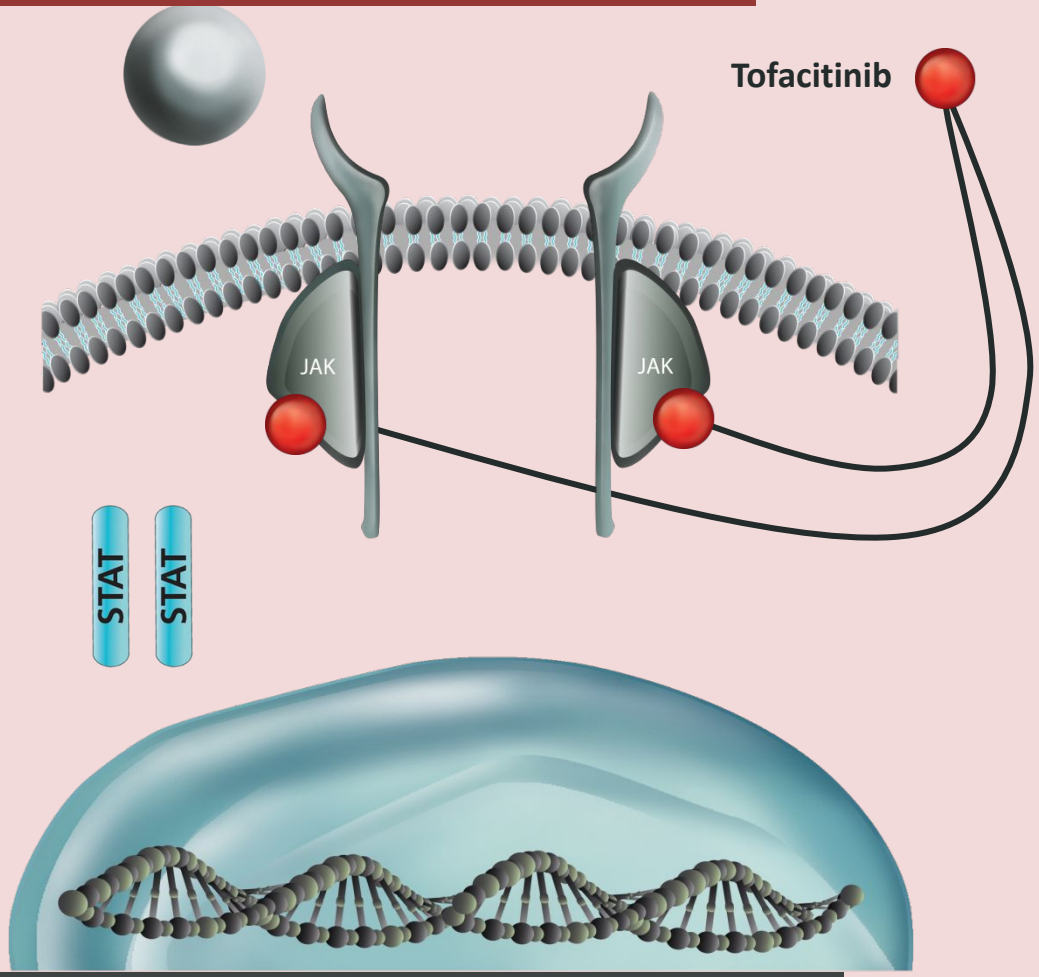
# Tofacitinib targets JAK intracellular signalling pathways

1 **Tofacitinib enters the cell and binds to the JAK phosphorylation site**

2 **Cytokine binding to its cell surface receptor leads to receptor polymerisation[1]**

3 **Tofacitinib inhibits the autophosphorylation and activation of JAK.[2] JAKs cannot phosphorylate the receptors, which therefore cannot dock STATs**

4 **JAKs cannot phosphorylate STATs, which cannot dimerise and move to the nucleus to activate new gene transcription of inflammatory mediators**




**Tofacitinib blocks the JAK signalling pathway at the point of JAK phosphorylation**

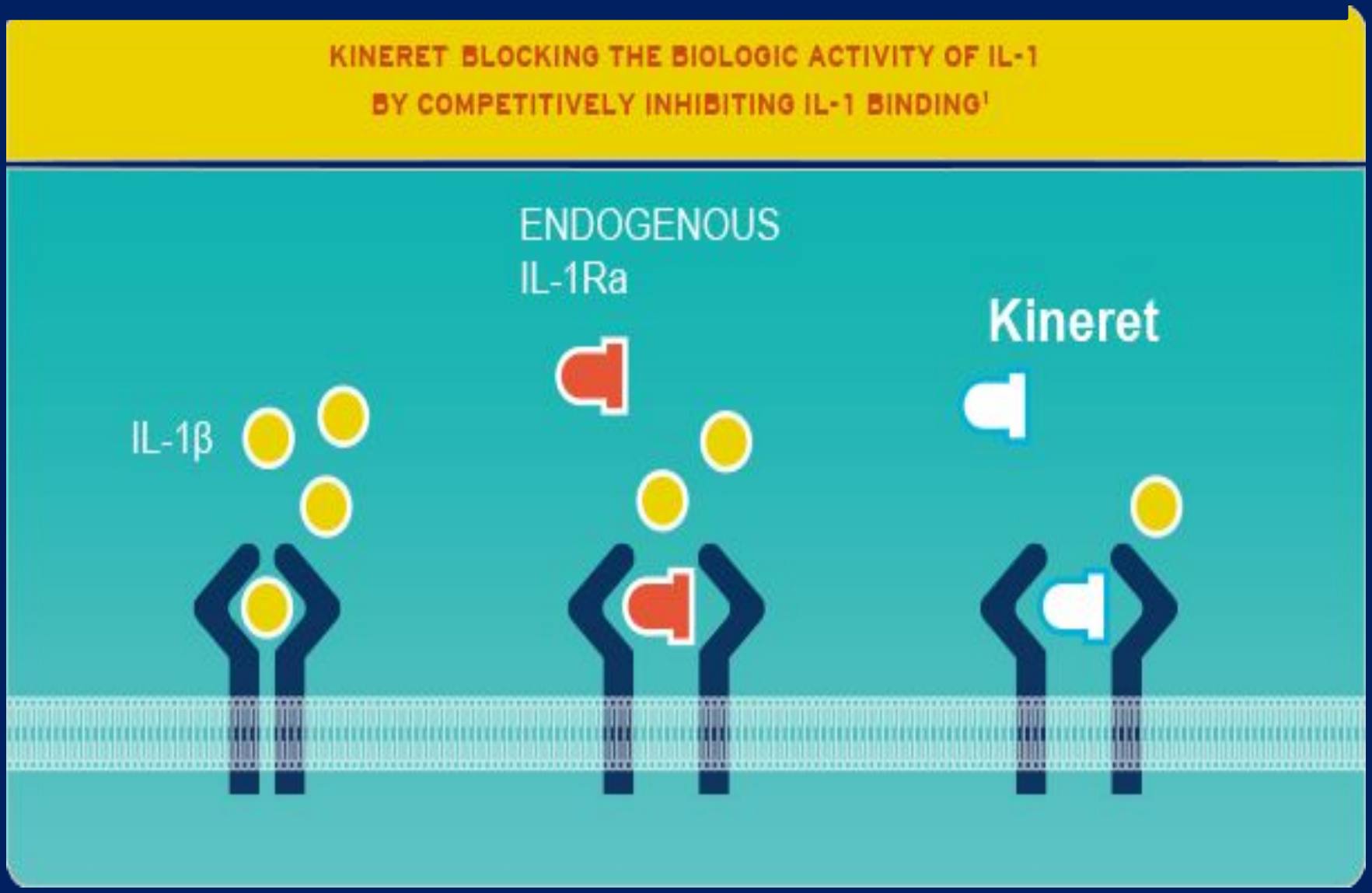


1. Shuai K, et al. *Nat Rev Immunol*. 2003;3:900–911,
2. Jiang JK, et al. *J Med Chem*. 2008;51:8012–8018.

JAK, Janus kinase;
STAT, signal transducer and activator of transcription.

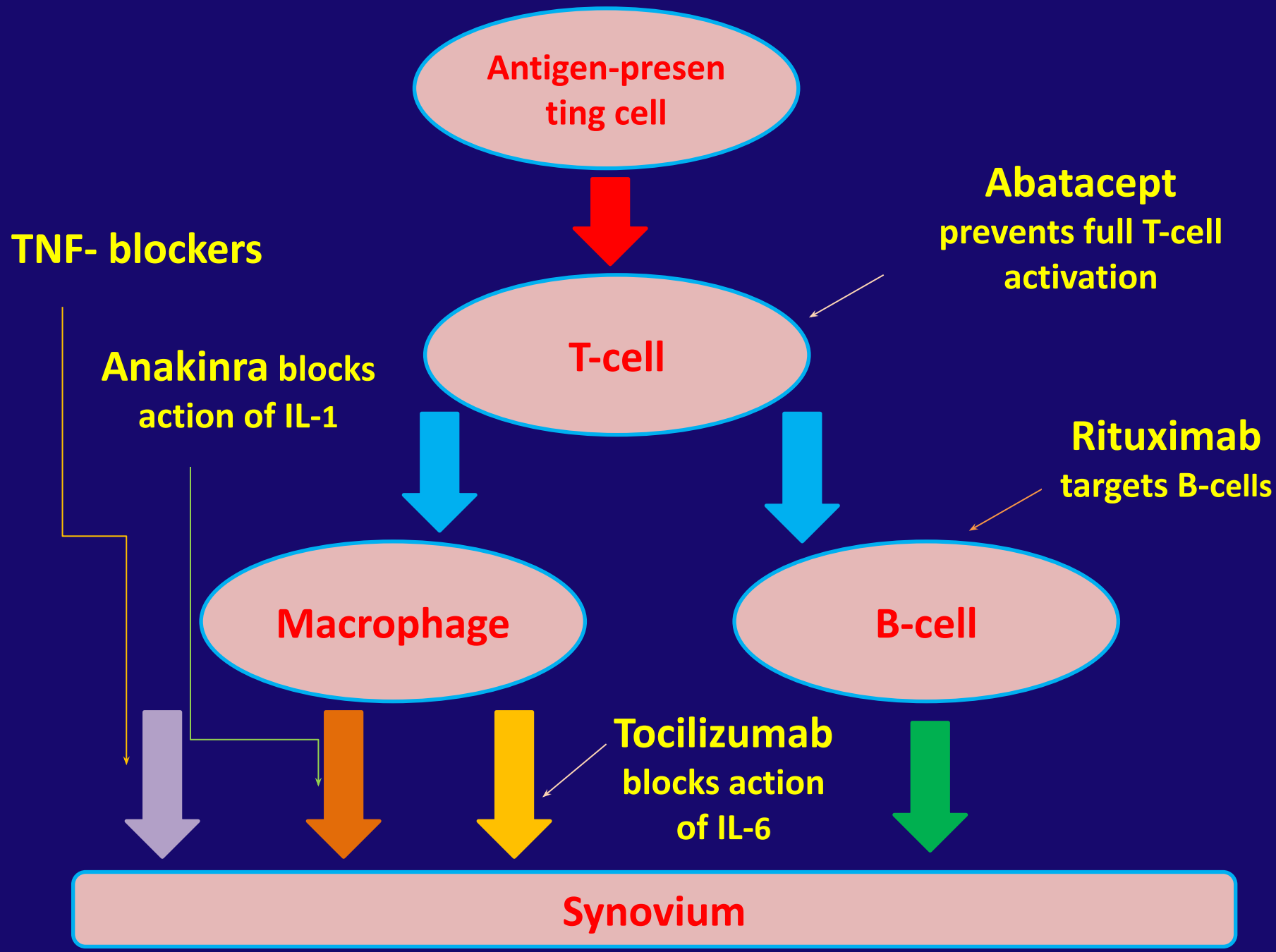
32

# **ANAKINRA** – recombinant form of IL-1 receptor antagonist



# Anakinra indications

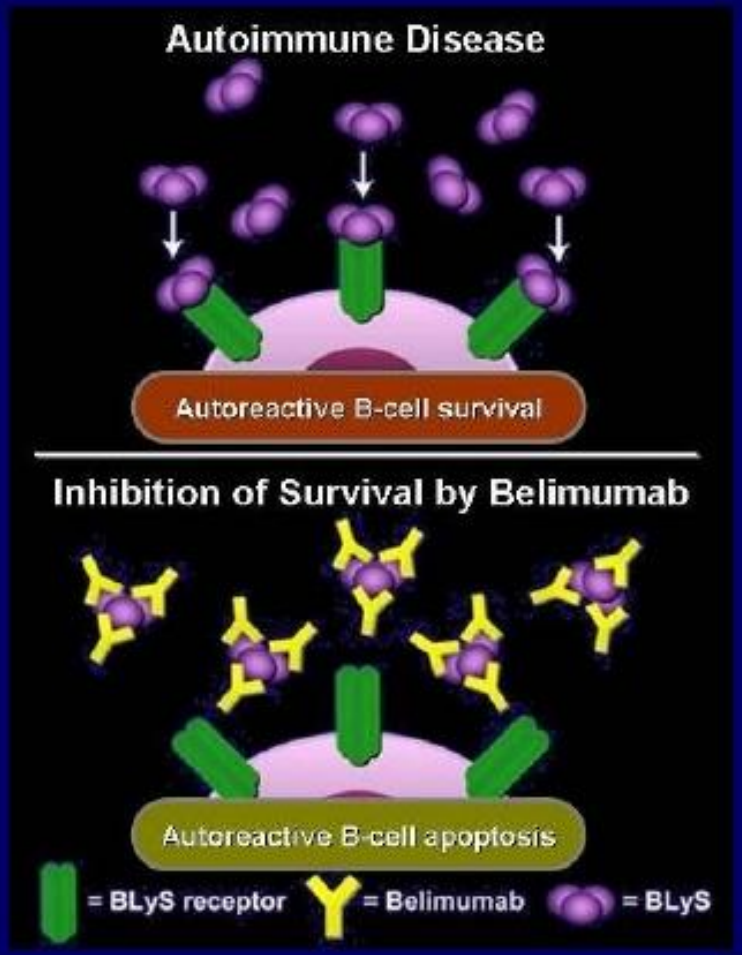
- Auto- inflammatory syndromes, periodic fevers
- Systemic onset juvenile inflammatory arthritis
- Adult-onset Still's disease
- Familial Mediterranean Fever/ Amyloidosis
- (limited use for the treatment of RA)


Antigen-presen
ting cell
Abatacept
prevents full T-cell
activation
TNF- blockers
T-cell
Anakinra blocks
action of IL-1
Rituximab
targets B-cells
Macrophage
B-cell
Tocilizumab
blocks action
of IL-6
Synovium

# Belimumab / Benlysta

**(anti-BLyS monoclonal antibody)**

- Fully-human monoclonal antibody
- Selectively targets and inhibits soluble BLyS
  - TNF family member that promotes B-cell differentiation, proliferation, and survival
  - Plays critical role in physiologic B-cell development and induces B cells to secrete immunoglobulins
- Inhibition of BLyS can result in autoreactive B-cell apoptosis




BLyS (B-Lymphocyte stimulator) = BAFF (B-cell Activating Factor)

# BENLYSTA / BELIMUMAB

## Indications

- **Adult patients with active, autoantibody-positive SLE who are receiving standard drug therapy**

## Contraindications

- Active glomerulonephritis
- CNS manifestations
- Concomitant use with other biologics or cyclophosphamide
- Prior anaphylactic reactions to Belimumab
- Pregnancy

# Screening before starting biological treatment

- Screening of TB (PPD / IGRA)
- Chest radiography
- Screening of viral hepatitis (HBV HCV)
- Blood analysis (WBC PLT count, Liver enzymes)

# Tuberculosis screening

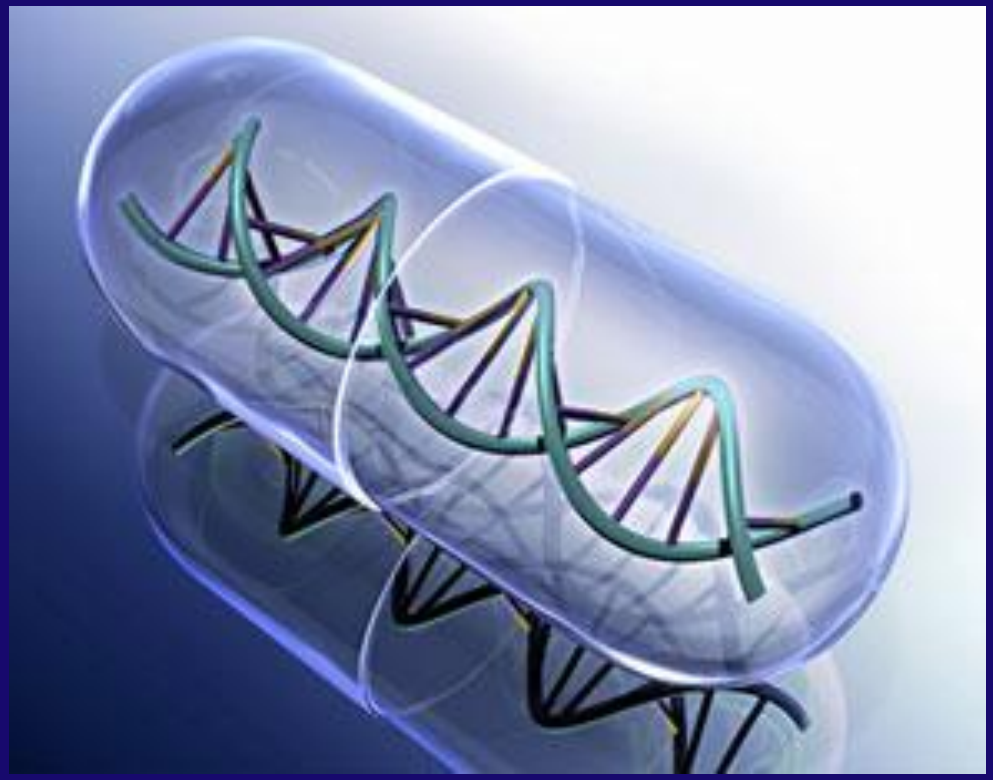
- Required screening of TB before starting of anti-TNF treatment
- When the TST (PPD) between 5-10 have to rely on the blood test IGRA to diagnose latent TB
- If the test TST ≥10 or IGRA is positive  should be treated as diagnosis of latent tuberculosis

## Box 1 Recommendations for vaccination in adult patients with AIRD treated with biologics

1. Thorough assessment of vaccination status before beginning treatment with a biologic agent;
2. Vaccination can be administered during therapy with anti-TNF agents, TCZ and ABA but ideally should be given before B cell depleting biologicals are prescribed; and in both cases with the disease stabilised.
3. Live attenuated vaccines should be avoided.
4. The influenza and pneumococcal vaccines are strongly recommended
5. Tetanus toxoid vaccination should be administered as in the general population, except if the patient has been treated with RTX within the last 24 weeks and is at high risk of developing tetanus, in which case passive immunisation with tetanus immunoglobulin is strongly advised.
6. There are no data to help advice about the use of HZV, HPV, hepatitis A and/or B, *Haemophilus influenzae* b, meningococcal vaccines and BCG.

ABA, abatacept; AIRD, autoimmune rheumatic diseases; HPV, human papillomavirus; RTX, rituximab; TNF, tumour necrosis factor.

Ferreira I, *et al. Ann Rheum Dis* 2014



# תודה על הקשבה