Immunopharmacology

Attila Megyeri

10 April 2019

Drugs discussed in immunopharmacology

- **drugs acting at the immune system**
  - **designed specifically to**
    - **suppress**
    - stimulate / **modulate**
- both suppression and modulation can **range from**
  - **aspecific** – all antigens / all response **to**
    - e.g. immunosuppressive drugs
  - **specific** – a single antigen
    - e.g. Rh0D immunoglobulin
    - e.g. vaccination

in between: partial specificity

Drugs related to immunopharmacology

- several drugs can exert immune reactions
  - undesired immunological reactions
    - hypersensitivity = allergy
- drugs can influence consequences of immune reactions (inflammation)
  - e.g. antihistamines (H_1 blockers), corticosteroids, NSAIDs
- drugs produced by immunological tools
  - (mostly monoclonal) antibodies – see biological therapy
  - not to influence the immune system but to treat other diseases – e.g. cancer etc.

Immunosuppression

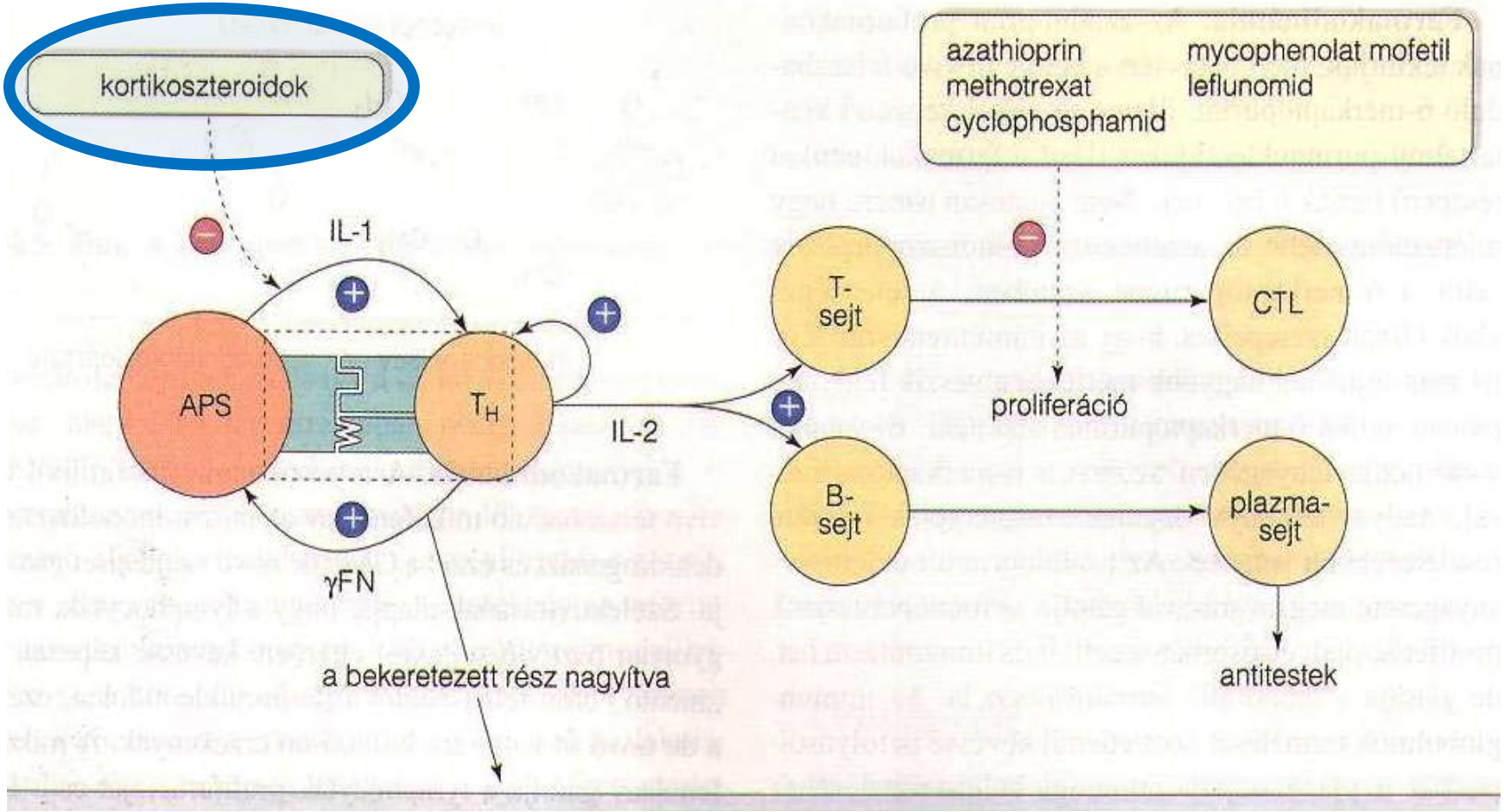
- transplantation
  - **prevention** and **treatment** of graft-**rejection**
  - **graft versus host disease**
- autoimmune diseases
  - rheumatoid arthritis
  - Sjogren's syndrome
  - psoriasis
  - systemic lupus erythematous (SLE)
  - multiple sclerosis (MS)

Classification of immunosuppressive drugs

- glucocorticoids
- calcineurin inhibitors
- antiproliferative agents and antimetabolites
  - antimetabolites
  - alkylating agents
  - mTOR inhibitors
- antibodies and fusion proteins
  - immunosuppressive Abs
  - anti-cytokines

biological therapies

Glucocorticoids



Mechanism of action of glucocorticoids

- bind to intracellular receptors
- ↓ transcription of certain cytokine-genes
  - IL-1, IL-2, IL-6, IFNα, TNFα
- ↓ communication among cells of the immune system
- ↓ **primarily** – but not exclusively – the **cellular immunity**
- ↓ chemotaxis of phagocytic / inflammatory cells
- ↓ bactericidal and fungicidal effects of phagocytes

Therapeutic use of glucocorticoids

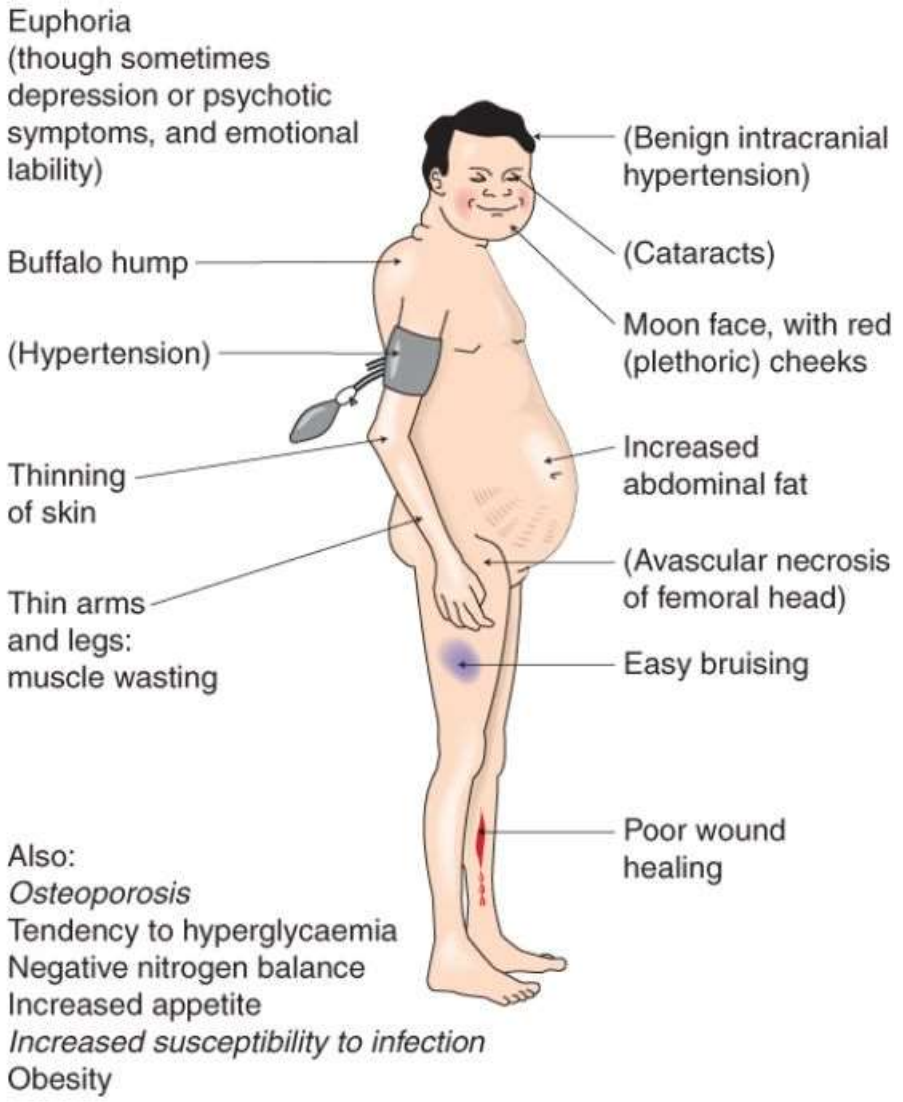
- alone or in **combination**

- transplant rejection / GVHD
  - also ↓ first-dose cytokine storm
- autoimmune disorders
- asthma / allergic disorders
- inflammatory bowel diseases

- prednisone → **prednisolone**
- methylprednisolone

Toxicities of glucocorticoids

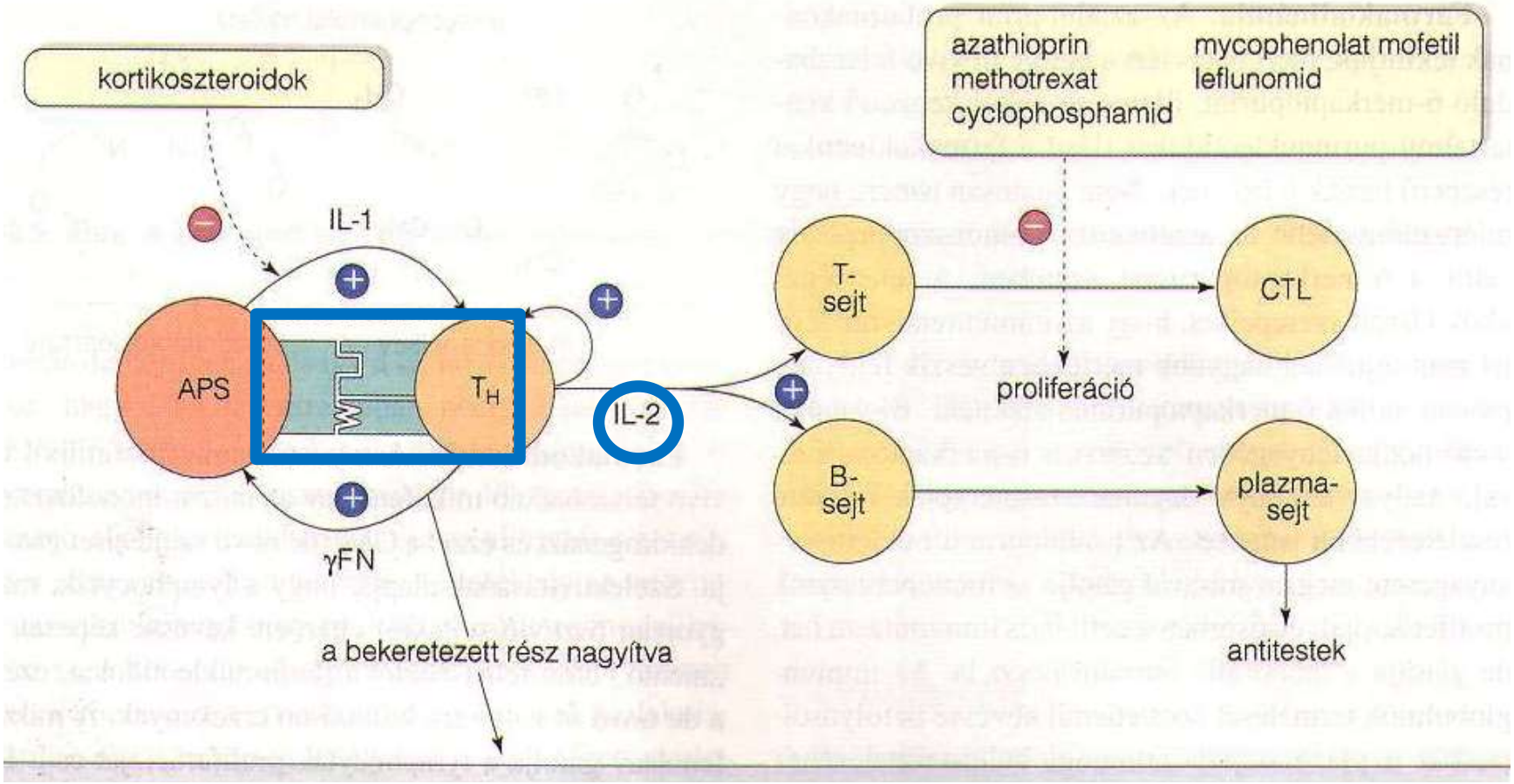
- long term use → serious adverse effects
- trend: reduced doses / rapid withdrawal
  - due to combination therapy



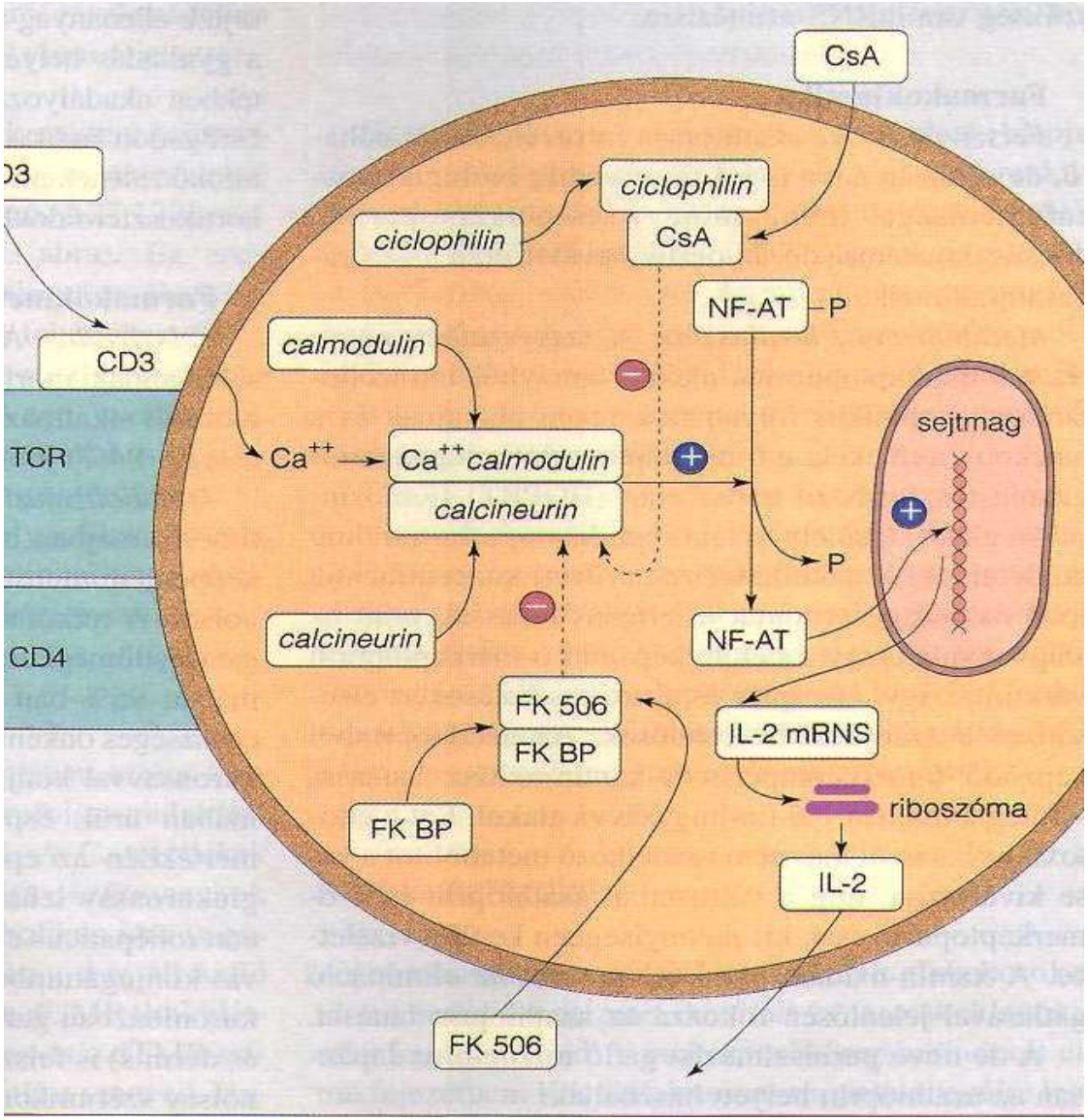
Calcineurin inhibitors

- cyclosporine (cyclosporin A)
- tacrolimus (FK506)
- pimecrolimus (topical treatment only)

Mechanism of action



Inhibition of phosphatase-activity of calcineurin



CsA = cyclosporine

FK506 = tacrolimus

FKBP = FK-binding protein

TCR = T-cell receptor

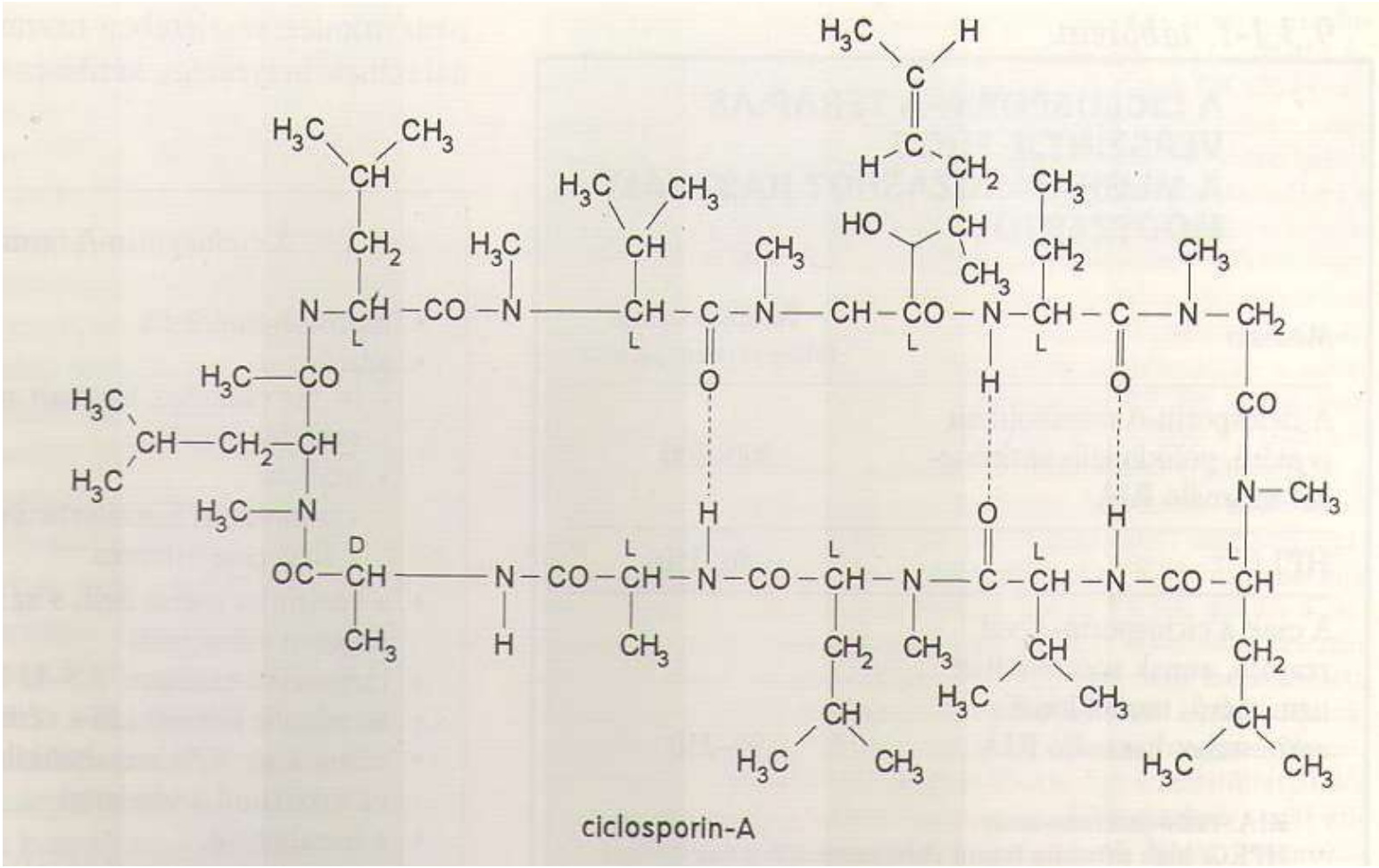
NF-AT = *Nuclear Factor of Activated T-cells*

Cyclosporine

- **produced by fungus**
  - *Tolypocladium inflatum (Beauveria nivea, Hypocladium inflatum gams)*
  - isolated from Norwegian soil in 1970
  - clinical introduction in 1983
- was No. 1 drug-promoter of allogenic transplantation
  - now tacrolimus is preferred

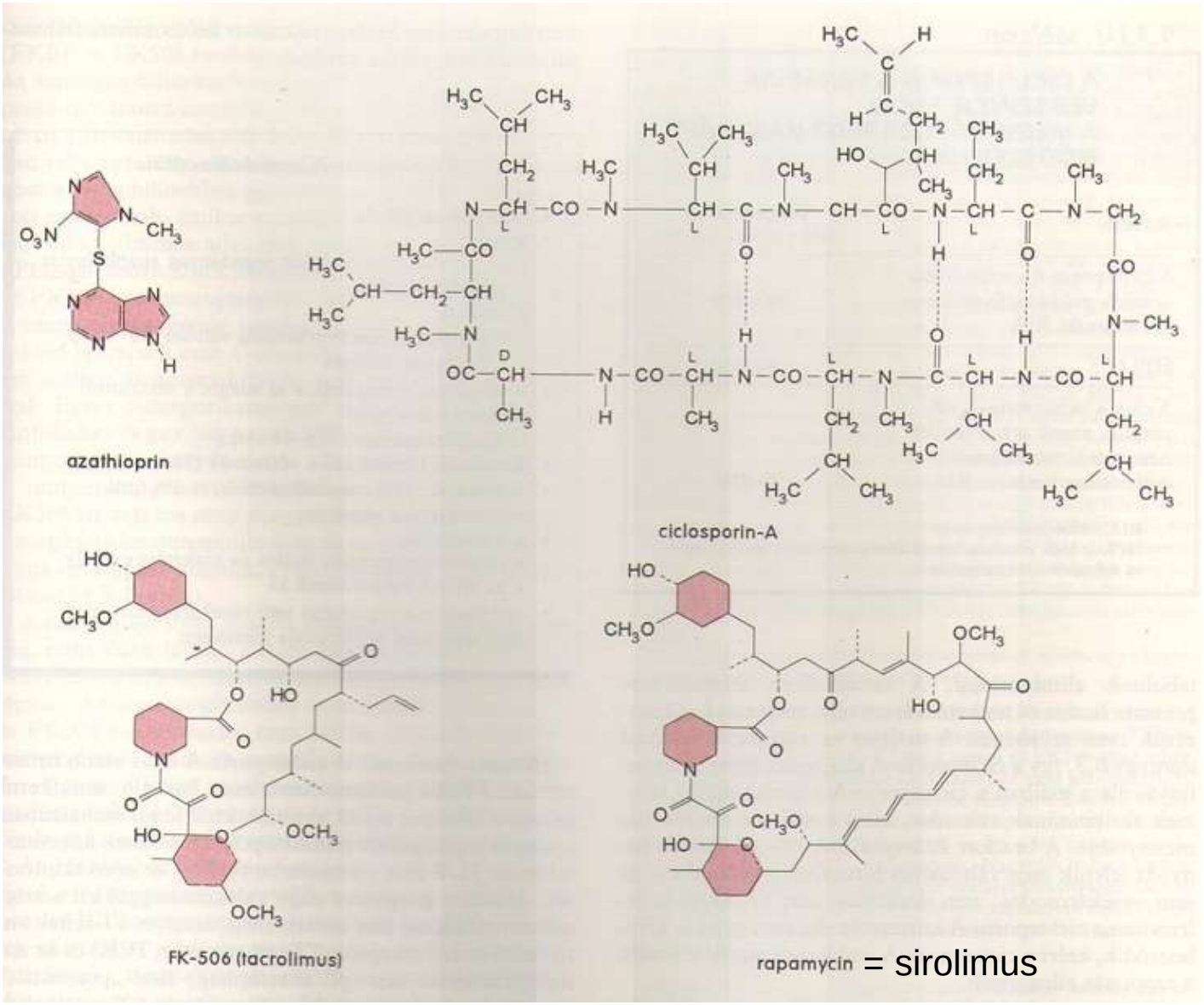
- inhibits the **cellular immunity**
- does **NOT** damage the **bone marrow**
- **nephrotoxic** effects

Cyclosporine



cyclic peptide (11 amino acids, 7 of which is N-methylated)
lipophilic / hydrophobic (molecular weight: 1203 Da)

Chemical structure of immunosuppressants



Pharmacokinetics of cyclosporine 1.

- hydrophobic, lipophilic
- routes of administration
  - i.v. (vehicle: Cremophor EL may cause hypersensitivity)
  - oral (Neoral – microemulsion + others / not interchangeable)
- variable oral bioavailability (20-50%)
- significant and variable first pass effect
- variable V_d (≈ 3,5-13 L/kgBwt)
- elimination
  - 99% metabolized primarily in liver
  - <1% unchanged in the urine

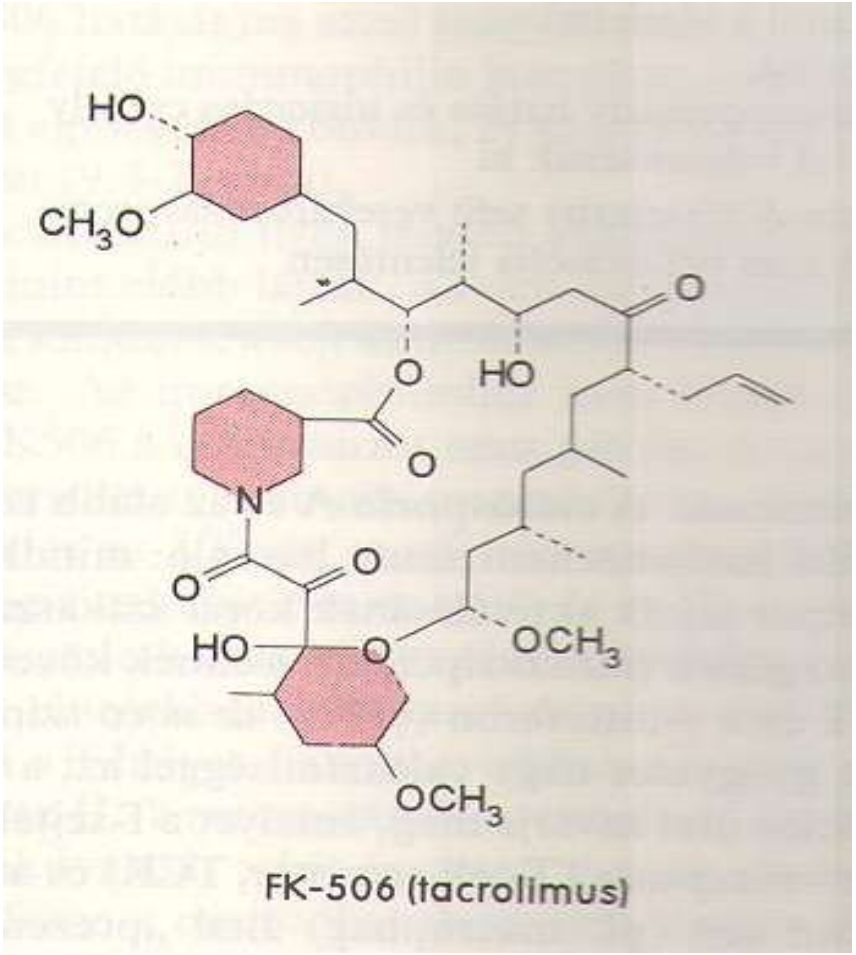
Pharmacokinetics of cyclosporine 2.

- metabolites
  - no significant immunosuppressive or toxic effects
- excreted primarily into **bile**
  - also excreted into breast milk (breast feeding is not recommended)
- terminal half-life in the blood: 19 hours (10-27 h)
- whole blood-levels must be monitored
  - temperature dependent distribution in blood
  - adjust dose individually
- blood-levels are NOT influenced by hemodialysis or kidney-damage

Cyclosporine

- therapeutic use
  - prophylaxis of solid-organ allograft rejection
    - in combination
  - autoimmune (e.g. rheumatoid arthritis, psoriasis)
    - not first line
- adverse effects
  - **nephrotoxicity**
  - hypertension
  - tremor, hirsutism, hyperlipidemia, gingival hyperplasia

tacrolimus (FK506)



FK-506 (tacrolimus)

- produced by a fungus (*Streptomyces tsukubaensis)*
- macrolide
- MolWt: 804 Da
- highly lipophilic

tacrolimus (FK506)

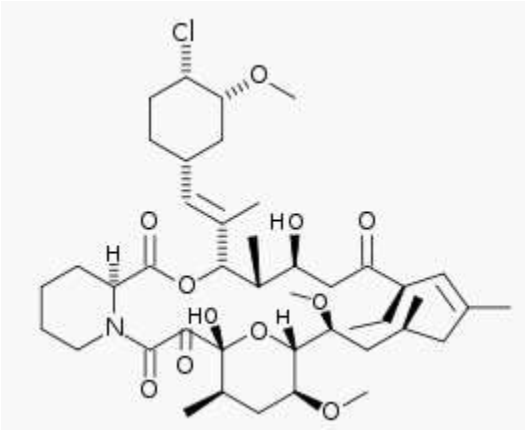
- more potent and slightly more effective
  - than cyclosporine
- pharmacokinetics
  - i.v. / oral – variable absorption
  - cP450 metabolism (98%) in liver
  - **biliary excretion**
    - also excreted into breast milk (breast feeding is not recommended)
  - variable half-life
    - in liver transplanted patients: 4.5-33 hours
  - individualized dosing
    - temperature dependent distribution in blood
    - somewhat easier blood level monitoring

tacrolimus (FK506)

- therapeutic use
  - prophylaxis of solid-organ allograft rejection
  - rescue therapy for cyclosporine
- adverse effects
  - **nephrotoxicity**
  - **hyperglycemia** and diabetes
    - new onset diabetes is more frequent than cyclosporine
  - neurotoxicity, GI symptoms, hypertension, hyperkalemia

pimecrolimus

- topically in atopic dermatitis
- macrolactam
- mechanism: same as cyclosporine/tacrolimus
  - binds to macrophilin-12
- suspicious for carcinogenicity
  - topical tacrolimus is similar



Antiproliferative agents

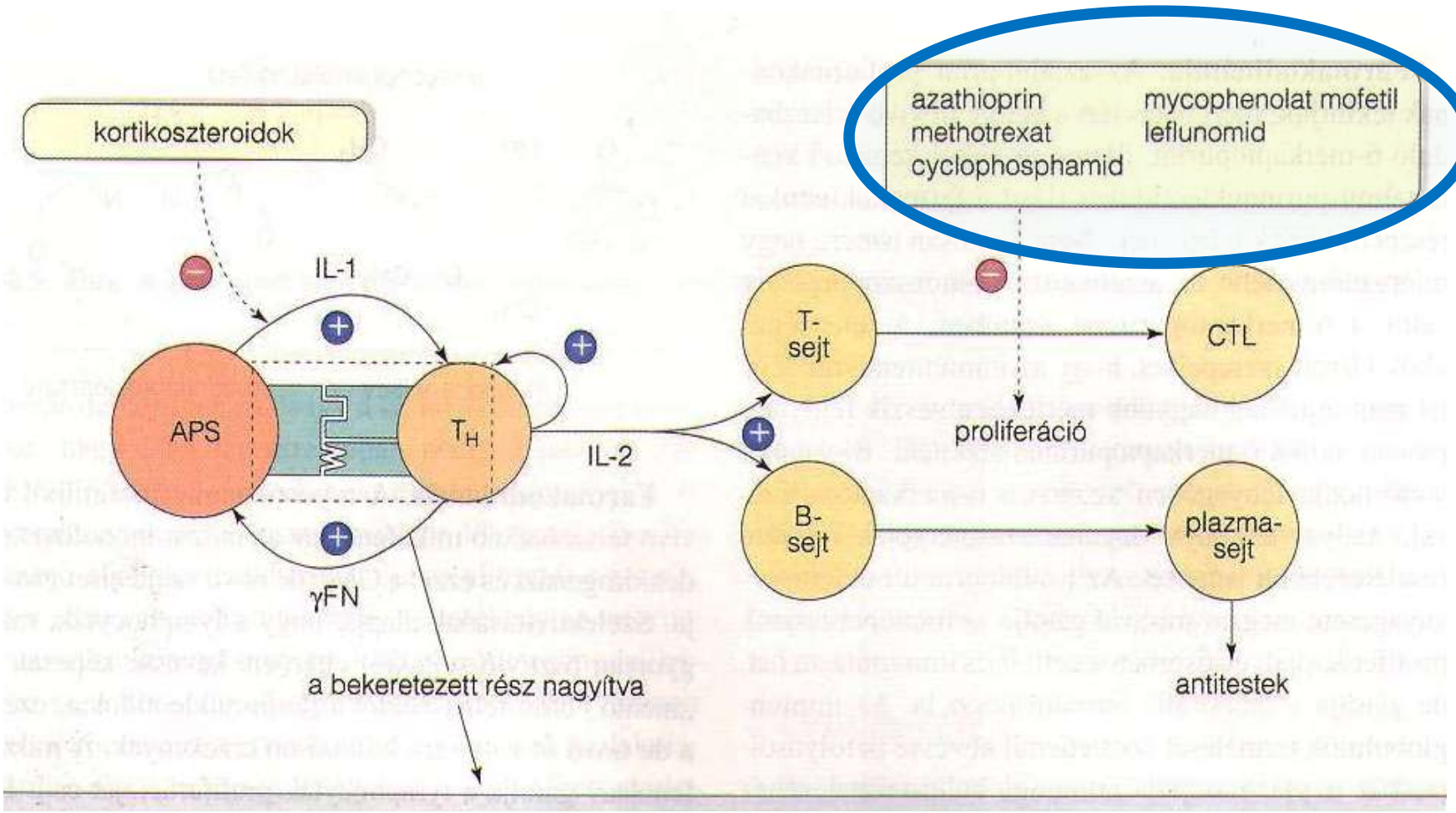
- cytotoxic agents
  - antimetabolites – e.g. azathioprine
  - alkylating agents – e.g. cyclophosphamide
- mTOR inhibitors – e.g. sirolimus (= rapamycin)

Cytotoxic agents

anticancer drugs: identity, similarity, difference

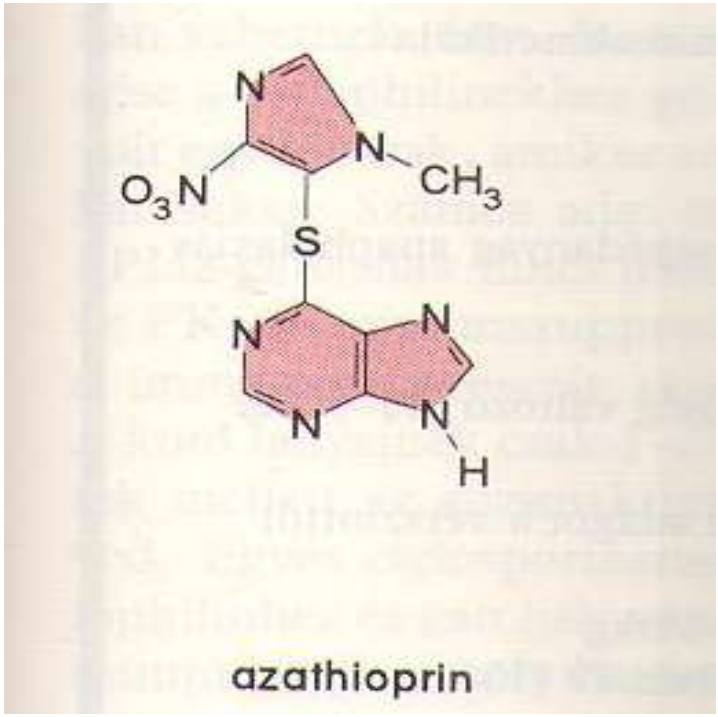
- **antimetabolites**
  - **purine** antimetabolites
    - **azathioprine → 6-mercaptopurine**
    - **mycophenolate mofetil**
  - **pyrimidine** antimetabolites
    - **leflunomide**
  - **folic-acid** antagonists
    - **methotrexate**
- **alkylating agents**
  - **cyclophosphamide**

Mechanism of action



selectivity ← application during the primary immune response

purine-antimetabolite: azathioprine



azathioprine → 6-mercaptopurine

intracellular activation

HGPRT: 6-MP → thioinosinic-acid

→ mercaptopurine containing nucleotides

(effect ~ tissue concentration)

indication: allogenic transplantation / autoimmune (SLE / RA / MS)

Why is it better for immunosuppression?

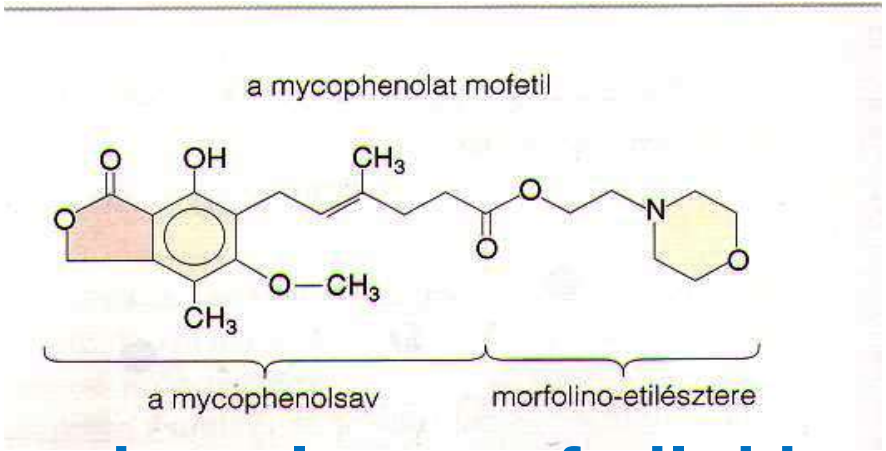
better distribution to immune cells ??

better conversion to 6-MP ??

catabolism – xanthine oxidase: 6-MP → 6-thiouric acid / **interaction with allopurinol**

✓hematolological toxicity
✓mutagenic potential
✓increased risk of malignant tumors

purine-antimetabolite: mycophenolate



mycophenolate-mofetil: kinetics

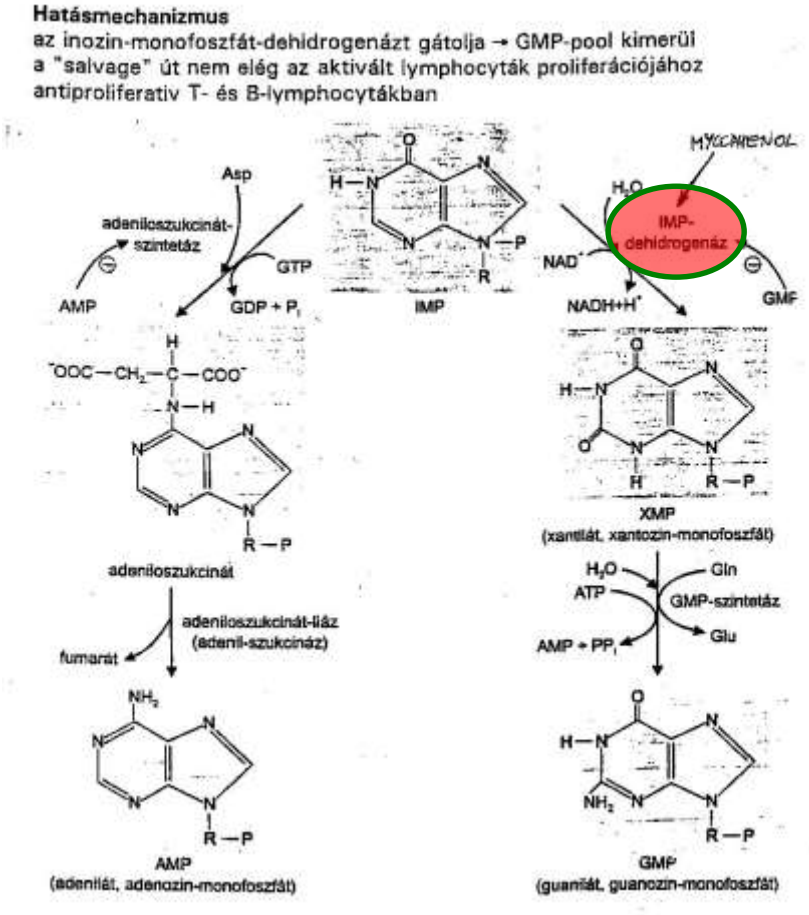
prodrug → liver: hydrolysis → active metabolite

mycophenolate-mofetil → *first-pass* effect → mycophenolic acid

elimination: conjugation with glucuronic acid → excretion (90% urinary)

hemodialysis does NOT remove it

mycophenolic acid inhibits the *de novo* synthesis of GMP

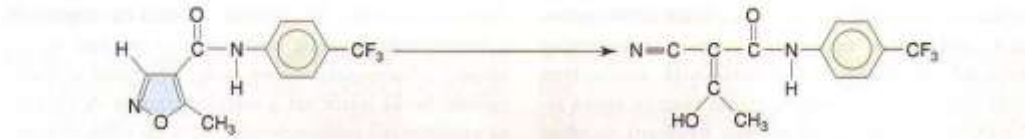


- inhibits inosine-monophosphate-dehydrogenase
- *de novo* synthesis of GMP is inhibited
- GMP-pool is not sufficient
- **selectivity**: the *salvage pathway* is NOT enough for proliferation of activated B- and T-lymphocytes

Clinical use of mycophenolic acid

- prevention and treatment of the rejection of **allogenic transplants** (kidney, liver, heart)
  - in combination with corticosteroids and cyclosporine
- side-effects
  - mainly gastrointestinal
  - leukopenia
  - teratogenicity (pregnancy category D)
- **NO significant renal toxicity**

pyrimidine-antimetab.: leflunomide



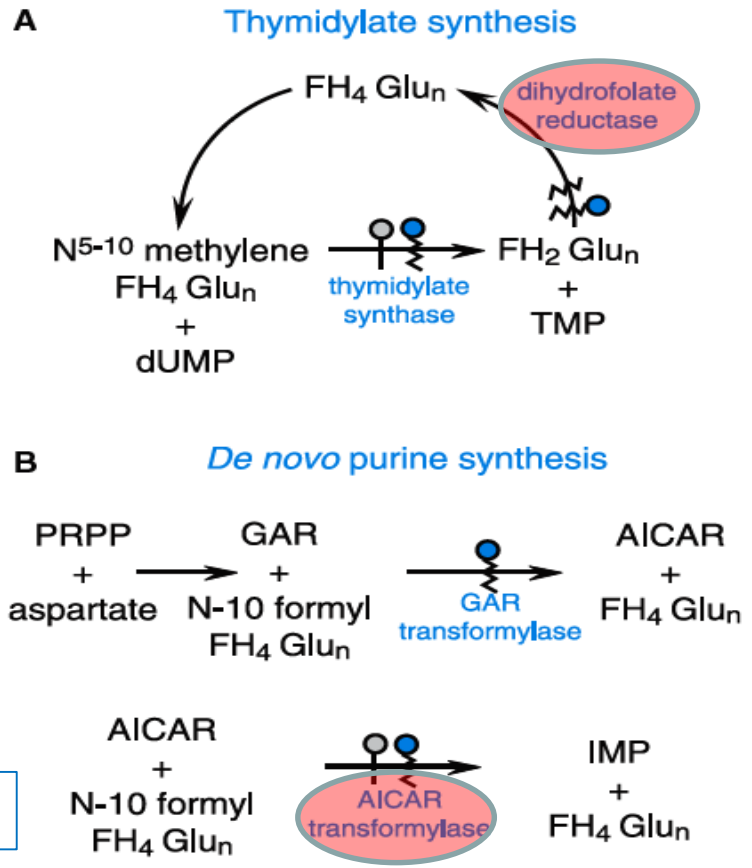
59.2. ábra. A leflunomid és a belőle az izoxazolgyűrű felnyílásával kialakuló aktív metabolit(A77.1726) szerkezete

- the **active metabolite of leflunomide** inhibits dihydro-orotate-dehydrogenase
- thereby the *de novo* synthesis of pyrimidines
- indication: **rheumatoid arthritis**, disease-modifying agent

- administration: oral
- half-life ≈ **14 days**
- **enterohepatic circulation**
- may be reduced by oral activated charcoal or *cholestyramine*
- long time to reach C_{ss}
  - loading dose
  - maintenance dose
- **teratogenic: pregnancy category=X**
- **may cause severe liver toxicity**

Methotrexate: mechanism of action

proliferation ↓



additional immuno↓

FIGURE 51–4 *Sites of action of methotrexate and its polyglutamates.* AICAR, aminoimidazole carboxamide; TMP, thymidine monophosphate; dUMP, deoxyuridine monophosphate; FH_2Glu_n, dihydrofolate polyglutamate; FH_4Glu_n, tetrahydrofolate polyglutamate; GAR, glycinamide ribonucleotide; IMP, inosine monophosphate; PRPP, 5-phosphoribosyl-1-pyrophosphate.

AICAR transformylase↓ → AICAR↑ → blocked ADA → adenosine↑ → RR block → proliferation↓

Methotrexate: clinical use

- **non-neoplastic**
  - low dose (a few mg weekly)
  - **rheumatoid arthritis**
  - severe psoriasis
  - transplantation (e.g. graft-versus-host disease)
  - Crohn's disease
- **neoplastic**
  - high dose (up to 5-7.5 g/m^2 in induction)
    - **with leucovorin rescue**
  - ALL
  - choriocarcinoma
  - non-Hodgkin lymphomas
  - other: e.g. breast, head and neck, ovary, bladder

Methotrexate: adverse effects

- bone marrow
  - hemorrhage / infection
- intestinal epithelium
- hepatotoxicity
  - fibrosis, cirrhosis: with long term, low dose
- renal toxicity
  - with high dose → hydration, alkalization
- teratogenicity

cyclophosphamide: ***prodrug*** → → alkylating bis(chlororethyl)amine-derivative

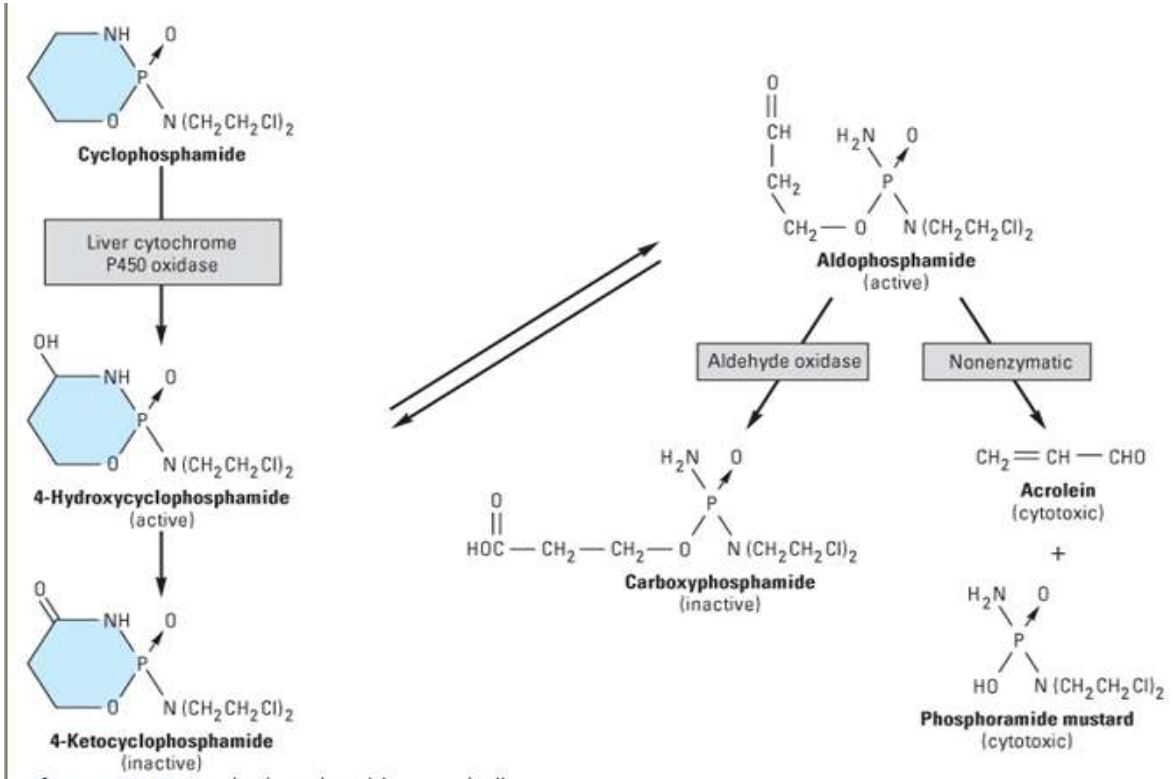


Figure 55-5. Cyclophosphamide metabolism.

for immunosuppresion:

lower dose

but potential late toxicites – leukemia / sterility

Cyclophosphamide: clinical use

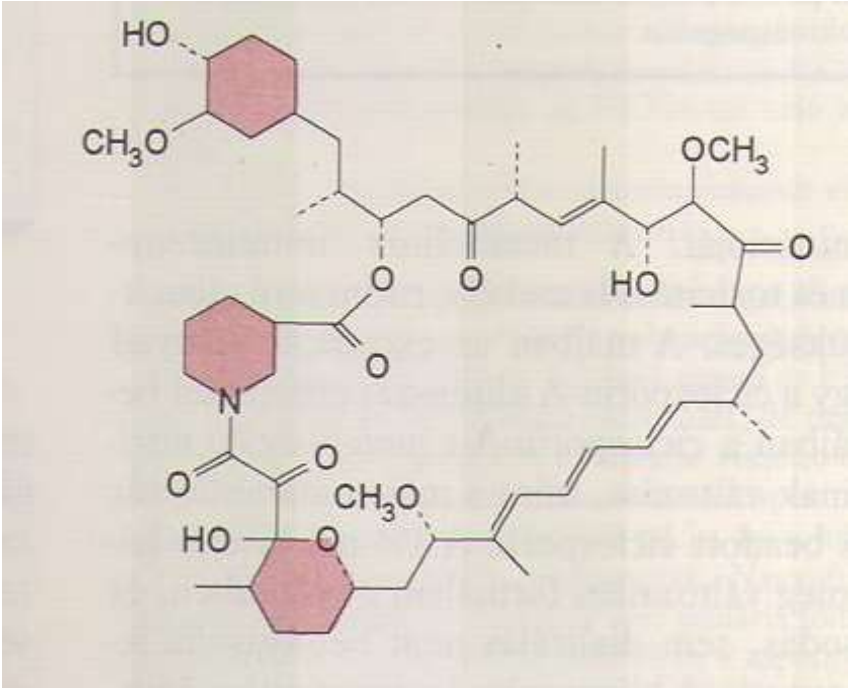
- oral and intravenous
- non-neoplastic
  - autoimmune disorders
    - SLE
    - Wegener's granulomatosis
    - autoimmune hemolytic anemia
    - acquired factor XIII antibodies
- neoplastic
  - breast, ovary
  - non-Hodgkin's lymphoma, CLL
  - soft tissue sarcoma, rhabdomyosarcoma
  - neuroblastoma, Wilms' tumor

Cyclophosphamide: adverse effects

- acute
  - nausea, vomiting
- delayed
  - bone marrow suppression
  - alopecia
  - hemorrhagic cystitis
    - prevent: hydration, mesna
- late
  - leukemia
  - sterility

mTOR inhibitors

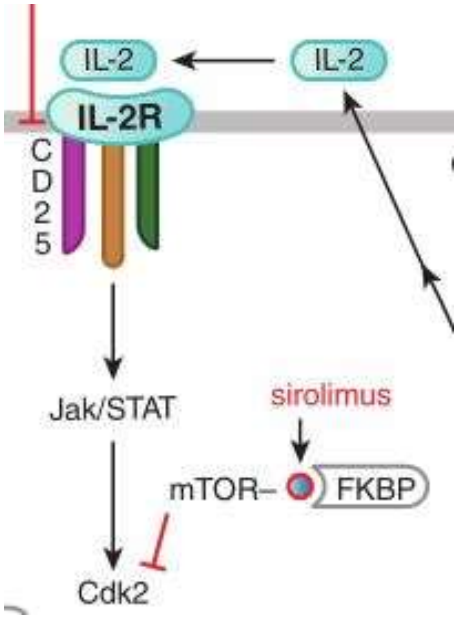
- sirolimus = rapamycin / everolimus / temsirolimus
- mTOR = **m**ammalian **t**arget **o**f **r**apamycin



sirolimus
macrocyclic lactone (similar to tacrolimus)

mTOR inhibitors

- inhibit downstream of IL-2
  - not like calcineurin inhibitors
- binds to FKBP-12
- the rapamycin-FKBP-12 complex ↓ mTOR
- blockade of G1 - S transition



- inhibition of
  - proliferation of T- and B-cells induced by cytokines (e.g. IL-2)
  - differentiation of B-cells to plasma-cells → production of antibodies

Pharmacokinetics of sirolimus

- low oral bioavailability (~15%)
- whole blood-level should be monitored
  - partitions into blood cells (blood:plasma=38)
- metabolized by CYP3A4
- biliary excretion
  - reduction of daily maintenance dose (by 33%) in hepatic impairment
- long half life
  - ~62h in renal transplant patients
  - loading dose

Clinical use of sirolimus

- systemic
  - prevention of the rejection of renal allografts
    - usually in combination with a reduced dose of calcineurin inhibitor and glucocorticoids
    - to avoid calcineurin inhibitors to protect kidney function
  - steroid refractory GvHD
  - autoimmune diseases
- topical
  - sirolimus eluting coronary stents
  - dermatologic disorders

Adverse effects of sirolimus

- **NOT** considered **nephrotoxic**
  - but should be used carefully
    - e.g. may increase nephrotoxicity of cyclosporine (if used together)
- ↑ serum **cholesterol** and **triglycerides** (dose dependent)
- **lymphocele** increased - close follow-up
- **delayed wound healing**
- other
  - anemia, leukopenia, thrombocytopenia
  - mouth ulcer / hypokalemia / GI effects

Antibodies and fusion proteins

- immunosuppressive
  - antibodies / fusion proteins
  - polyclonal or monoclonal
  - against lymphocyte cell surface antigens
  - against cytokines

Drugs binding to surface molecules of lymphocytes ("biological drugs") / anticytokines

- IL-1R-antagonist of natural origin
  - **anakinra**
- **antibodies**
  - polyclonal
    - antithymocyte-globulin (ATG)
  - monoclonal
    - murine (full mouse): muromonab-CD3
    - chimeric (xi) / humanized (zu) / human
      - **basiliximab (target: IL-2-receptor α-chain)**
      - **daclizumab (target: IL-2-receptor α-chain)**
      - alemtuzumab (target: CD52)
      - natalizumab (target: integrin α4)
- **fusion molecules**
  - abatacept
- **immunotoxins**
  - zolimomab aritox (target: CD5)
  - denileukin diftitox (target: IL2R α-chain)
  - brentuximab vedotin (target: CD30)
- fusion molecules and antibodies for psoriasis
  - alefacept (target: CD2)
  - efalizumab (target: CD11a)

- **TNF-α inhibitors**
  - infliximab (chimeric)
  - adalimumab (human)
  - etanercept (fusion molecule)
  - certolizumab pegol (humanized Fab + PEG)

Anakinra

- recombinant, non-glycosylated human **interleukin-1 receptor antagonist**
  - plus one N-terminal methionine (17.3 kDa protein)
- used in **rheumatoid arthritis** (as DMARD)
  - ***not*** *first line*
  - monotherapy and in combination (with anti-TNF-α agents)

Antibodies

- polyclonal
  - antithymocyte-globulin (ATG)
- monoclonal
  - 100% murine amino-acid sequences
    - muromonab-CD3
  - chimeric (**xi**, ≈ 75% human)
    - basili**xi**mab (IL-2R-α/CD25)*
  - humanized (**zu**, ≈ 90% human)
    - dacli**zu**mab (IL-2R-α/CD25)*
    - alemtu**zu**mab (CD52)*
    - natali**zu**mab (integrin-α4)*
  - fully human (**u**, 100% human)
    - adalim**u**mab (TNF-α)*

*target molecule in parenthesis

Humanized antibodies

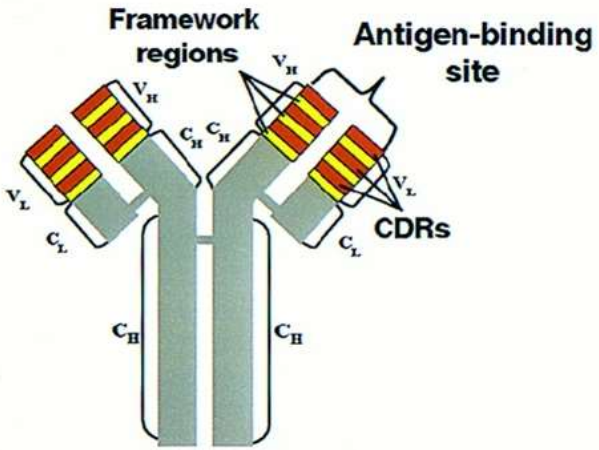
human amino-acid sequences:

- chimeric: F_c part
- humanized: F_{ab} part also, with the exception of the *complementarity determining region* (CDR)
- human: completely human

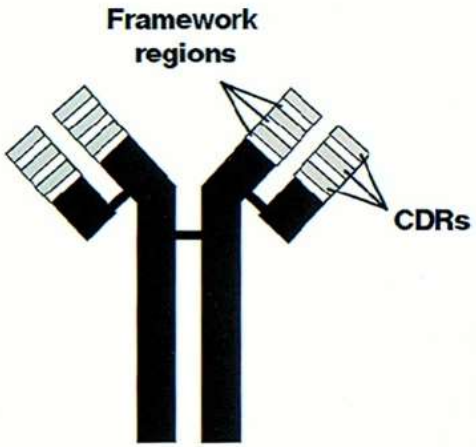
Advantages of humanization of antibodies

- half-life is longer
- reduced immunogenicity
- more effective activation of human effector mechanisms
  - ADCC (Antibody Dependent Cellular Cytotoxicity)
  - complement activation

Mouse Antibody

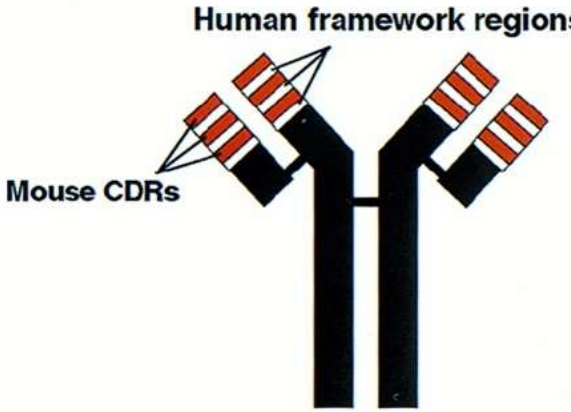


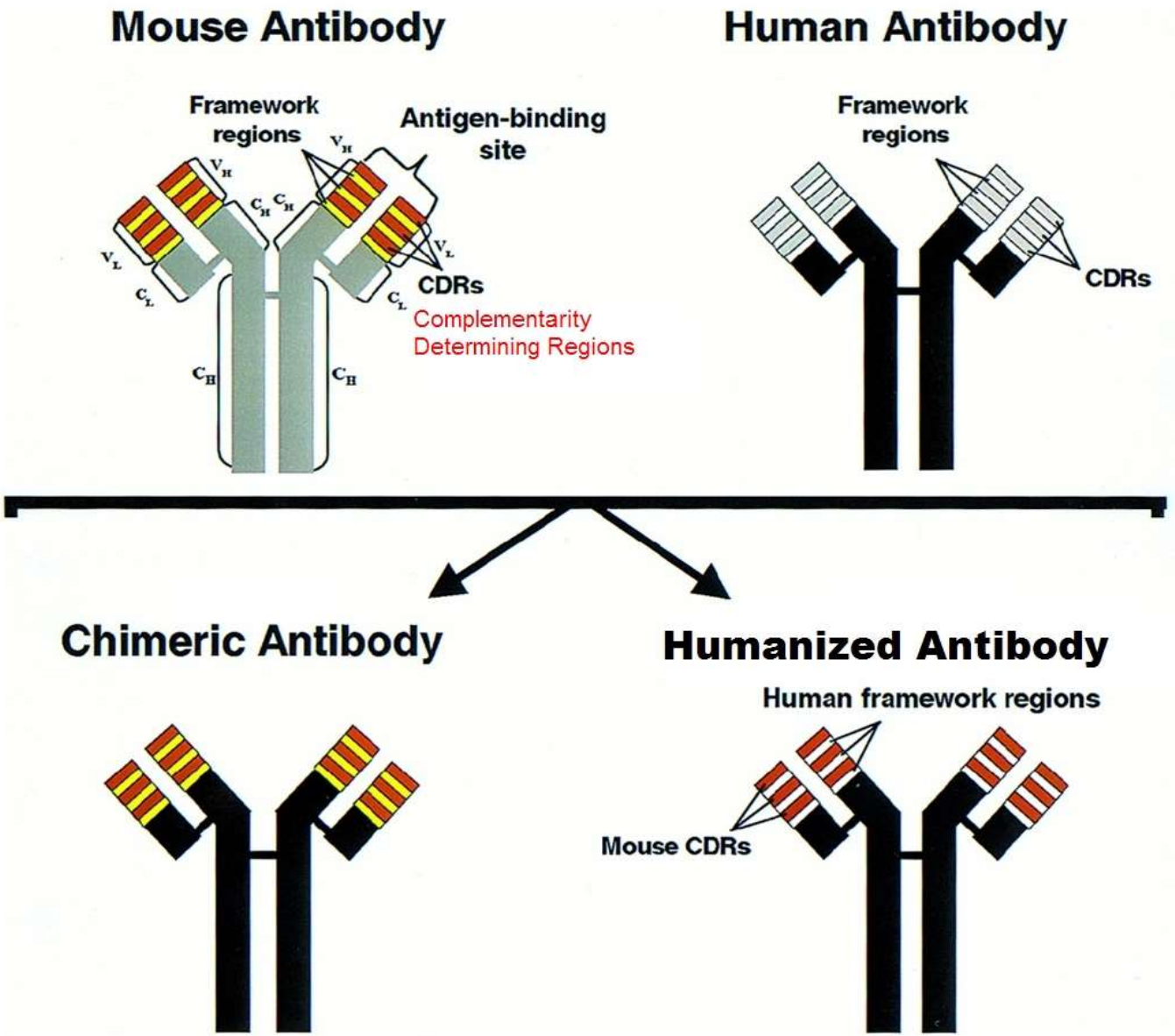
Human Antibody

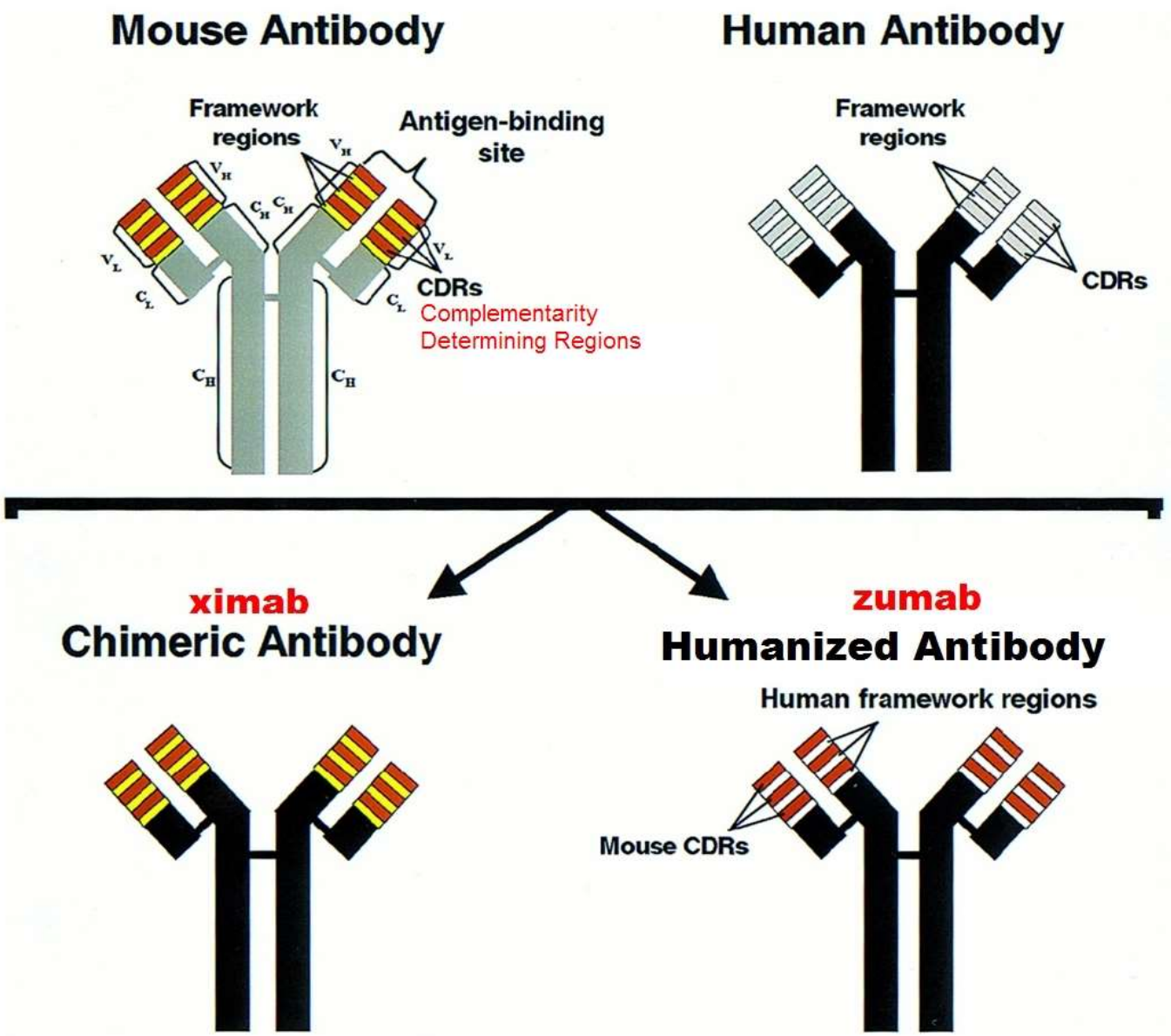


Chimeric Antibody

Humanized Antibody




Mouse Antibody
Framework regions
Antigen-binding site
CDRs
Complementarity Determining Regions
Human Antibody
Framework regions
CDRs
Chimeric Antibody
Humanized Antibody
Human framework regions
Mouse CDRs


Mouse Antibody
Framework regions
Antigen-binding site
CDRs
Complementarity Determining Regions
Human Antibody
Framework regions
CDRs
ximab
Chimeric Antibody
zumab
Humanized Antibody
Human framework regions
Mouse CDRs

CURRENT MONOCLONAL ANTIBODY NOMENCLATURE

UNIQUE PREFIX	TARGET TISSUE		SOURCE ORGANISM		CONSERVED SUFFIX
variable	*-o(s)-*	bone	*-u-*	human	-mab
	-vi(r)-	viral	*-o-*	mouse	
	-ba(c)-	bacterial	*-a-*	rat	
	-li(m)-	immune	*-e-*	hamster	
	-le(s)-	infectious lesions	*-i-*	primate	
	-ci(r)-	cardiovascular	*-xi-*	chimeric	
	-mu(l)-	musculoskeletal	*-zu-*	humanized	
	-ki(n)-	interleukin	*-axo-*	rat/murine hybrid	
	-co(l)-	colonic tumor			
	-me(l)-	melanoma			
	-ma(r)-	mammary tumor			
	-go(t)-	testicular tumor			
	-go(v)-	ovarian tumor			
	-pr(o)-	prostate tumor			
	-tu(m)-	miscellaneous tumor			
	-neu(r)-	nervous system			
	-tox(a)-	toxin as target			

Examples:				
	Beva	ci	zu	mab
	Ri	tu	xi	mab
	Ala	ci	zu	mab
	Glemba	tum	u	mab

Nomenclature of monoclonal antibodies

			prefix	substem A and B		suffix: monoclonal antibodies and fragments **mab**
		name	unique name, distinct syllable	target class, (therapeutic use)	biological origin murine, human	
immune	murine	muromonab-CD3	a name coined before the acceptance of the present rules of nomenclature			
	chimeric	infliximab	inf	lim	xi	mab
		basiliximab	basi	lim	xi	mab
	humanized	daclizumab	dacli	lim	zu	mab
		omalizumab	oma	lim	zu	mab
		efalizumab	efa	lim	zu	mab
		natalizumab	nata	lim	zu	mab
	fully human	adalimumab	ada	lim	u	mab
						mab

trastuzumab (Herceptin®)

humanized mab → *human* Fc → activation of human effector-mechanisms :
ADCC (antibody-dependent cellular **cytotoxicity**)
complement

- target: Her2 (a member ot the EGFR-receptor family)
- activation of Her2
  - promote the formation of metastasis
  - inhibits apoptosis

- effects of trastuzumab
  - inhibition of proliferation
  - induction of apoptosis
  - Fcγ-receptor mediated ADCC

indication: Her2 overexpressing breast cancer

Polyclonal antibodies
against surface molecules of lymphocytes

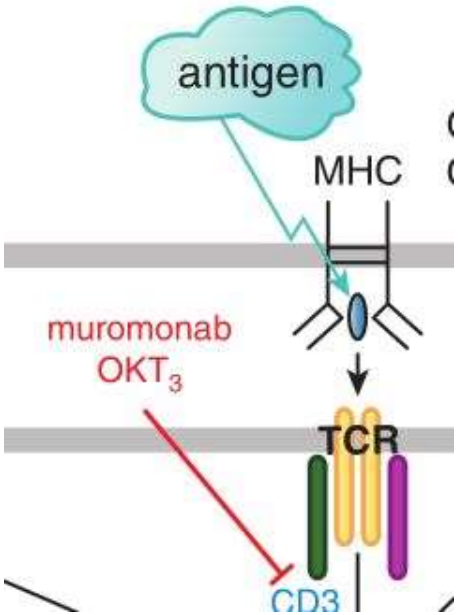
- **antithymocyte globulin** (ATG)
- source
  - purified gamma globulin from serum of rabbits immunized with human thymocytes
- mechanism
  - several antibodies against surface molecules of human T lymphocytes
  - direct cytotoxicity / blockade of lymphocyte function
- use
  - treatment and prophylaxis of rejection
  - may improve graft survival
- toxicity
  - xenogeneic proteins → may induce severe side effects
    - common: chills, fever, hypotension
    - rare: serum sickness, glomerulonephritis, leukopenia, anaphylaxis
    - prevent/treat:
      - premedication: glucocorticoids, paracetamol, antihistamin
      - slow infusion
    - anti-ATG antibodies

Monoclonal antibodies
against surface molecules of lymphocytes

- against **CD3**
  - muromonab-CD3
  - use: *treatment* of acute organ rejection
- against the α-chain of **IL-2R**
  - basili**xi**mab (chimera)
  - dacli**zu**mab (humanized)
  - use: *prophylaxis* of acute organ rejection (in combination)
- against **CD52**
  - alemtu**zu**mab
  - use: induction in transplantation/CLL, low-grade lymphomas / MS
- against **integrin α4**
  - natali**zu**mab
  - use: multiple sclerosis (MS) / Crohn's disease

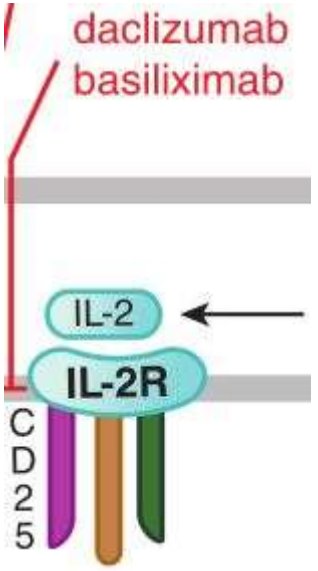
muromonab-CD3 (OKT3)

- use
  - treatment of allograft-rejection
  - **no longer marketed** but FDA approved (introduced in early 1980s)
- adverse reactions
  - **cytokine-release syndrome**
    - onset: ≈ 30 min / duration: hours / **first dose is the worst**
    - reason: activated T-cells release TNF-α, IL-2, IL-6, IFN-γ
    - symptoms:
      - high fever, chills/rigor, headache, tremor
      - nausea, vomiting, diarrhea, abdominal pain
      - malaise, myalgias, arthralgias, generalized weakness
      - rare: skin, CV, CNS (potentially fatal)
    - prevention
      - **glucocorticoid pretreatment**
  - immunogenic
    - **antimurine antibodies** are produced in the human patient

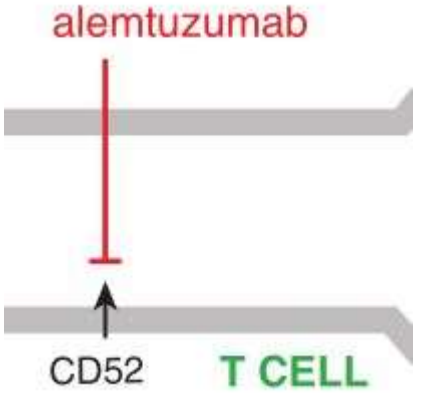


basiliximab / daclizumab

- mechanism
  - target: IL-2R α chain (CD25)
  - expressed in activated lymphocytes
- use
  - prophylaxis of acute organ **rejection** (in combination)
  - $t_{1/2}$
    - daclizumab: 20 days ↔ basiliximab 7 days
- toxicity
  - **no cytokine release**
  - **anaphylaxis** may occur

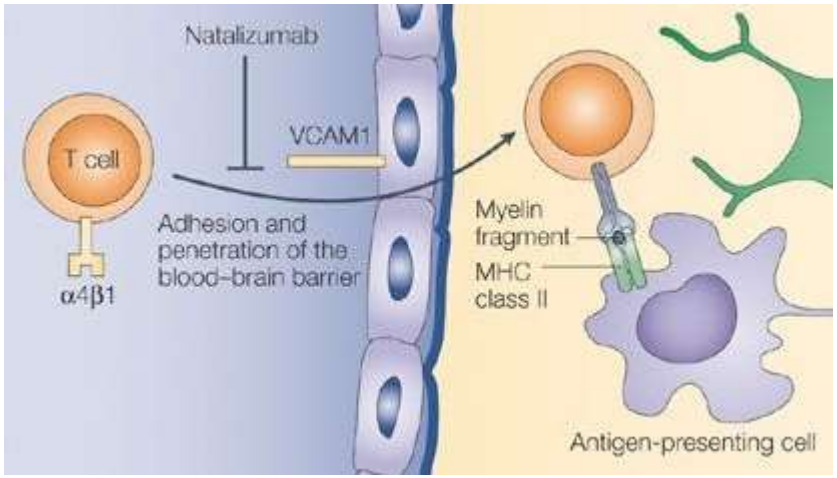


alemtuzumab



- mechanism
  - target: CD52
  - expressed on lymphocytes, monocytes, macrophages, NK cells → apoptosis induction
- use
  - induction of immunosuppressive therapy
    - e.g. in transplantation to avoid early high dose steroids
    - no long term data / further clinical experience is needed
  - refractory acute rejection
  - CLL (and low-grade lymphomas) / MS

natalizumab



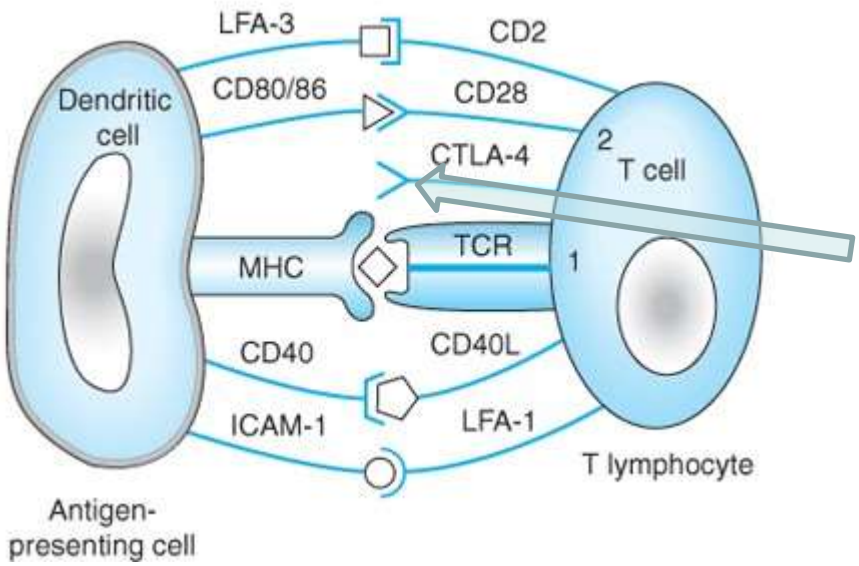
- mechanism
  - target: **integrin α4** subunit
  - inhibits T-cell penetration into the CNS
- use
  - multiple sclerosis
  - Crohn's disease
- toxicity
  - progressive multifocal leukoencephalopathy ?

Progressive multifocal leukoencephalopathy (PML)

- JC virus + immunosuppression
- 70-90% of population is infected
- progressive damage of the white matter at multiple locations
  - fast progression / lethality
- associated drugs (current FDA black-box warnings)
  - rituximab
  - natalizumab
  - brentuximab vedotin
  - efalizumab

Fusion molecules 1.

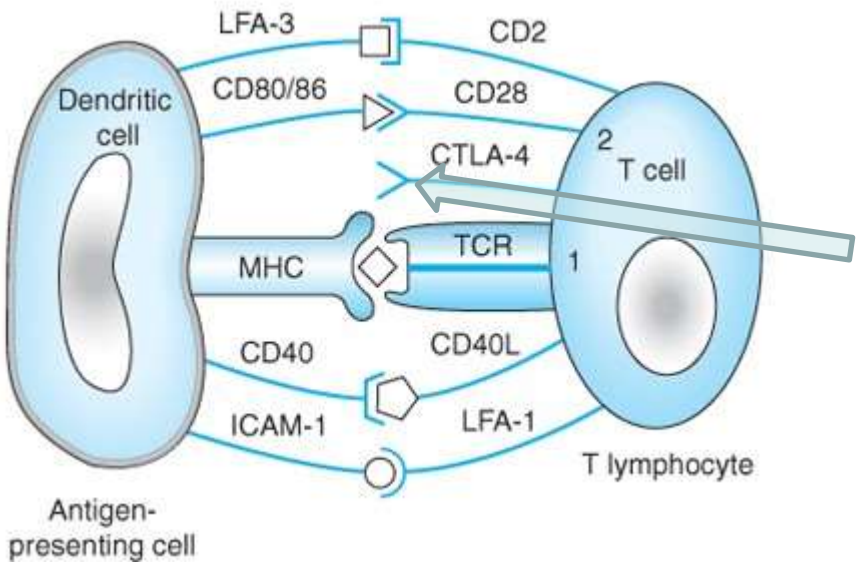
- **abatacept** consists of
  - 1. extracellular part of CTLA-4
    - binds abatacept to CD80/86 on the surface of the APC
  - 2. human IgG1 Fc
- binds to CD80/86 – **inhibits co-stimulator function**
- indication: **rheumatoid arthritis** if inadequate response to anti-TNFα



T-cell activation is regulated by T-cell-derived CTLA-4

Fusion molecules 2.

- **belatacept**
  - second-generation CTLA4-Ig
  - higher affinity for CD80 and CD86, 10x more potent
  - used in maintenance therapy after organ transplantation (2011)
  - to limit toxicity of standard immunosuppression e.g. cyclosporine
    - better renal function



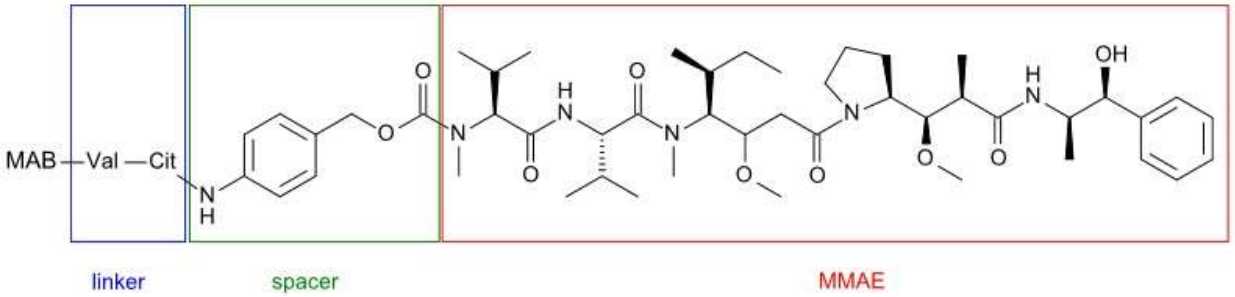
T-cell activation is regulated by T-cell-derived CTLA-4

Immunotoxins 1.

- denileukin diftitox (target: IL-2R)
  - recombination of **IL-2** and the catalytically active fragment of **diphtheria toxin**
  - kills cells expressing IL2R
  - indication: recurrent/refractory CD25 positive primary **cutaneous T-cell lymphoma**
  - AE: capillary leak syndrome
    - hematocrit ↑ / edema / shock / multiple organ failure

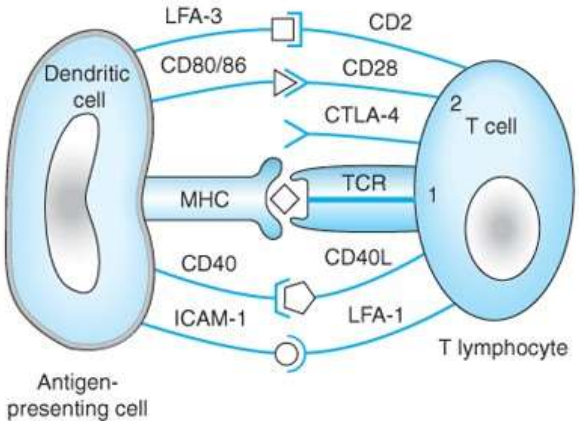
Immunotoxins 2.

- brentuximab vedotin (target: CD30)
  - anti-CD30 chimeric IgG1 + MMAE
    - binding → internalization → release of MMAE → blockade of tubulin polymerisation
  - indication (**but only after failure of other therapies**)
    - anaplastic large cell lymphoma
    - Hodgkin's disease
  - risk of progressive multifocal leukoencephalopathy (PML)



Fusion molecules and antibodies used in psoriasis

- psoriasis
  - memory effector T-cells
  - CD2 expression – ligand LFA-3
- alefacept
  - LFA-3 + F_c portion of human IgG1
  - inhibits memory effector cell activation
  - NK cell binding - apoptosis
- efalizumab (target: CD11a – LFA-1)
  - inhibits binding to ICAM-1 – T-cell penetration
  - withdrawn in 2009 because of PML risk



LFA: leukocyte function associated antigen

Anticytokines

- IL-1R-antagonist
  - anakinra
    - a recombinant, nonglycosylated form of the human interleukin-1receptor antagonist (IL-1Ra)
    - competitively inhibits IL-1 binding to the IL-1 type I receptor
    - moderately to severely active rheumatoid arthritis in adults after failing DMARDs
- antibodies against the α-chain of IL-2R
  - basiliximab / daclizumab
    - prevent IL2 binding – lymphocyte activation
    - indication: renal transplantation
- TNFα- inhibitors
  - infliximab (chimeric) – RA / IBD / psoriasis
  - adalimumab (human) – RA / psoriatic arthritis
  - etanercept (fusion molecule) – 2x EC domain + F_c of IgG1
    - Crohn's disease, rheumatoid arthritis, psoriasis

TNF-α inhibitors

- mechanism
  - bind TNF-α → prevent TNF-α effects
- use
  - rheumatoid arthritis
  - Crohn's disease / UC
  - psoriatic arthritis
- toxicity
  - infliximab: infusion reaction
  - etanercept: injection-site reactions
  - ↑ risk of infections, malignancies

Other immunosuppressive agents

- glatiramer (copolymer-1)
- omalizumab (target-molecule: IgE)

Other immunosuppressive agents

Glatiramer (Copolymer-1).

mixture of random synthetic peptides containing 40-100 of four aminoacids (alanine, lysine, glutamate, tyrosine)

molecular weight 4700-13 000 dalton

clinical indication: sclerosis multiplex-- for relapsing-remitting

30% decrease in exacerbations

administration: daily, subcutaneous

probably inhibits the immune reaction against myelin basic protein

reduces frequency of relapses

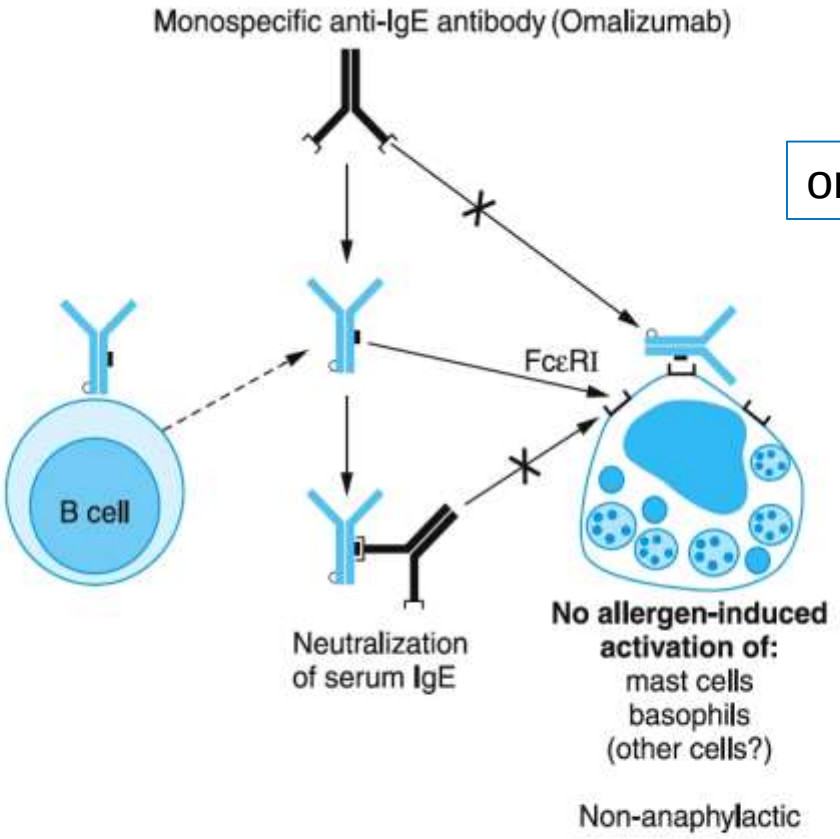
.

Other immunosuppressive agents

omalizumab (target: Fc-part of IgE)

anti-antibody antibody

indication: asthma bronchiale



only in severe cases

iv./ sc.
2-4 weeks

anaphylaxis
tumors?

FIGURE 27–3 Mechanism of Action of Omalizumab. *Omalizumab is a monospecific anti-IgE antibody.* Specific B lymphocytes produce IgE antibodies. The Fc region of IgE heavy chains binds with high affinity to receptors (FcεRI) in the plasma membranes of mast cells and basophils (and other cells). Allergen interacts with the antigen-binding site of cell-bound IgE, causing FcεRI cross-linking and cell activation. Omalizumab neutralizes the free IgE in the serum by binding to the Fc regions of the heavy chains to form high-affinity IgE-anti–IgE complexes. This prevents the IgE from binding to FcεRI, thereby blocking allergen-induced cell activation.

Main risks of immunosuppressive treatment

- increased susceptibility to **infection**s, including opportunistic pathogens (e.g. Candida, CMV, Listeria …)
- cytotoxic agents→damage to cell-renewal systems (bone marrow, mucous membranes)
- **cyclosporine → nephrotoxicity**
- late consequences: increased incidence of **malignancies**

Anti Rh(0)-D immunoglobulin

- for **preventing Rh hemolytic disease of the newborn**
- primary antibody response to a foreign antigen can be blocked if **specific antibody to that antigen** is administered passively at the time of exposure to antigen
- a concentrated (15%) solution of **human IgG** containing a higher titer of antibodies against the Rho(D) antigen of the red cell
- within 24-72 hours after the birth of an Rh-positive infant **– TO THE MOTHER**
- also in miscarriages, ectopic pregnancies, or abortions

Immunomodulators

- What is modulation?
  - not suppression
  - may increase the immune responsiveness
- When these drugs are used?
  - immunodeficiency disorders
  - (chronic) infectious diseases
  - cancer
- Problem
  - systemic effects ↔ limited efficacy

Immunomodulators

- **Natural origin**
  - Endogenous regulators and derivatives
    - **Cytokines**
      - Interferons
      - Colony-stimulating factors
      - Other cytokines (e.g. TNFα)
  - Microbial origin (BCG)
  - Other natural origin (pegademase)
- **Synthetic**
  - levamisol / inosiplex / **imiquimod** / **thalidomide**

Cytokines

- **Interferons**
  - IFNα
  - IFNβ
  - IFNγ
- **Colony-stimulating factors**
  - G-CSF
    - filgrastim, PEGfilgrastim
    - lenograstim (glikozilált)
  - GM-CSF
    - molgramostim
    - sargramostim
- **Interleukins**
  - IL2 (aldesleukin)
  - IL11 (oprelvekin)
- **Other** cytokines: TNFα

Interferons

- **IFNα**
  - antiviral (e.g. **hepatitis C és B**)
  - antitumor (e.g. melanoma)
- **IFNβ**
  - **multiple sclerosis**
- **IFNγ**
  - increases IL1 production → helper T-cell activation
  - macrophages activated
  - indication: **chronic granulomatous disease**

Colony Simulating Factors
(Colony Simulating Factor = **CSF)**

- origin of name: *in vitro* enhanced colony formation by bone marrow cells
  - G-CSF: granulocyte
  - GM-CSF: granulocyte-macrophage
  - M-CSF: monocyte-macrophage
  - multi-CSF: = interleukin-3

Main indications of ganulocyte colony-stimulating factor (G-CSF)

- neutropenia due to cytotoxic drugs
- promotion of recovery after transplantation of hematopoietic stem cells
- mobilization of hematopoietic stem cells from the bone marrow to the peripheral blood
- severe chronic neutropenia (idiopathic, cyclic)

- **Interleukins**
  - IL-2 aldesleukin
    - indications
      - metastatic renal cell cancer
      - malignant melanoma
  - IL-11 oprelvekin
    - indication
      - cancer chemotherapy caused thrombocytopenia

- **Other cytokines:** TNFα
  - indication: intraarterial injection in case of
    - malignant melanoma
    - soft tisse sarcoma of extremities

Agents of microbial origin

BACILLUS CALMETTE-GUÉRIN (BCG)

an attenuated culture of the bacillus of

Calmette and Guérin strain of *Mycobacterium bovis*

treatment and prophylaxis of carcinoma *in situ* of the urinary bladder (intravesical instillation)

Other immunomodulators of natural origin

Pegademase-bovine = pegylated adenosine deaminase

- **indication**: SCID (*Severe Combined Immune Deficiency*) due to the lack of adenosine deaminase
- **advantages of pegylation**:
  - half life is increased from minutes to days,
  - reduces the immunogenecity of the molecule

Synthetic immunomodulators

- **imiquimod**
  - **synthetic** imidazoquinoline amine
  - mechanism
    - stimulate peripheral mononuclear cells to release interferon alpha
    - stimulate macrophages to produce TNFα / IL-1 / IL-6 / IL-8
  - **topical** treatment of
    - genital and perianal warts (condyloma acuminatum)
    - actinic keratoses (SCC precursor?)
    - primary basal cell carcinomas (no absorption)

- **thalidomide**
  - used in: **multiple myeloma** / erythema nodosum leprosum
  - mechanism ?? (angiogenesis ? / TNF-α ?)
  - **teratogenicity** (see Contergan) / increased risk of **deep vein thrombosis**

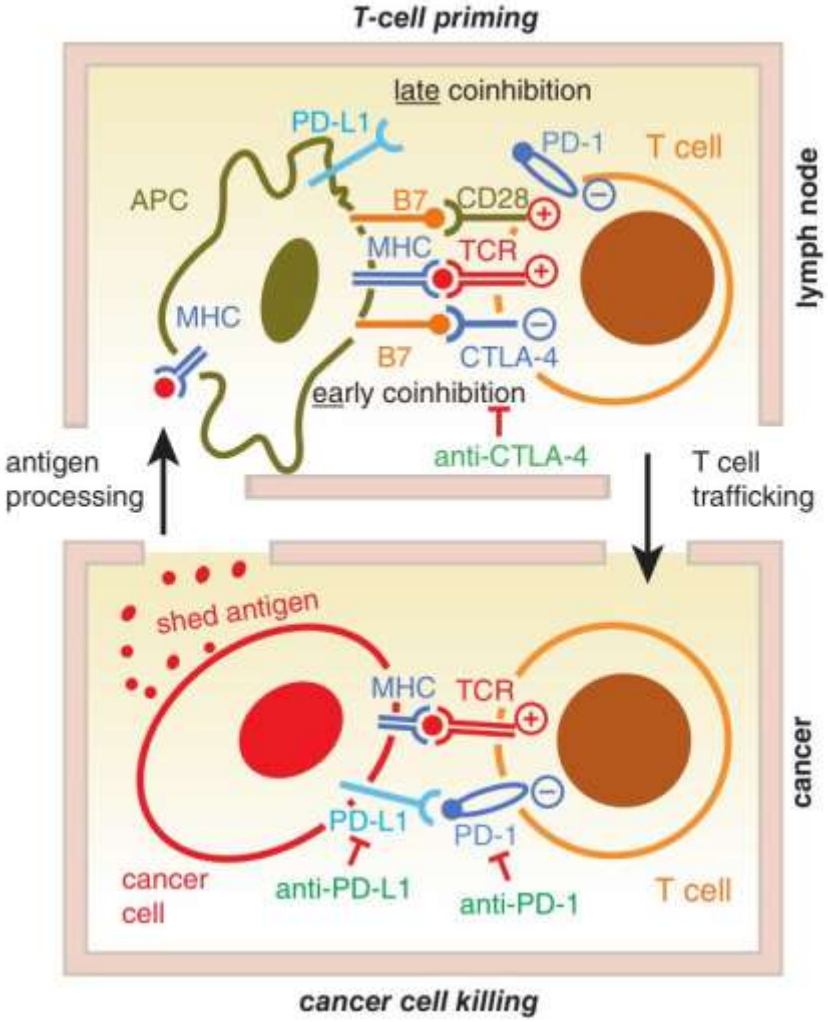
- **Immunomodulatory derivatives of thalidomide**
  - **lenalidomide**
    - effect on cytokine regulation and T-cell proliferation is higher than thalidomide
    - similar effect, lower risk of teratogenicity
    - **multiple myeloma** (primary and relapsed/refractory) / myelodysplastic syndrome (5q31 deletion)
  - **pomalidomide**
    - also myriad mechanisms of actions
    - **relapsed/refractory multiple myeloma**

Synthetic immunomodulators

(older not used)

- levamisole
  - antihelminthic (short term)
  - adjuvant therapy with 5-fluorouracil after surgical resection in patients with Dukes' stage C **colon cancer** (only **historical**)
  - **rheumatoid arthritis**
  - danger of **agranulocytosis** (withdrawn)
- inosiplex
  - stimulation of cellular immunity (how?)
  - enhance antiviral response ?

Immune checkpoint inhibitors in cancer therapy



striking clinical efficacy (not in all patients)

blocking mAbs to CTLA-4, PD-1, or PD-L1

ipilimumab (anti–CTLA-4)
late-stage melanoma

atezolimumab (anti–PD-L1)

nivolumab (anti–PD-1)
melanoma, NSCLC, RCC, H&N cancer, Hodgkin

pembrolizumab (anti–PD-1)
melanoma, NSCLC, urothelial cancer, Hodgkin, H&N cancer

inflammatory toxicities