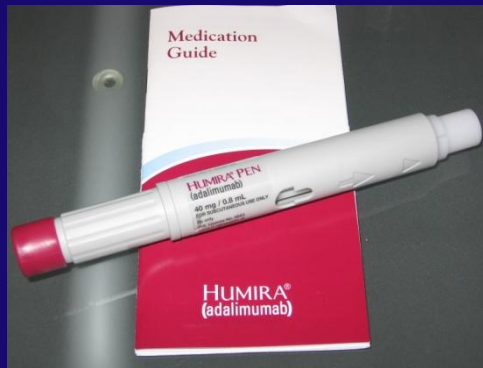


Biologics in Rheumatology

Dr Ira Novofastovski

HaEmek Medical Center, Afula

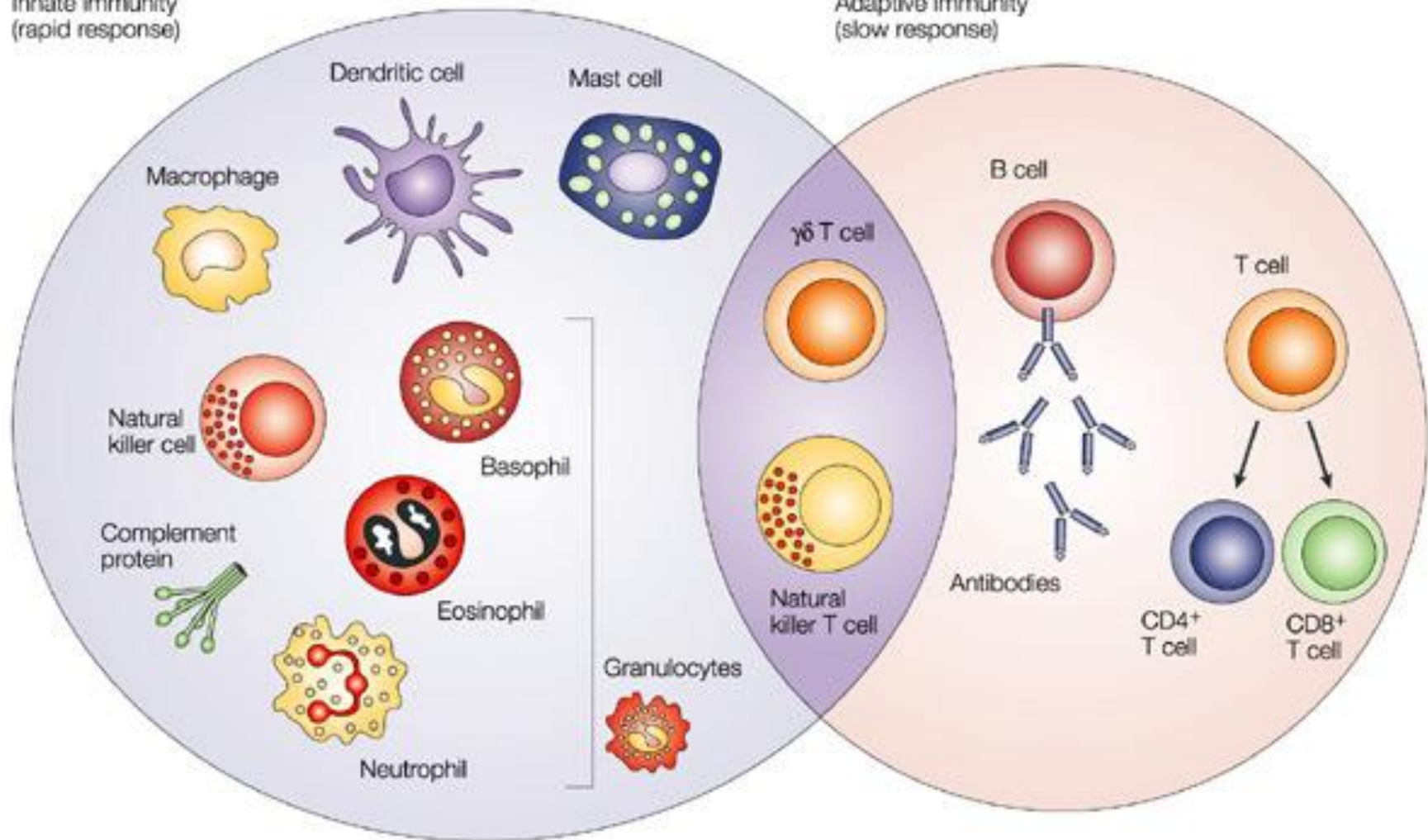


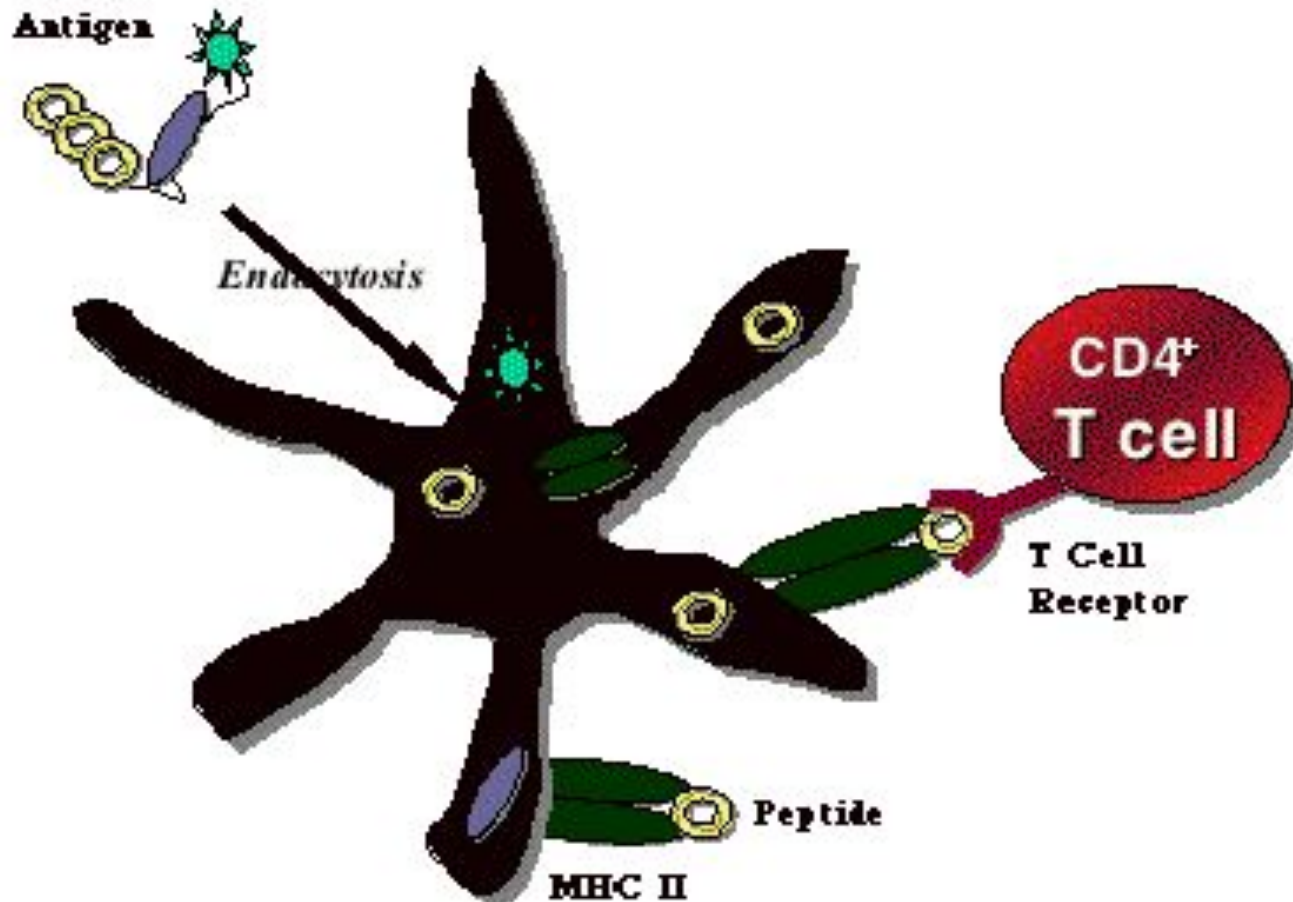
List of diseases treated with biologic drugs

- 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)

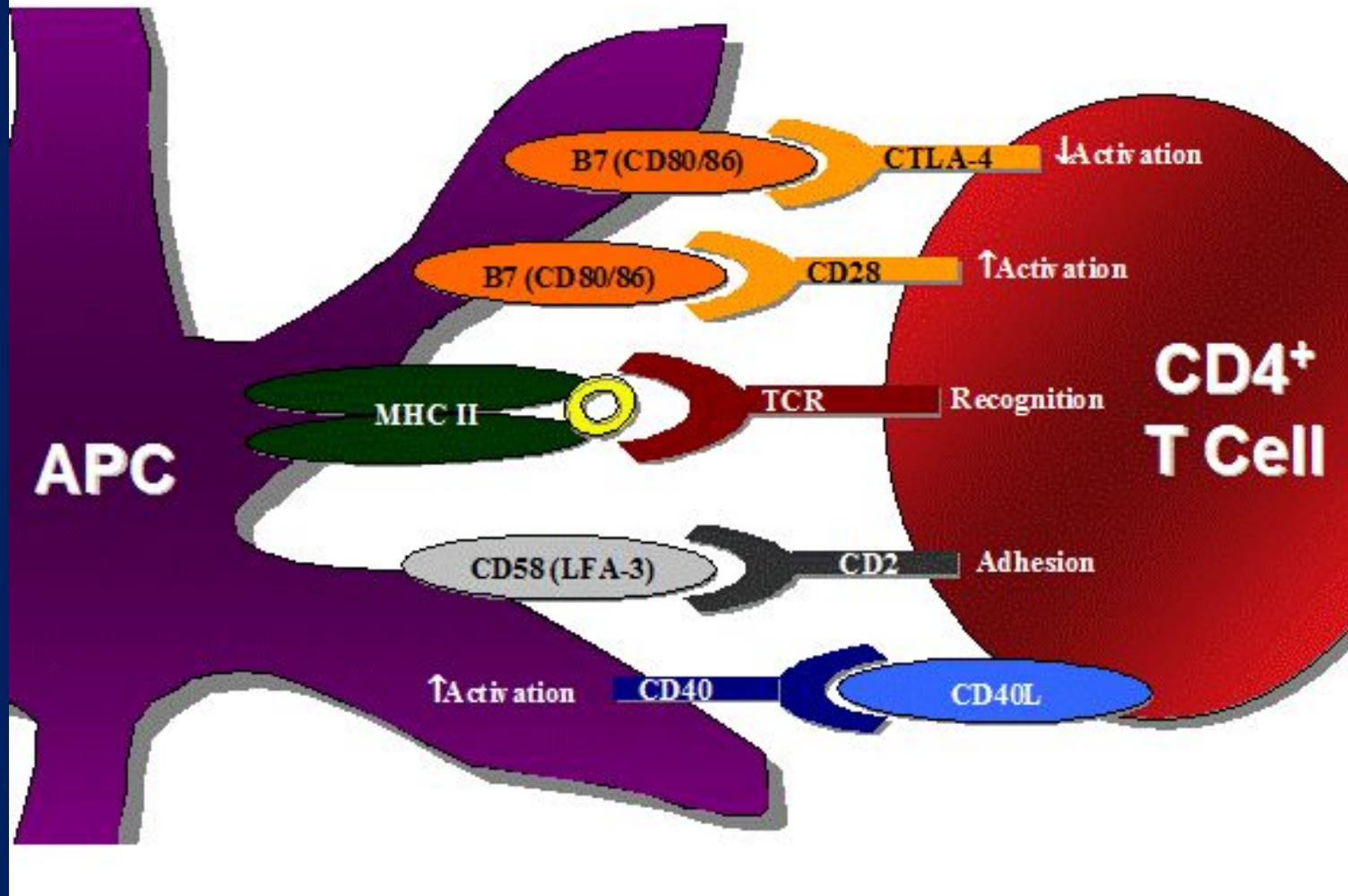
Adaptive immunity
(slow response)

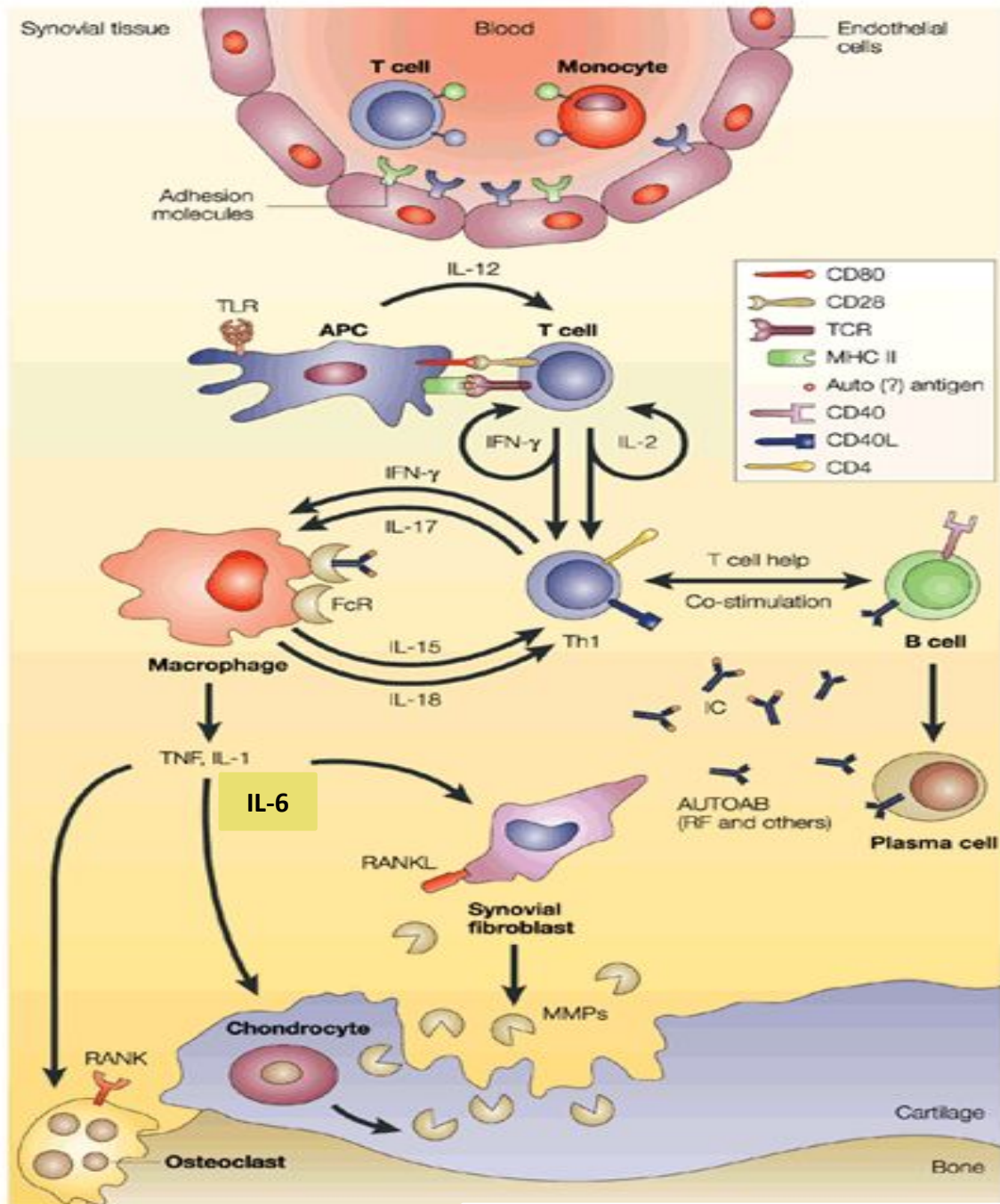




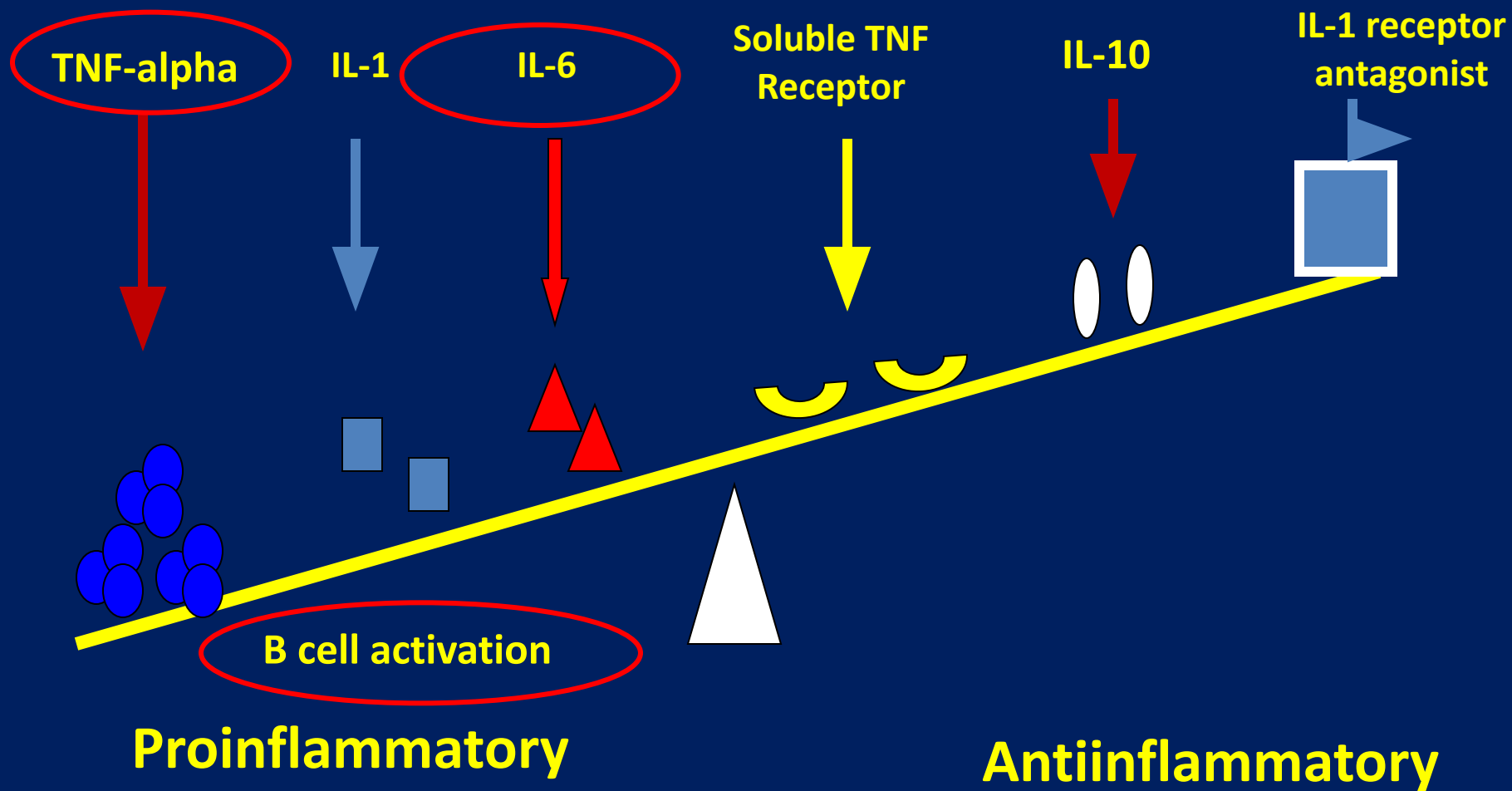
Antigen Presenting Cell (APC)

APC and T cell Interactions





Cytokines disequilibrium in joints of patients with RA



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), Etanercept (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----->

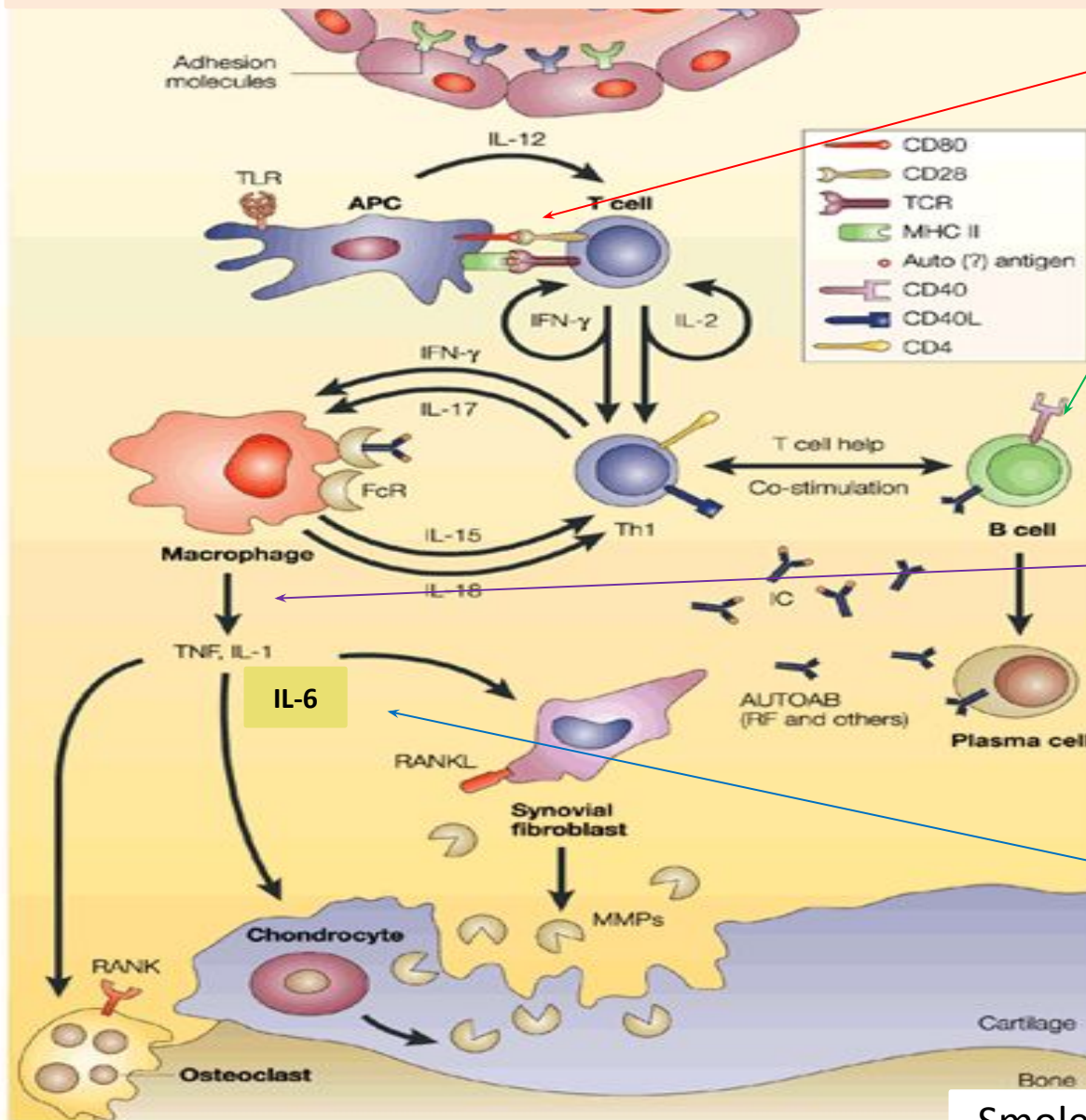
✦ Treat to Target recommendations published

✦ 'Drug free remission' in a subgroup shown in multiple studies

2010

2011----->

Current Biological Targets in RA



CTLA-4lg / Abatacept

Anti-CD20 / Rituximab

Pro-inflammatory cytokines targeted hitherto:

- TNF / INF, ETN, ADA, GOL
- IL-1 / Anakinra

IL-6 / Tocilizumab

Small molecule Tofacitinib

Infliximab

Adalimumab

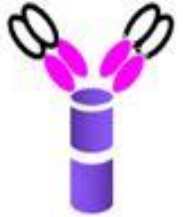
Golimumab

Certolizumab

Etanercept

Abatacept

Tocilizumab



Chimera

Human

Human

Humanized
Pegylated

Human protein

Humanized

Human constant region

Mouse variable region

Humanized variable region

Recombinant human Variable region

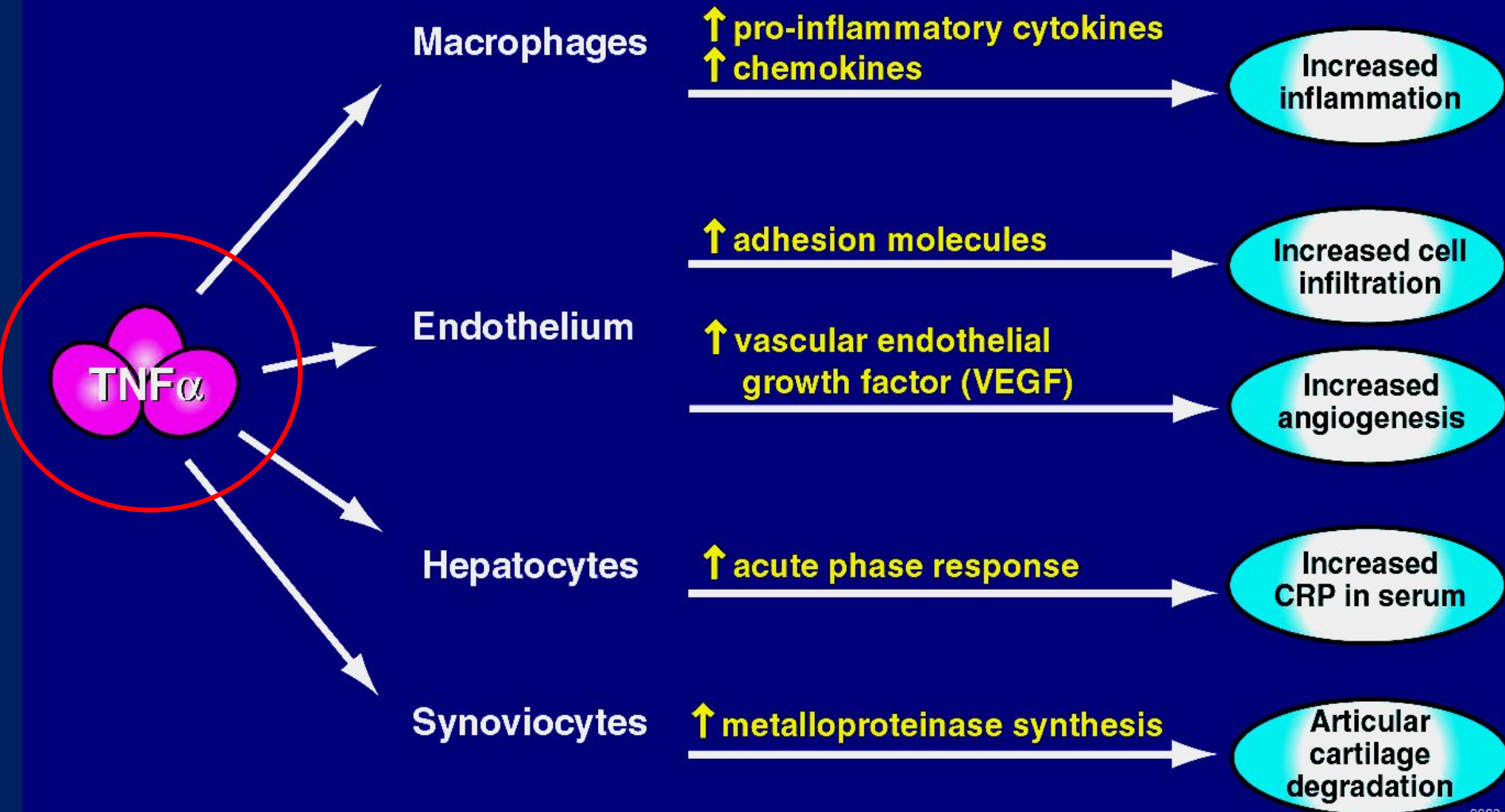
Human variable region

Polyethylenglycol

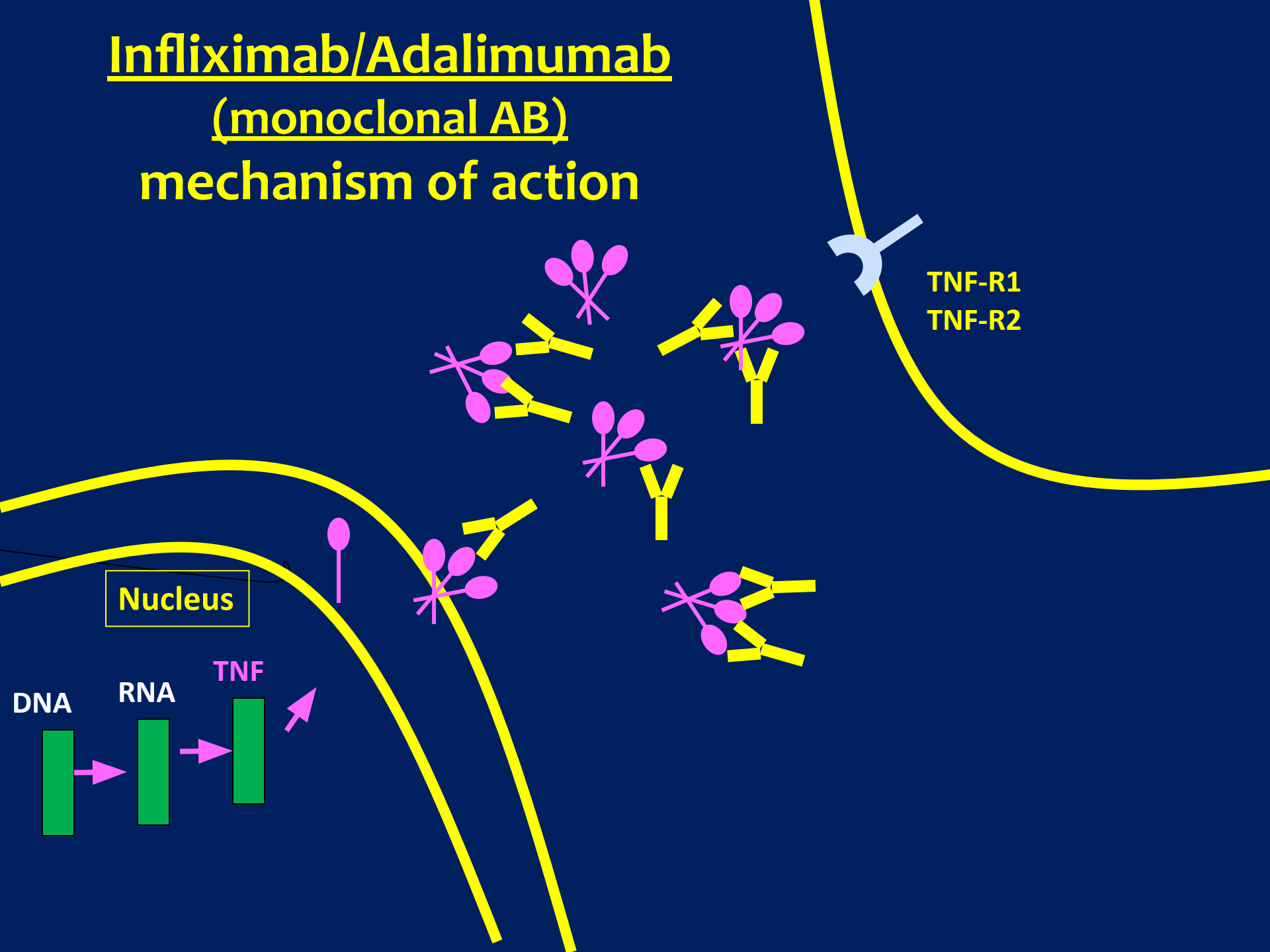
Human fusion protein

Human constant region like protein

Key Actions Attributed to TNF α

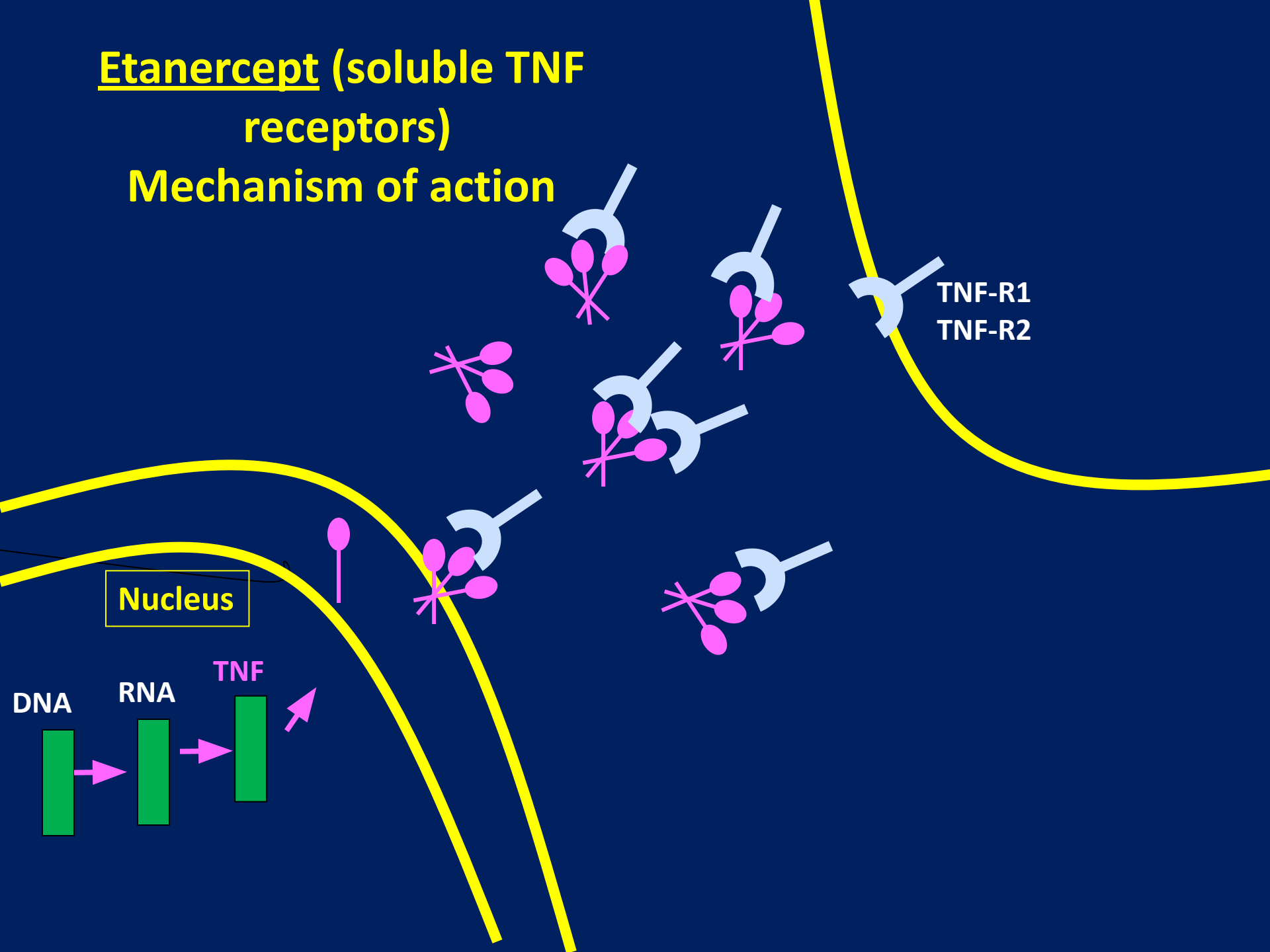


Infliximab/Adalimumab (monoclonal AB) mechanism of action



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 proinflammatory cytokines



- Antigen presentation



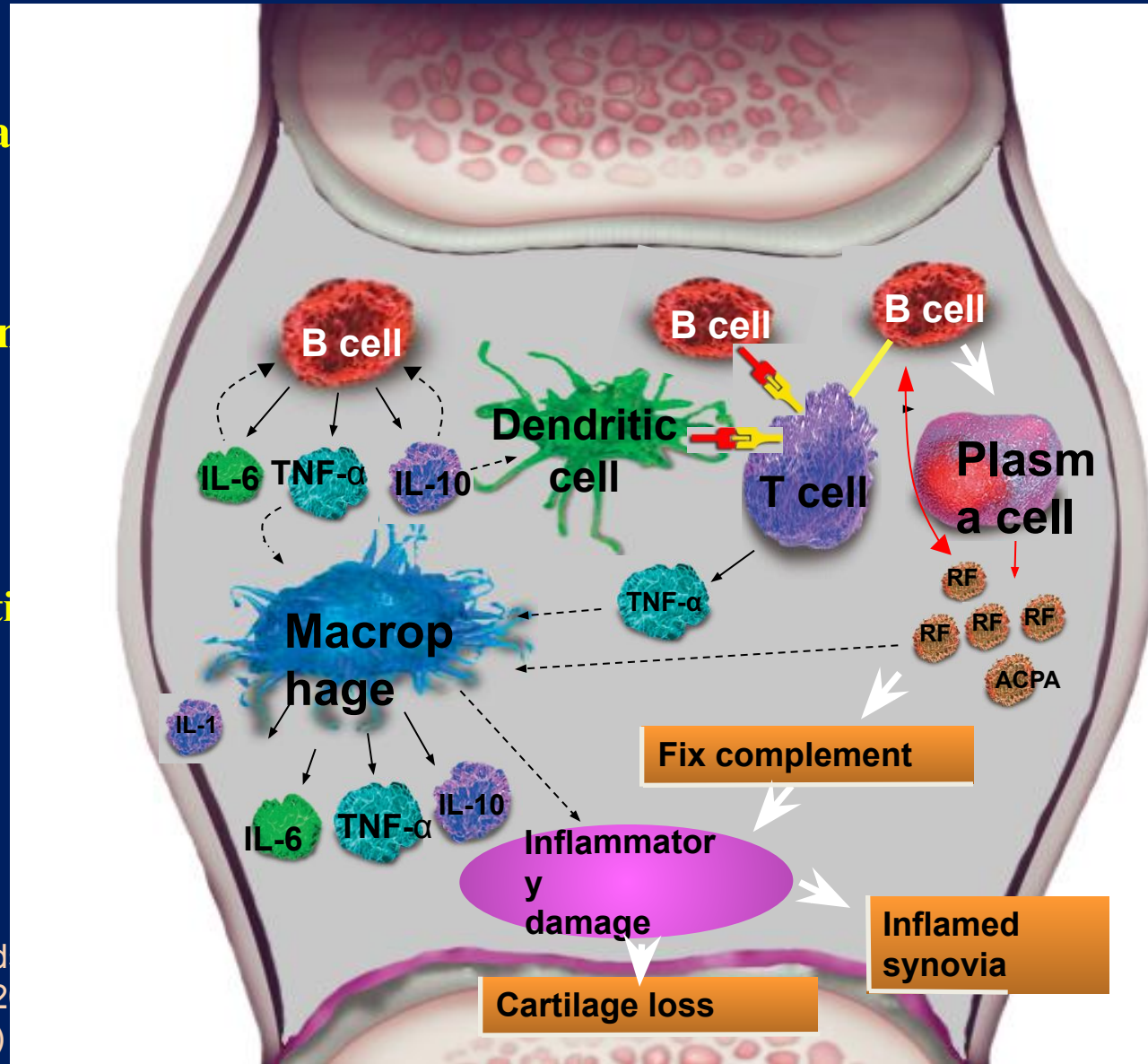
- T-cell activation



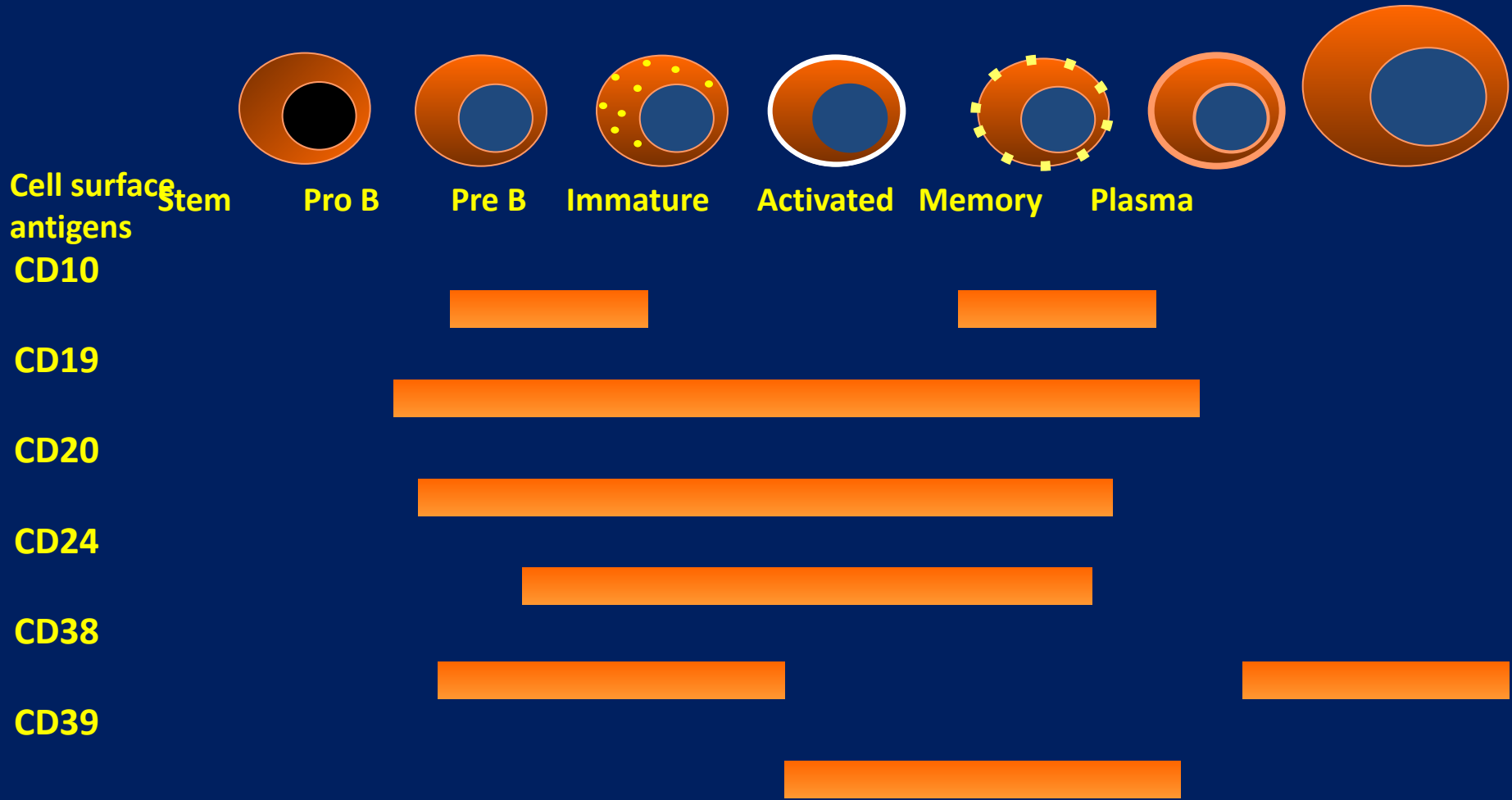
- Autoantibody production and self-perpetuation



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

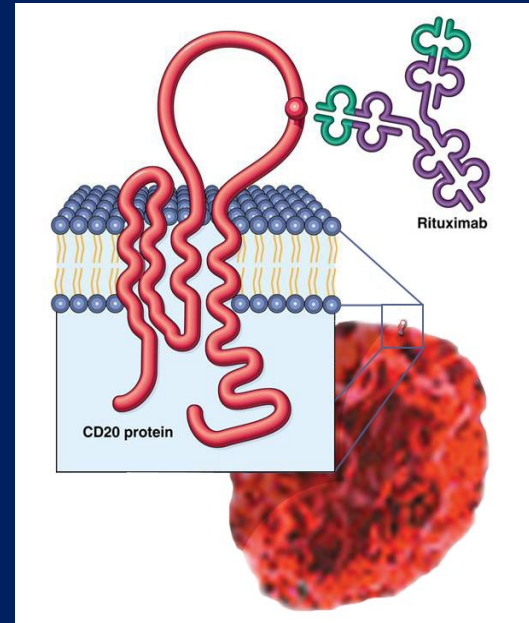


Steps in the Maturation of B Cells



Rituximab

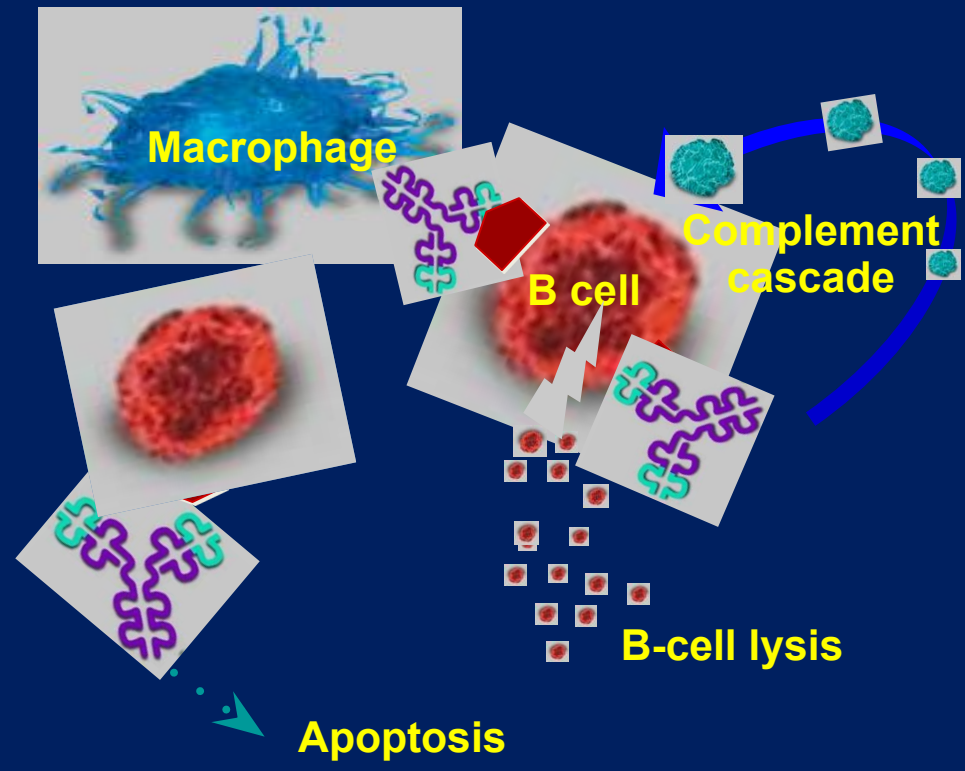
- Rituximab is a genetically engineered anti-CD20 therapeutic monoclonal antibody that *selectively* depletes CD20+ B cells



- 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

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



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)

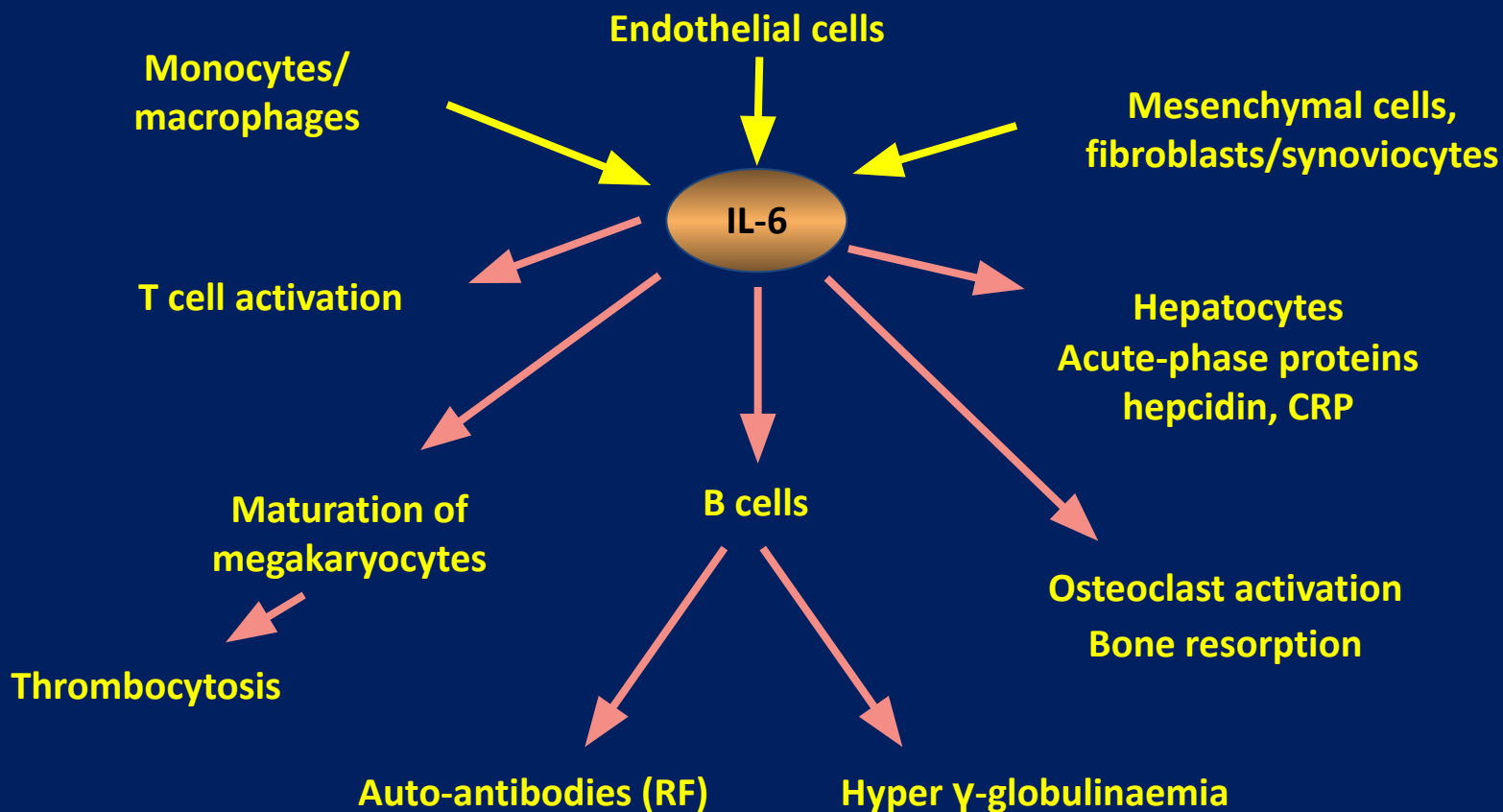
	MTX (n=40)	Rituximab (n=40)	Rituximab + CTX (n=41)	Rituximab + MTX (n=40)
All events*	85	88	85	85
RA exacerbation	55	40	37	18
Hypotension**	18	30	29	18
Hypertension**	15	18	7	25
Nasopharyngitis	15	10	7	15
Arthralgia	8	8	5	13
Back pain	8	13	7	3
Hyperglycaemia	10	5	7	8
Cough	—	15	5	8
Flushing	8	13	5	3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

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

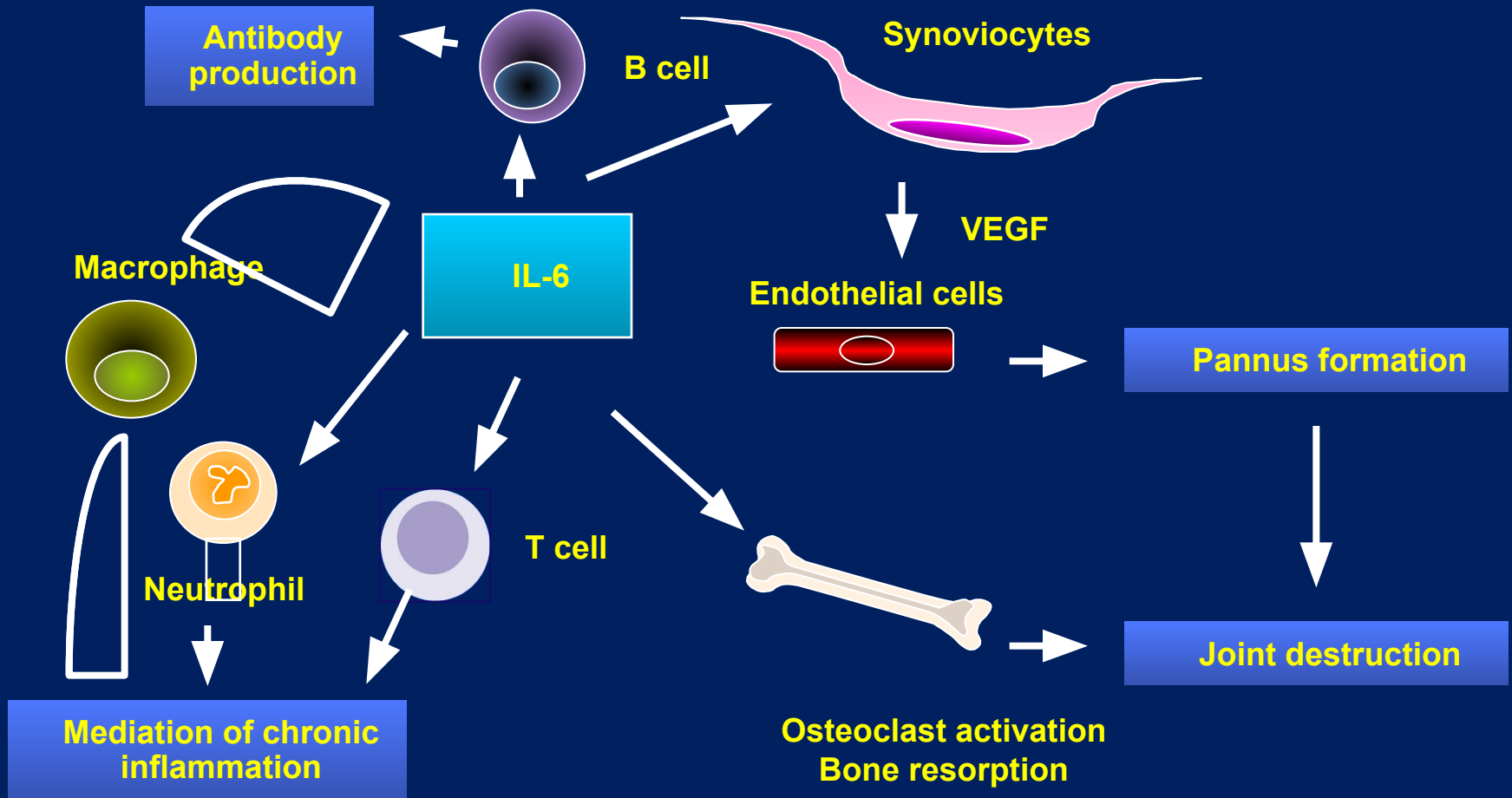
*% of patients reporting an event

**Hypo/hypertension defined as >30 mmHg change in diastolic or systolic blood pressure

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



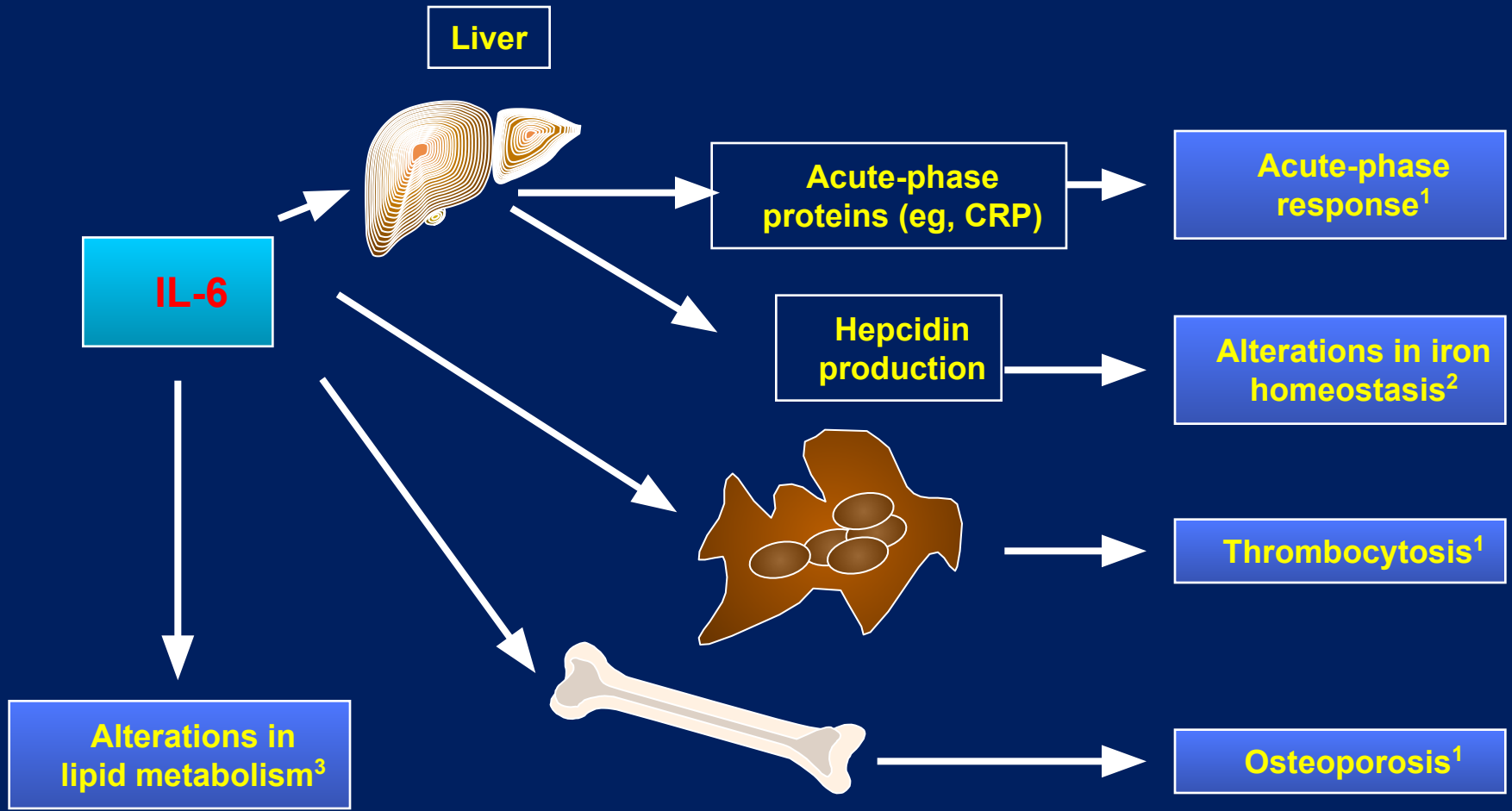
Articular effects of IL-6 in RA^{1,2}



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



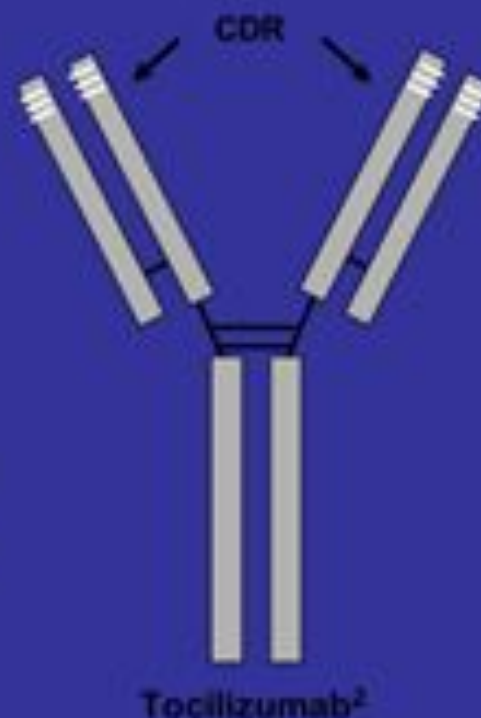
1. Choy E. *Rheum Dis Clin North Am.* 2004;30:405-415;

2. McGrath H et al. *Rheumatology.* 2004; 43:1323-1325;

3. Al-Khalili L et al. *Mol Endocrinol.* 2006; 20:3364-3375.

Tocilizumab

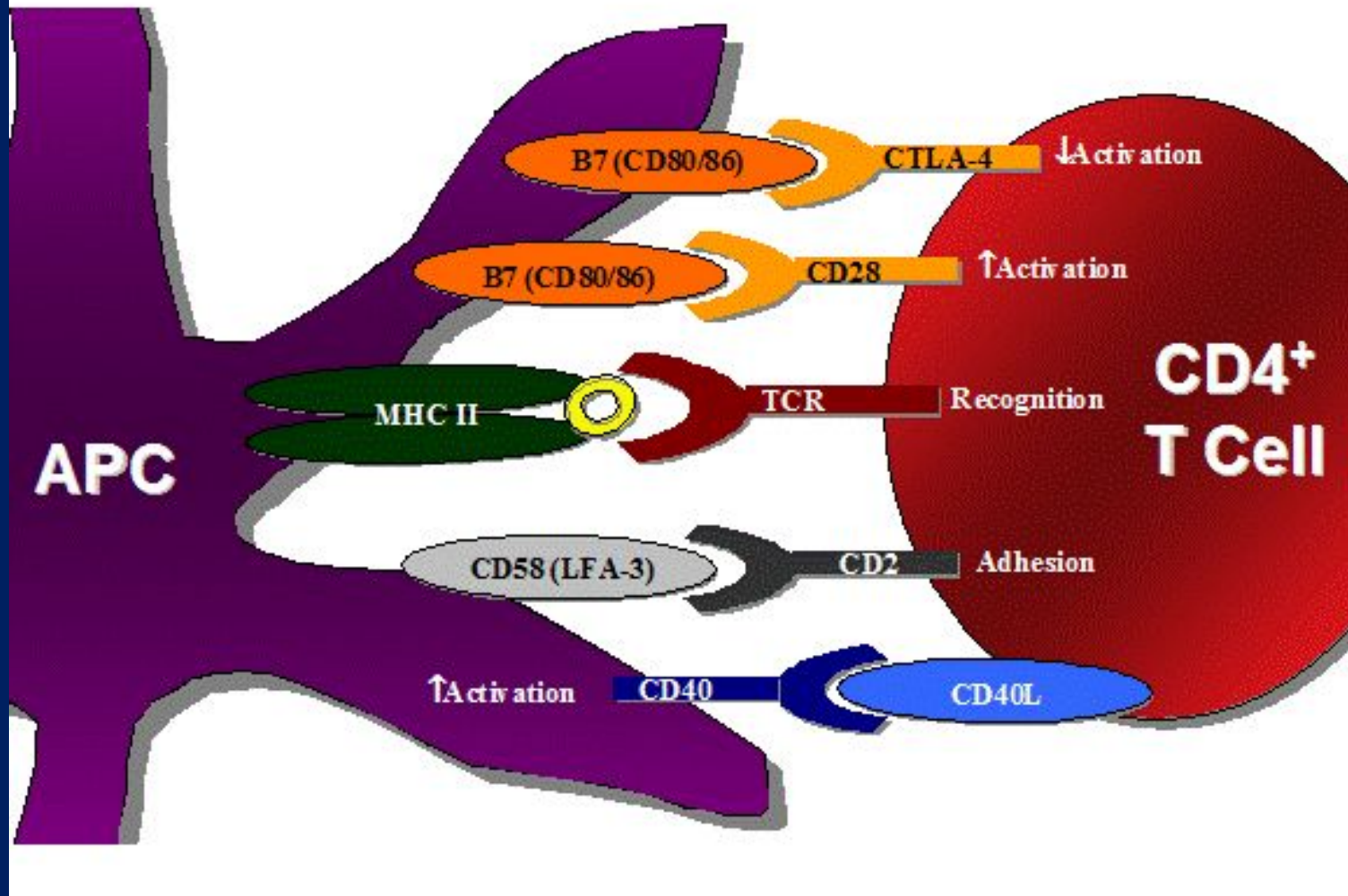
- Humanized monoclonal antibody¹
- Binds to membrane-expressed and soluble forms of IL-6R¹
- Blocks IL-6 binding to its receptor¹
- Inhibits IL-6R mediated signaling¹



CDR, complementarity-determining region.

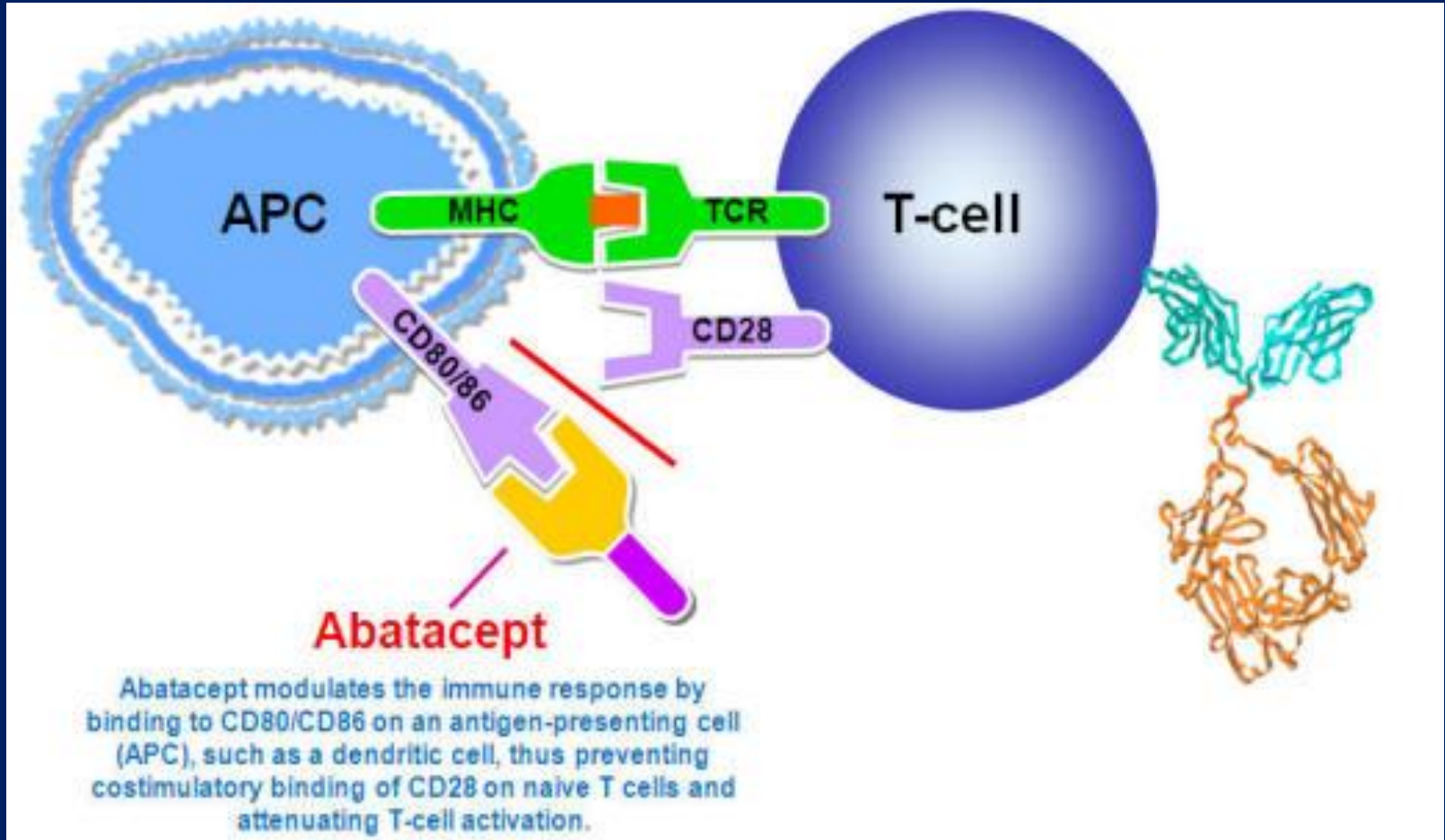
1. Smolen JS et al. *Arthritis Res Ther*. 2006;8(suppl 2):S5.
2. Roche-generated image. P-MOA-ND-001.

APC and T cell Interactions



ABATACEPT / ORENCIA

Costimulation blockade in RA

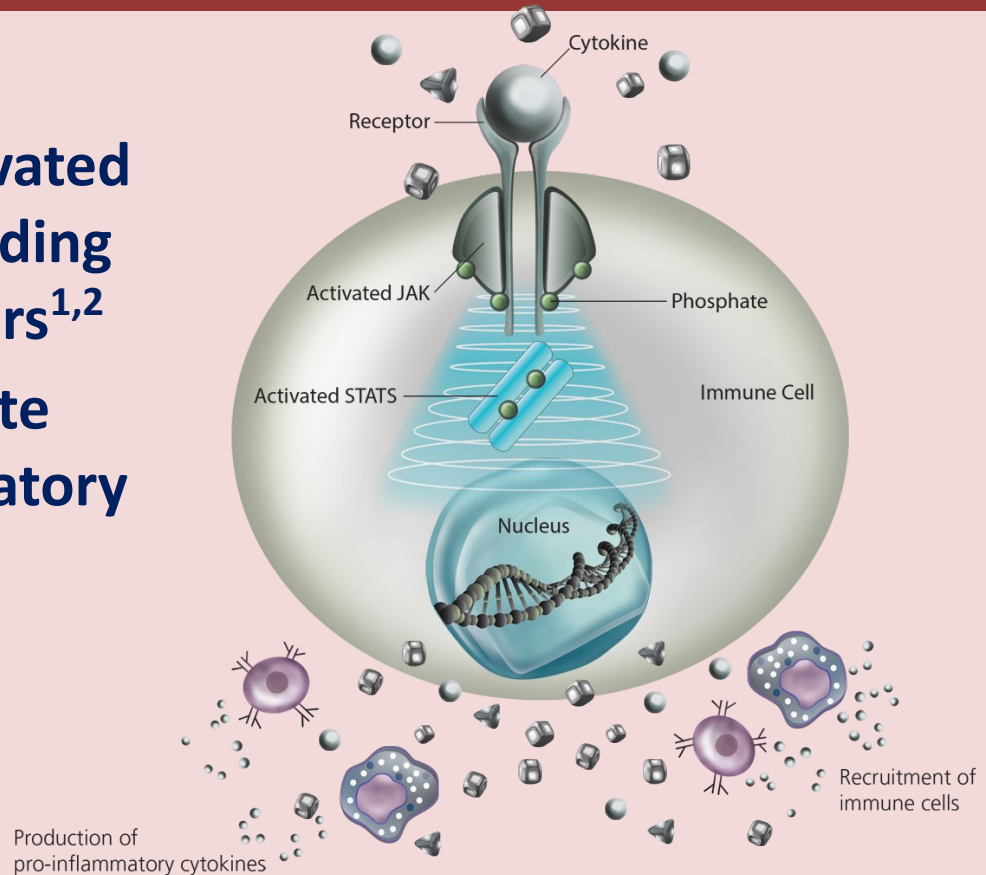


XELJANZ (Tofacitinib): a new class of oral RA therapy that targets inflammation from inside the cell

- 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 responses¹



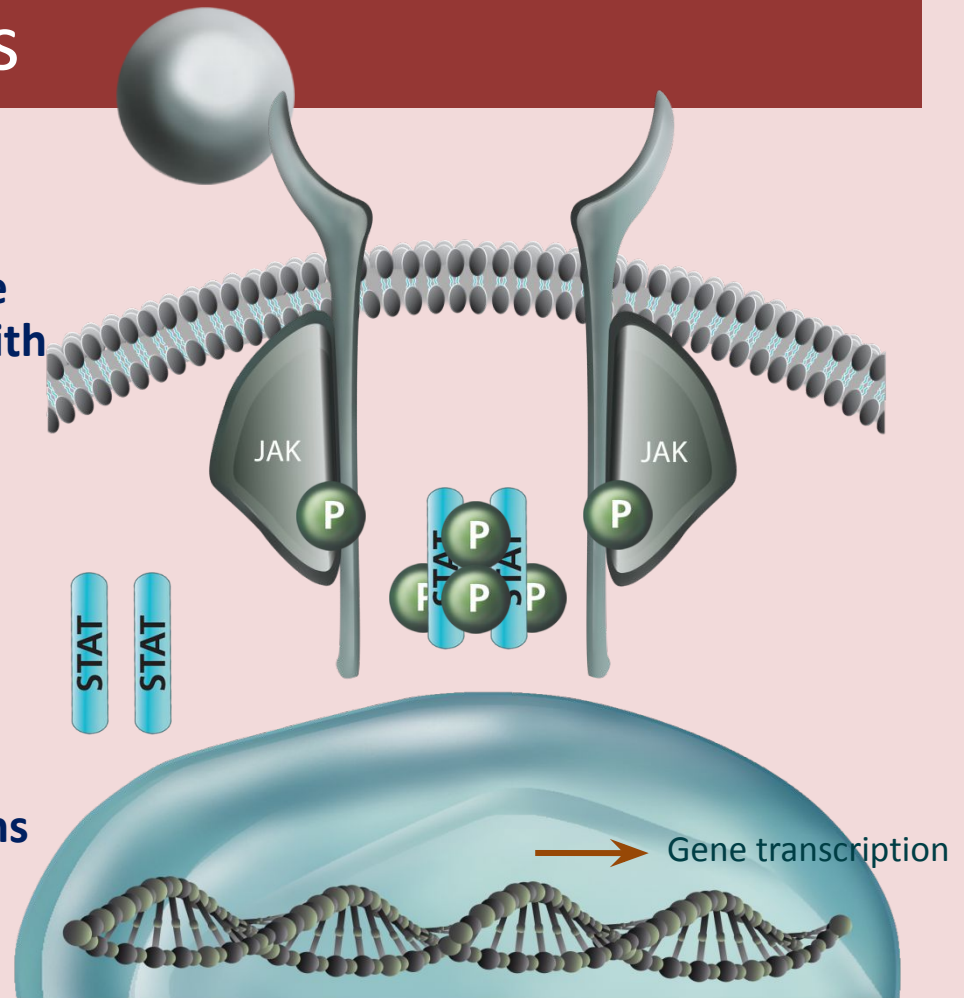
JAKs play a central role in immune and inflammatory responses

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

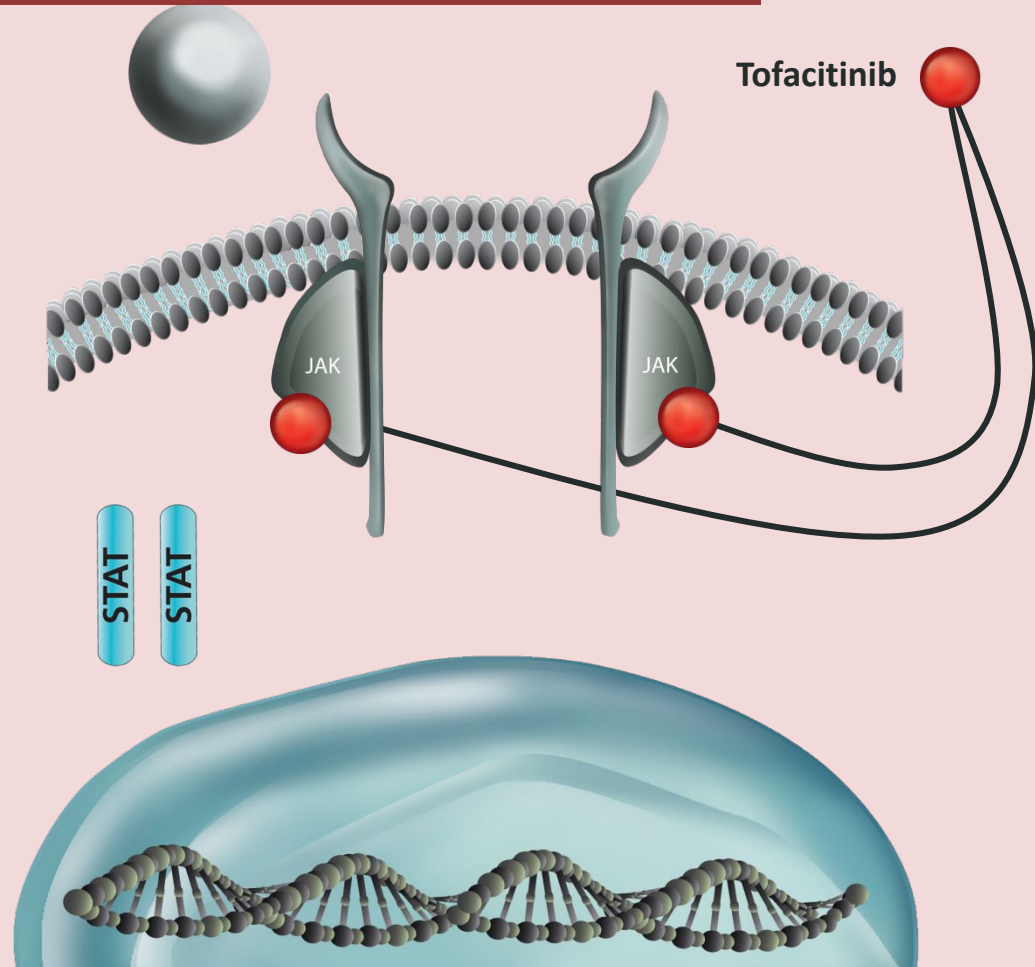
Tofacitinib targets JAK intracellular signalling pathways

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

2 Cytokine binding to its cell surface receptor leads to receptor polymerisation¹

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



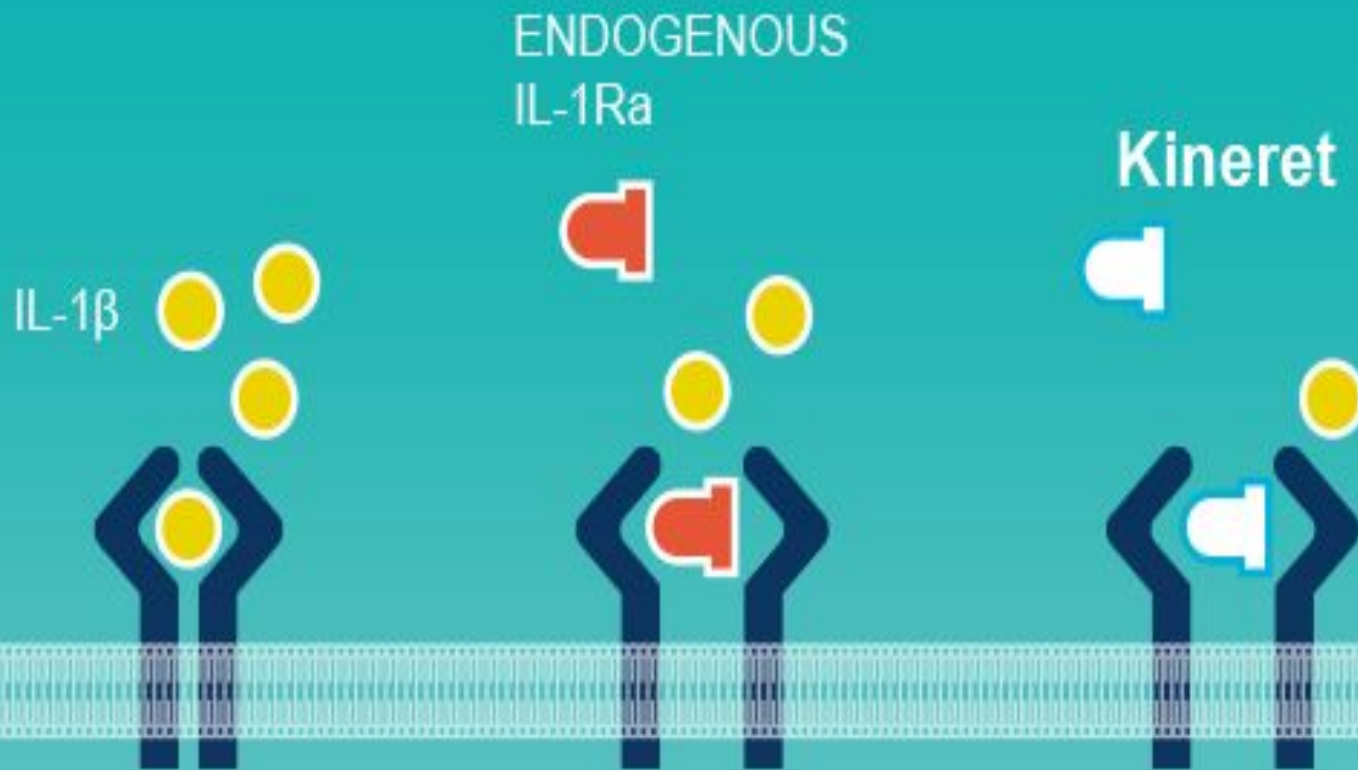
Tofacitinib blocks the JAK signalling pathway at the point of JAK phosphorylation

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

2. Jiang JK, et al. *J Med Chem*. 2008;51:8012–8018.

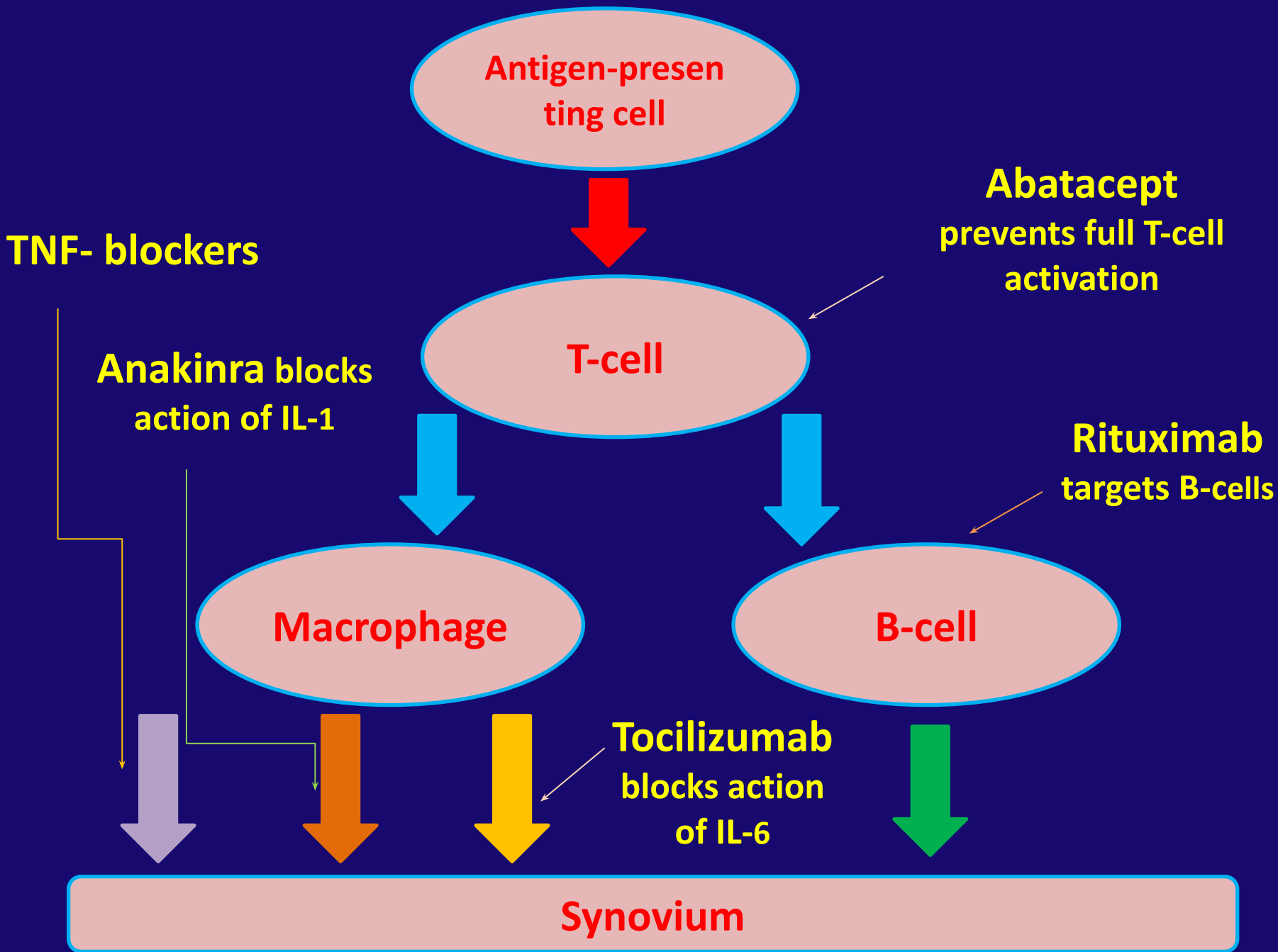
ANAKINRA – recombinant form of IL-1 receptor antagonist

KINERET BLOCKING THE BIOLOGIC ACTIVITY OF IL-1
BY COMPETITIVELY INHIBITING IL-1 BINDING¹



Anakinra indications

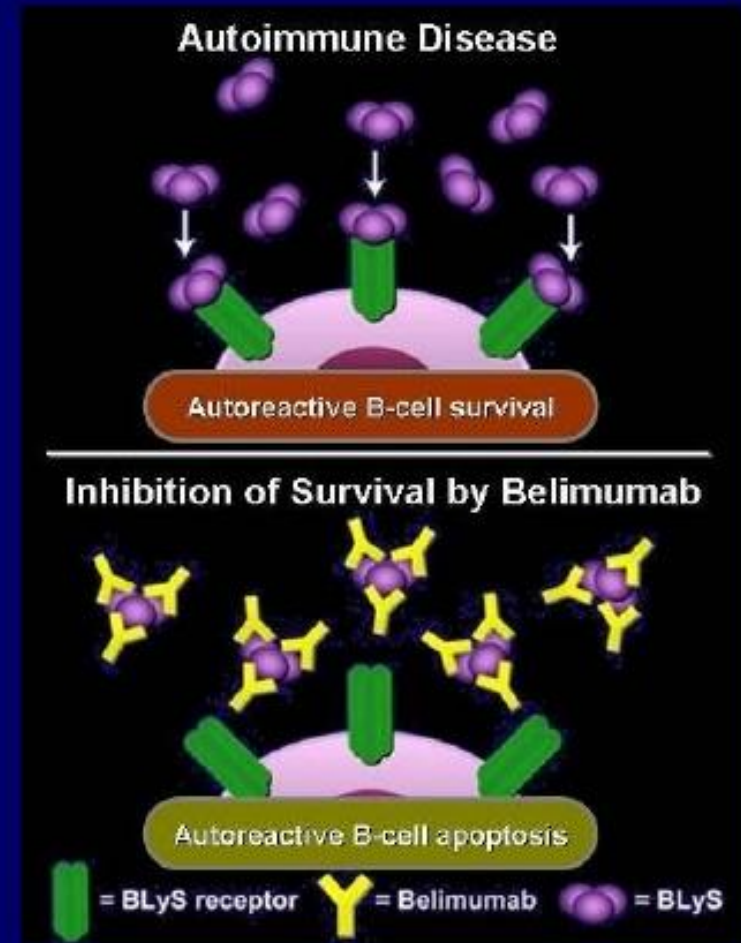
- Auto-inflammatory syndromes, periodic fevers
- Systemic onset juvenile inflammatory arthritis
- Adult-onset Still's disease
- Familial Mediterranean Fever/ Amyloidosis
- (limited use for the treatment of RA)



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)

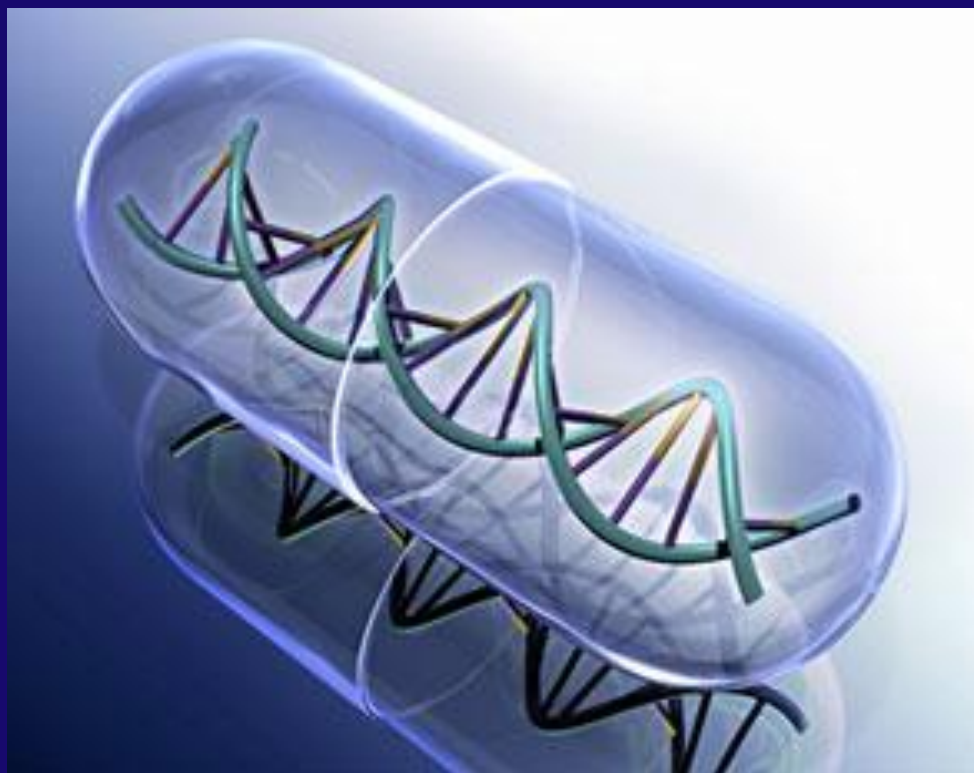
Tuberculosis screening

- 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.



תודה על הקשבה