Biological treatment - principles, technology, examples

Biological drug

- „Biodrugs, biologics, targeted treatment “

  Recombinant proteins, peptides, antibodies, hormones

  substances derived from blood / plasma and recombination variants

- „Biologicals, Biopharmacy, Biopharmaceuticals“

  - recombinant proteins, peptides, antibodies, hormones

  + Stem cells, xenotransplantation, gene and antisense therapy

Biological drugs

- designed to specifically target a biological phenomenon, gene, protein, or group of genes or proteins thought to be involved in the disease.

Traditional/Classical vs. Biological drug

Small molecule <1kDa
Production of chemical synthesis / isolation of plant
Less critical steps in the synthesis
Very well characterized
Molecular mechanism of action usually better described
Linear dose-response relationship
Mostly non-immunogenic

Usually with pharmacokinetic interactions at P450

large, complex molecules, commonly proteins> 50 kDa
manufactured using living organisms / cells

- risk contamination
- own "inherited„ activity

Complex heterogeneous structure matrix from which was drug isolated
More difficult to characterize (3D conformation)

mechanism of action is complex, sometimes not fully understood

Usually immunogenic
Mostly without interaction at P450

Traditional/Classical vs. Biological drug

Often a small molecule, different from endogenous substances	Often very similar / identical with the molecules of the human body.
Expose its effects throughout the whole body	Usually targeting the center of disease/anormality.
Limited efficacy for some states	Can be used to treat previously difficult-to-treat diseases.
Easy handling and formulation of DDF	The difficult adjustment to DDF

Research and development of Biological drugs

- The development of biologics is 10 - 15 years, costs 1.5 billion USD
- Biologics are produced by the genetically modified host cells (bacterial, yeast, mammalian and plant) into which was inserted the genetic information stored in DNA.
- The first drug produced by biotechnological procedure was insulin (in 1978, registering 1982).
- The discovery of biotechnological production of pharmaceuticals, respectively. monoclonal antibodies, was in 1984 awarded the Nobel Prize.

Targeted effects of biologicals

- A specific effect of biologics is targeted - a specific target structure, antigen, enzyme, signal path (e.g. tumor cells).
- Biologics are able to identify the damaged cells for destruction by the immune system.
- Can prevent the growth and proliferation of cells that cause disease.
- Can deliver drug directly to the **target** which increases the effectiveness of treatment.

History

- 1972 - obtained recombinant deoxyribonucleic acid (rDNA)
- 1975 - first monoclonal antibody (MAb).
- This was followed by the establishment of the first biotech pharmaceutical companies. USA - Genentech Europe - Biotech
- 1982 - The first biotech product was - recombinant insulin (Genentech, marketed by Eli Lilly)
- 1986 monoclonal antibody OKT3 (OrthoCloneR) recombination. IFN

Examples of Biological drugs

1) Imunomodulating biologics

MAb (Infliximab) and fusion proteins (etanercept), IFN

2) Hormones – insulin, GH

3) Vaccines – e.g. HVB, HPV

4) Growth factors – erytropoetin, trombopoetin, CSF

5) Enzymes for the treatment of hereditary diseases (monogenic) (e.g. Imiglucerase for the treatment of Gaucher disease)

6) Biologics influencing homeostasis- f. VII, F VIII, F IX, other inh. Of coaglation or activators of fibrinolysis

7) Gene therapy (e.g.. Alipogen tiparvovek – LPL gene)

Advantages for the patients

- Better efficiency vs. "Classical" drugs
- Biologicals are used under the supervision of experts in specialized centers.
- targeted, personalized treatment, which is always personalized
- the patient undergoes a more detailed examination before medication
- better understanding of the basic properties of the drug and its effects
- better solution of possible ADRs, their early detection

Risks and disadvantages of biologic drugs in general

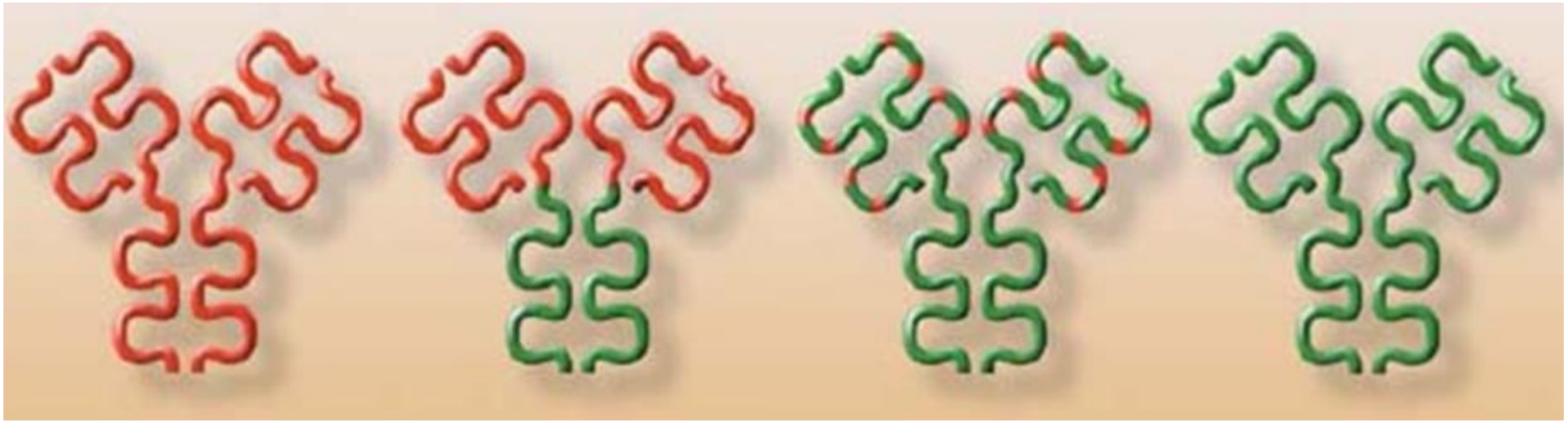
- carcinogenicity
- allergenic potential
- contaminants from the source cells
- stabilizing additives (cryopreservation stabilizers)
- sterility
- stability, variability of drugs (biotechnology products)
- adverse effects - dead teenager in first stage CT - liver toxicity after gene therapy of congenital deficiency of the enzyme using an adenoviral vector (1999)

Nomenlature

- Derived from biochemical name (Pegasys -PEG IFN)
- The name given by the manufacturer - unrelated to the effect of the origin
- Hormone with different tradename (Serostim, Saizen, Zorbtive)
- MAB- system root words and suffixes

Nomenclature of MAB

- Generally: suffix -mab
- Letter before suffix:
  - o – of mice origin
  - a - rat origin
  - e - hamster origin
  - i - of primates
  - u – of human origin (human cell line production)
  - zu – humanized
  - xi - chimeric



Mouse MAb
100% of the mice orig.
Hypersensitivity
High levels of Ab
(not used clinically)

Chimeric MAb
34% of mice orig.
Hypersensitivity
Low levels of circulating Ab
(rituximab infliximab)

Humanized
5-10% mice orig. MAb
Hypersensitivity
Low levels of Neutralizing Antibodies
(Trastuzumab Certolizumab)

Human MAb
100% human
Hypersensitivity
Low levels of Neutralizing Antibodies
(panitumumab adalimumab)

Nomenclature of MAB

Sometimes encoding indication

- lim - immune
- bac - bacterial
- cir- cardiovascular
- tu - malignity

E.g. rituximab - chimeric MAB to treat Non-Hodgkin. lymphomas

alemtuzumab - humanized antibody to the CD52 glycoprotein CLL

Production of biological drugs

Isolation from natural sources - historically:

- insulin from the pancreas of cattle, pigs (recombinant today)
- h-choriogonadotropin - from the urine of pregnant women (today recombinant)
- hirudin - Medical leeches (*H. officinalis*) (today synthetic / recombinant)

The production of biological drugs - recombinant technology

- DNA extraction
- product / synthesis according to library
- transformation / DNA transfection into producer cells
- production
- purification
- stabilization
- testing (biological activity - CT I-III)
- registration (RCT + IV)

The production of biological drugs - recombinant technology

- DNA extraction
- product / synthesis according to library
- transformation / DNA transfection into producer cells
- production
- purification
- stabilization
- testing (biological activity - CT I-III)
- registration (RCT + IV)

The production of biological drugs - recombinant technology

Transformation/transfection with use of

plasmid
- start of replication
- marker of selection
- polycloning site (enables insertion of DNA of foreign origin)
- transcription promoter and terminator

selection

The production of biological drugs - recombinant technology

- production microorganisms
  - bacteria
  - yeast
- Tissue cultures of higher organisms
- Cell-free expression systems
- Genetically modified animals, plants

The production of biological drugs - recombinant technology

- Production by microorganisms

  - Bacteria - optimized E. coli strains (mutations of periplasmatic and membrane protease)

  - Yeasts - S. cerevisiae - Pichia pastoris ?

The production of biological drugs - recombinant technology

E. Coli

- The synthesis of proteins **without posttranslational modifications**
- Cheap medium, mutated forms of E. coli with advantageous properties - increase the stability of the gene product ...
- Modification of wall, transformation of plasmid (DNA product introduction) - thermal shock, electroporation
- Selection - resistance to antibiotics / cell culture media
- Production of the peptide together with peptide sequences which ensure binding to an affinity carrier
- Renaturation

- E.g. IFN , GSM, insulin, growth hormone ...

The production of biological drugs - recombinant technology

S. Cerevisieae

- suitable for the synthesis of proteins **with posttranslational modifications**
- Haploid yeast - the possibility of hybridization
- Easy , economical cultivation generation time of 2h
- GRAS - " Generally regarded as safe"
- Mutants with advantageous properties - increase the stability of the gene product ...

The production of biological drugs - recombinant technology

S. cerevisieae

- modification of cell wall, transformation of plasmid (various vectors)
- selection - auxotrophic strains (disabled biosynthetic pathway for AA, NA); plasmid introduce this gene – only transformed yeast are viable in selection media (ATB)
- production of the peptide together with peptide sequences which ensure binding to an affinity carrier
- renaturation
- E.g. insulin, growth hormone ...

The production of biological drugs - recombinant technology

Pichia pastoris

- higher genet. stability, possibility of similar glycosylation of proteins as in humans

The production of biological drugs - recombinant technology

Tissue cultures of higher organisms

- About 60% of recombinant proteins

positives: same way of modifications as in humans

a wide variety of products

eliminates ethical / technical problems (isolation, animal cells, the lack of material)

negatives: higher risk of contamination

(rich medium, slower growth, expensive, difficult cultivation)

The production of biological drugs - recombinant technology

Tissue cultures of higher organisms

primary cultures (subculturing or passaging not possible)/ cell lines (tumor)

mostly adherent cell lines - release trypsin

Medium: ions , glucose, vitamins, nucleotides , lipids, calf serum (source of growth factors, hormones + PDGF, EGF, FGF, ...)

pH control, morphology

Vectors (details are kept secret): plasmids , viral plasmids (retroviruses), polycations (DEAE dextran)

Part of the transfected DNA are regions of DNA increasing production (in units of g / L medium)

Selection (principles similar to those of S. cerevisiae .)

The production of biological drugs - recombinant technology

Tissue cultures of higher organisms

CHO – chinese hamster ovary

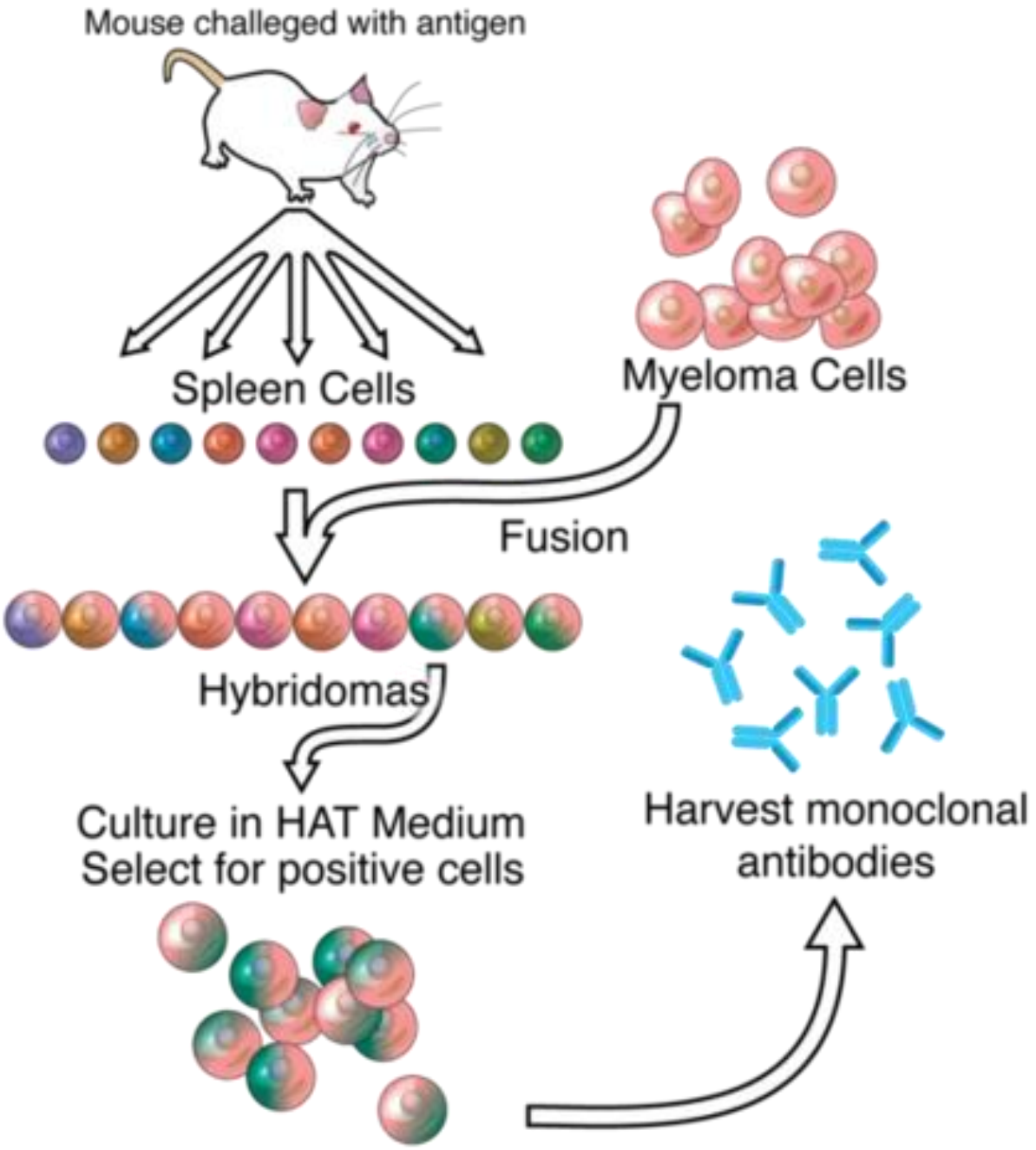
NS0, Sp2/0-Ag14 – mouse plasmocytome cells (leukocytes) – auxotrophic for L-glutamine

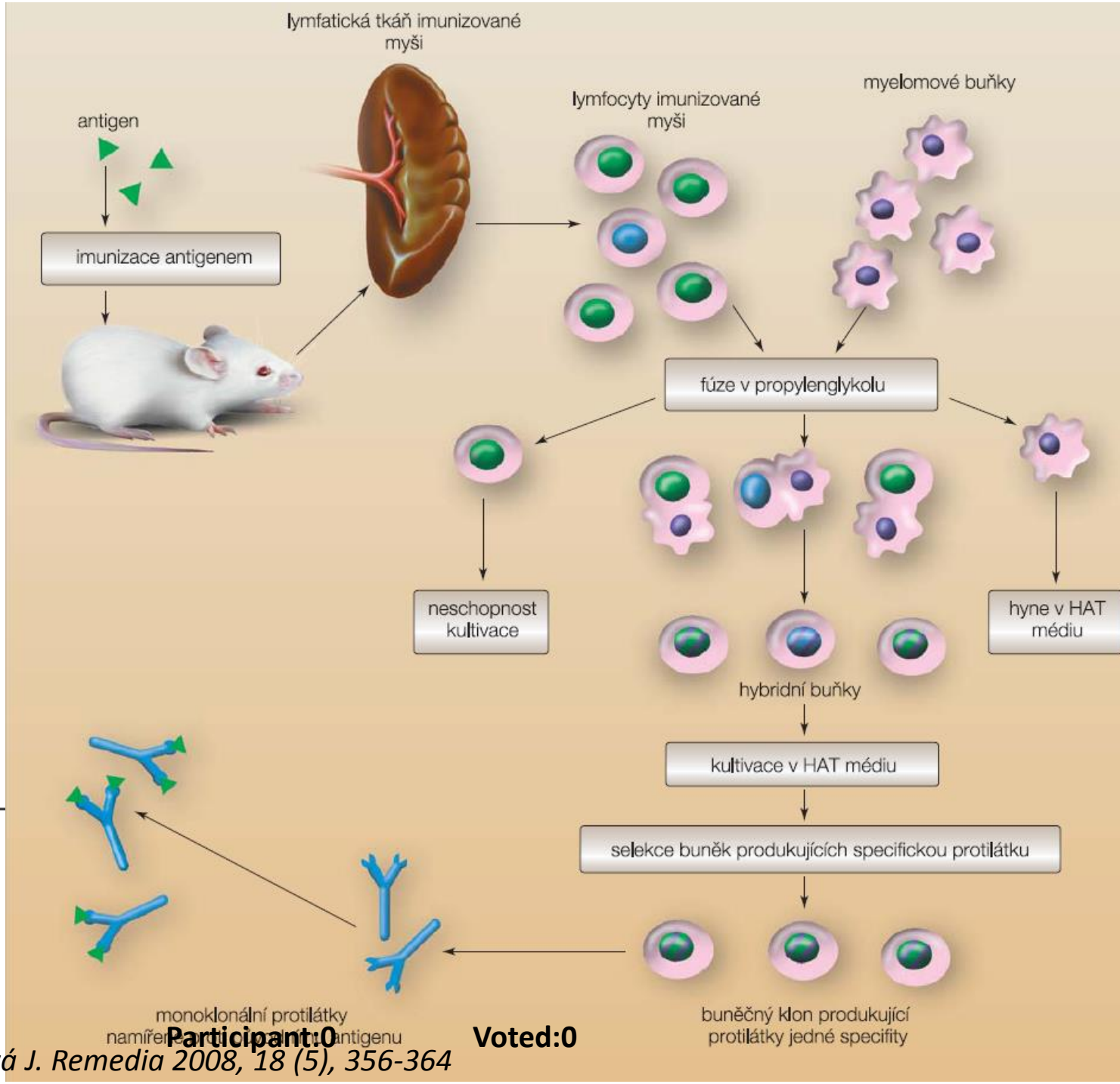
BHK 21 (baby hamster kidney – syrian hamster)

The production of biological drugs - recombinant technology

Tissue cultures of higher organisms

production of „hybridomes“


Mouse challeged with antigen
Spleen Cells
Myeloma Cells
Fusion
Hybridomas
Culture in HAT Medium
Select for positive cells
Harvest monoclonal
antibodies



Participant:0 **Voted:0**

Sobotková M, Bartůňková J. Remedia 2008, 18 (5), 356-364

The production of biological drugs - recombinant technology

Transgenic plants

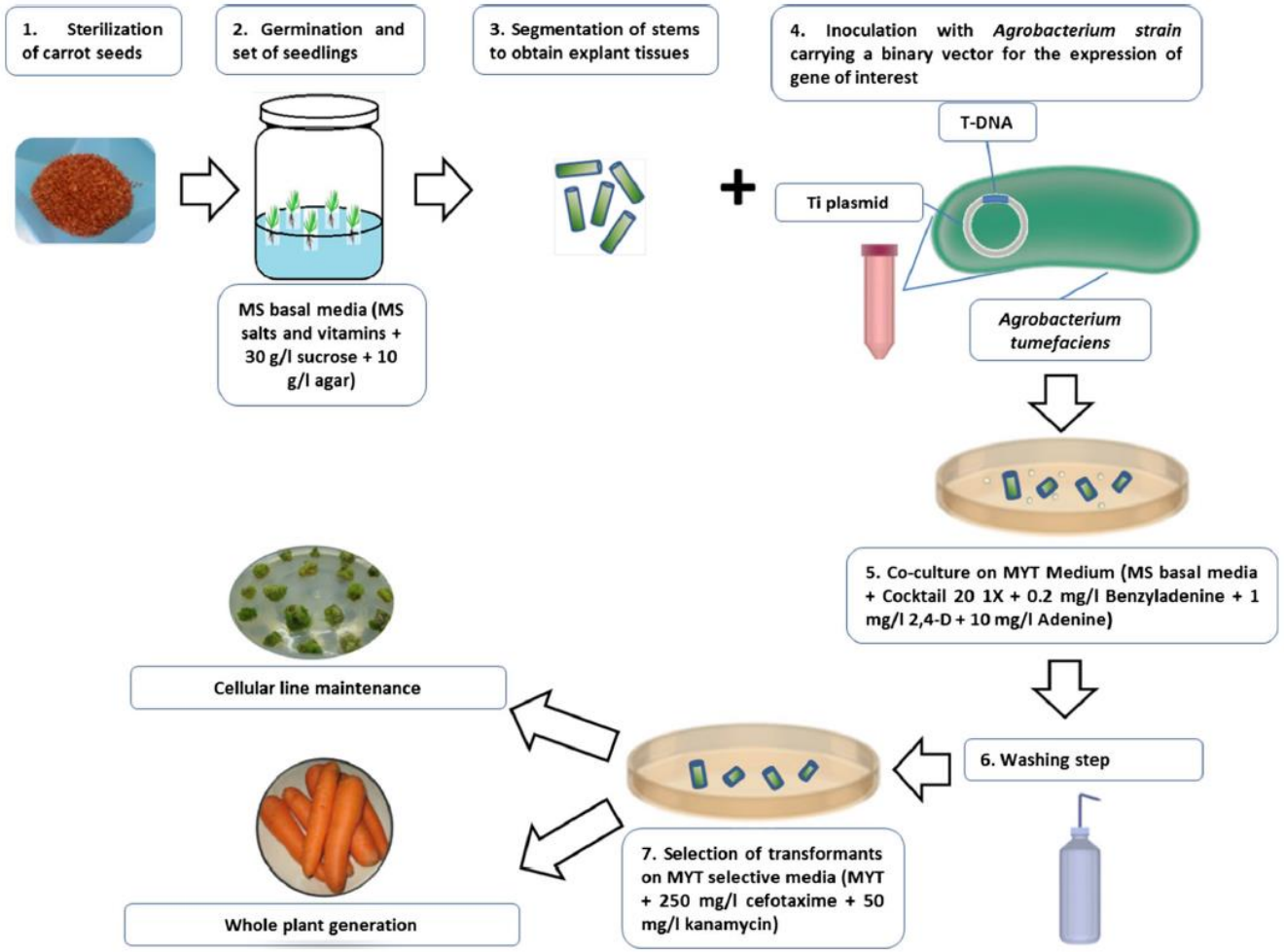
„**Edible vaccines** " - production of the immunogenic protein (like the polio vaccine)

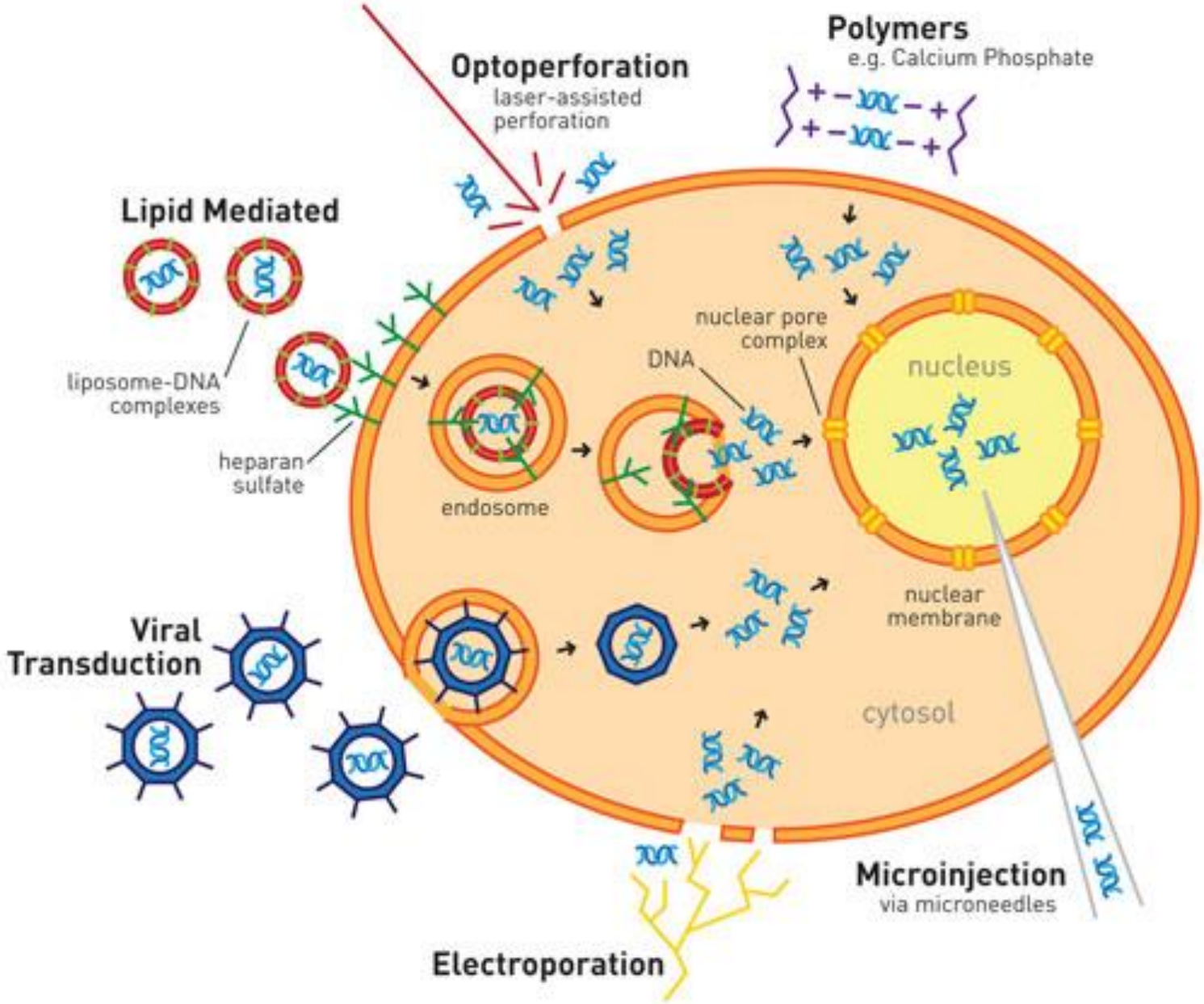
culturing plant tissue culture in agar
Agrobacterium transfection (+ recombinant plasmid)
selection, planting

tobacco (Nicotiana tabacum), Arabidopsis thaliana

PRX - 112 - 06/2014 - 1st patient treated with recombinant protein from the plant (Protalix Biotherapeutics) Gaucher disease - deficit of glucocerebrosidase

„…active recombinant proteins systemically through oral administration of plant cells expressing biotherapeutic proteins...“


1. Sterilization of carrot seeds
2. Germination and set of seedlings
3. Segmentation of stems to obtain explant tissues
4. Inoculation with *Agrobacterium strain* carrying a binary vector for the expression of gene of interest
T-DNA
Ti plasmid
Agrobacterium tumefaciens
MS basal media (MS salts and vitamins + 30 g/l sucrose + 10 g/l agar)
5. Co-culture on MYT Medium (MS basal media + Cocktail 20 1X + 0.2 mg/l Benzyladenine + 1 mg/l 2,4-D + 10 mg/l Adenine)
6. Washing step
7. Selection of transformants on MYT selective media (MYT + 250 mg/l cefotaxime + 50 mg/l kanamycin)
Cellular line maintenance
Whole plant generation


Optoperforation
laser-assisted perforation
Polymers
e.g. Calcium Phosphate
Lipid Mediated
liposome-DNA complexes
heparan sulfate
endosome
DNA
nuclear pore complex
nucleus
nuclear membrane
cytosol
Viral Transduction
Microinjection
via microneedles
Electroporation

The production of biological drugs - recombinant technology

3 generation of biologicals

1) " copies " of human proteins

2) modified proteins (AAs substitution, glycosylation, PEGylation) - better pharmacokinetics, pharmacodynamics - e.g. glargine, PEG-IFN

3) de novo designed proteins / MAB

Contaminants from manufacture process

- Microorganisms - antigenic structures, pyrogenicity , sepsis
- Viruses
- DNA - ? Consequences?
- Custom product in improper 3D structure
- Contaminating proteins
  - antigenicity
  - stability (protease)
  - safety (growth factors, hormones, toxins)

➡ Purification - affinity gel / permeation chromatography

Contaminants from manufacture process

Purification - affinity gel / permeation chromatography

Purity ± 98-99 %

➡ **Verification of the biological activity of each batch !**

- Biochemical methods , cell lines or animal (e.g. Epoetin)

= Time-consuming , cost , accuracy

The risk of functional damage of biologicals

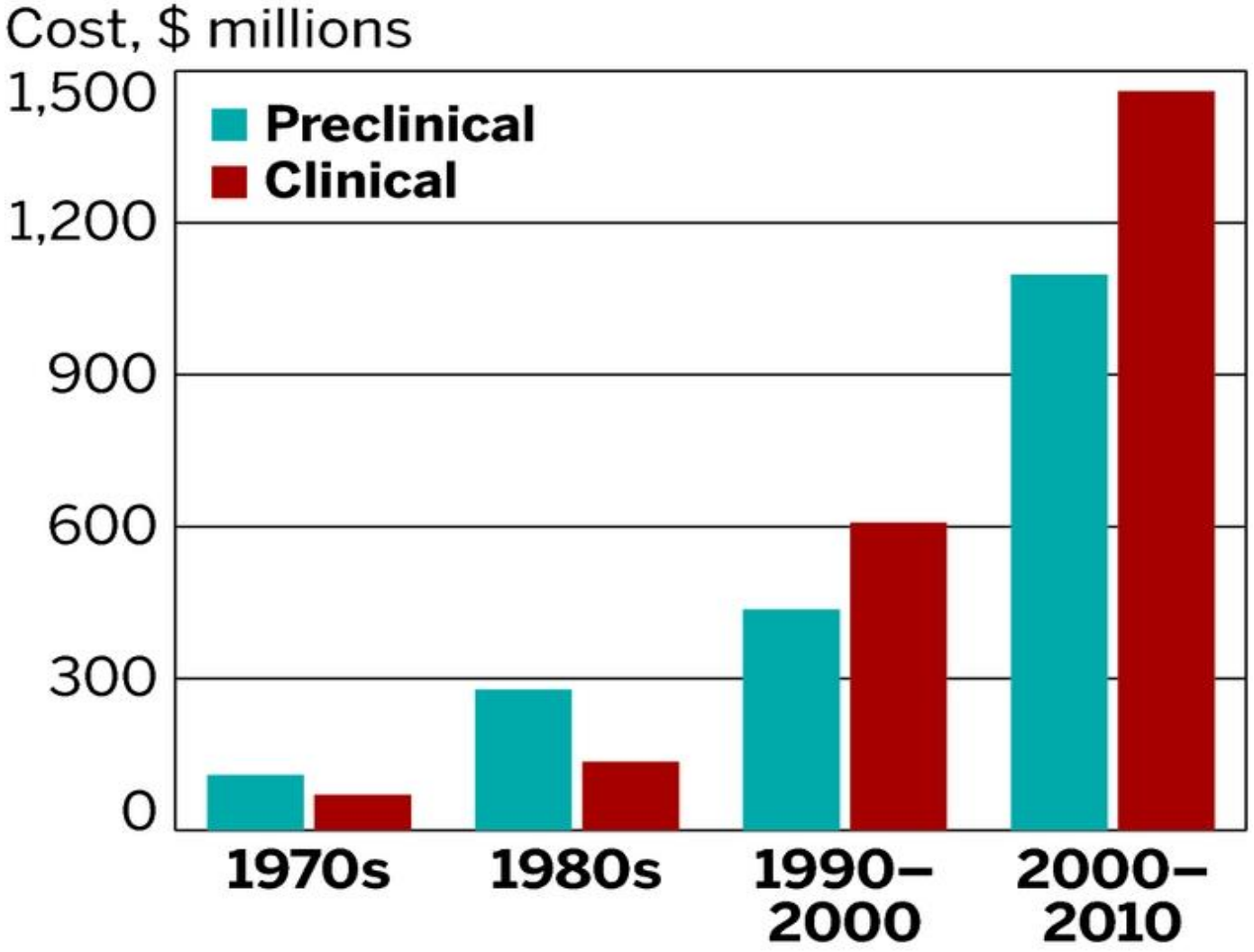
- denaturation
- precipitation
- deamination
- mismatch of SH groups (= incorrect 3D)
- oligomerization, aggregation, covalent binding
- hydrolysis
- isomerization
- racemisation
- formation imides
- oxidation

Multiple stabilizers
cryopreservation

metal chelation

checking the pH, osmolarity , strengthening the hydrophobic bonds

Costs of drug development



Costs of the treatment

- Biological therapy is more expensive than "traditional" drugs
- Reasons - significantly higher development costs
  - Demanding and complex testing
  - The nature of products and higher costs after launch
  - Higher costs for production, storage, transportation, shorter expiration

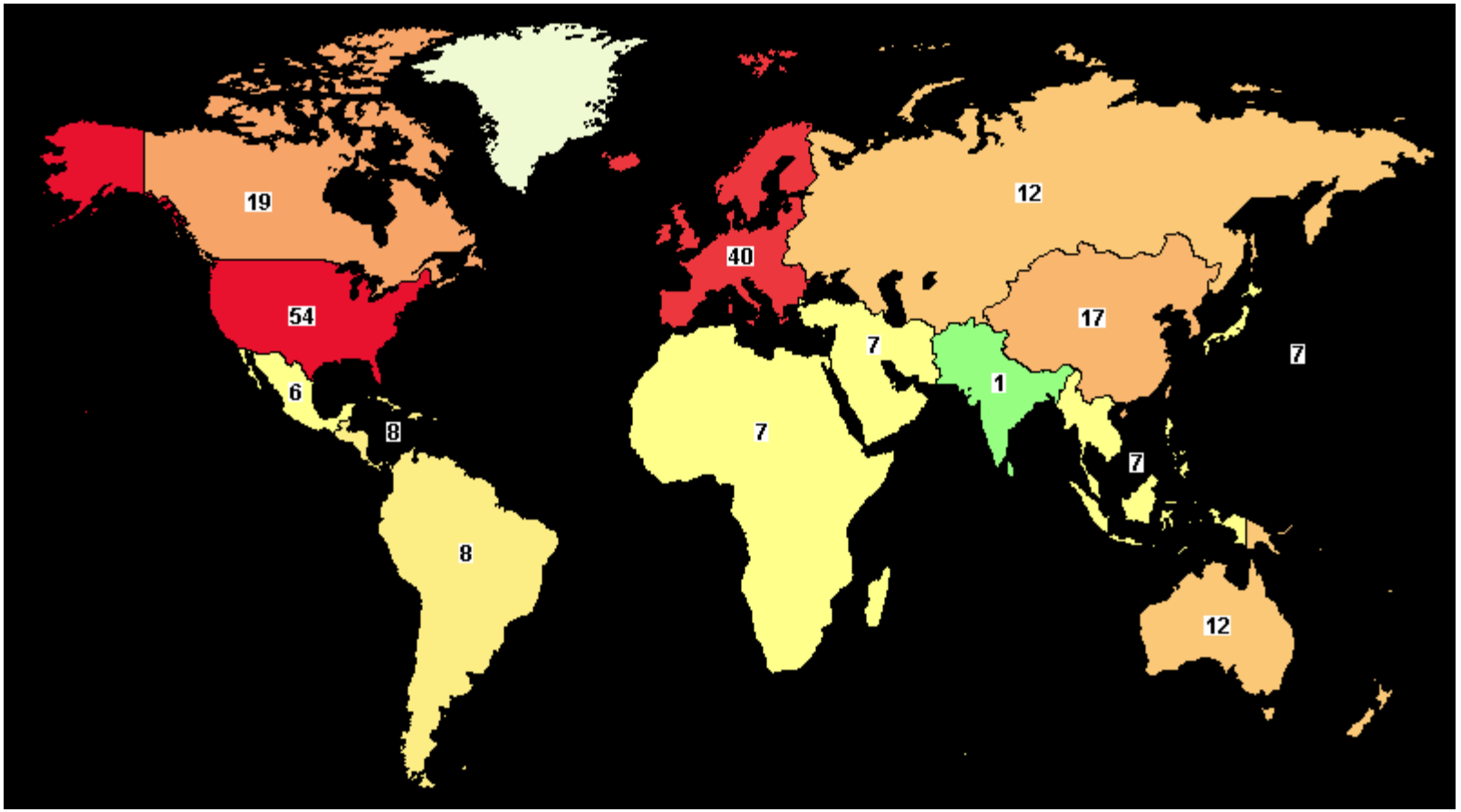
  consequences: **lower numbers of treated patients** (up to 2 orders !!!)

Despite that: effective and in many cases can save money in terms of direct and indirect costs

direct costs: shorter hospitalization, reducing the number of surgical procedures, reduce the cost of follow-up treatment , ...
indirect costs : accelerating the patient's self-sufficiency, reducing the costs of absenteeism, cost reductions in social support and care allowances , reducing the cost of informal care and nursing

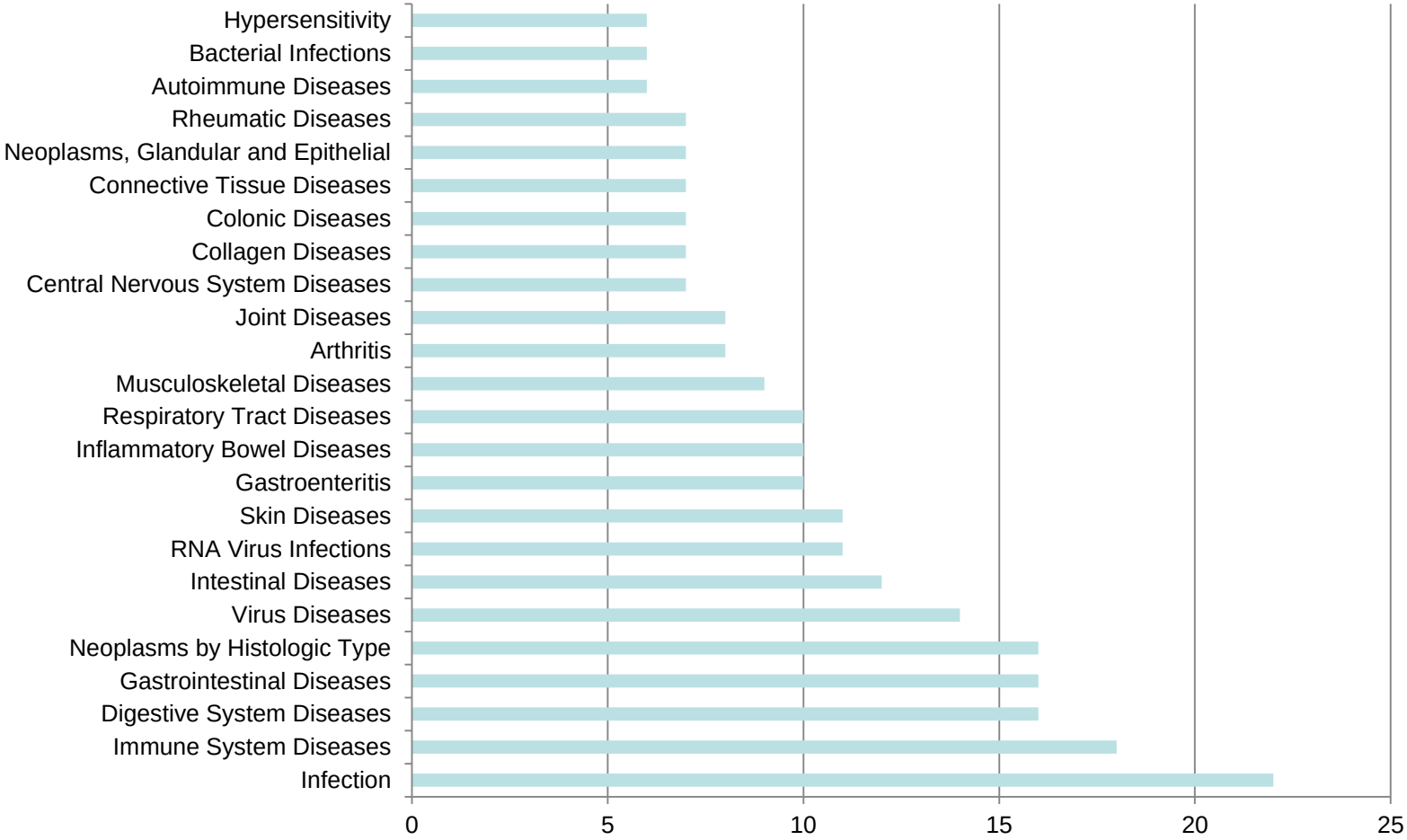
103 CT on biologicals

2017, biological | Open Studies | Phase 1, 2, 3, 0 | NIH, U.S. Fed, Industry, Other)



103 CT on biologicals

(2017, biological | Open Studies | Phase 1, 2, 3, 0 | NIH, U.S. Fed, Industry, Other)



BIOSIMILARS

BIOSIMILARS

" Copy" of biotechnology drugs

- produced after the expiry of patent protection on the original biotechnology drugs

- In the US, for the same group uses the term „Follow -on Biologics“ , abbreviated „fobs“ .

The standard procedure for the registration of generic medicines with defined structure (ie . bioequivalence study) is inapplicable

BIOSIMILARS

- Biosimilars drugs are similar, but **not identical** with the original biological drug.
- Biosimilars are **not automatically therapeutically interchangeable** with the original biological drug .
- **small change** process in biosimilars may cause an **entirely different drug**.
- Biosimilars pass before entering the market or **shorter simplified clinical trials** , but disproportionately more complex than with generics

BIOSIMILARS

- after completeng „Centralised registration Procedure“ (mandatory for the registration of medicinal products manufactured with sophisticated technology, particularly biological drugs)
- compared the effectiveness and quality in studies similar to those that are required for orig. preparation
- included in European Directives
- determining whether the product was evaluated in the same dosage form, strength, by the same route of administration as the ref. product and whether it was used in the same indication e.g. growth hormone: 12 months
- comparative study of efficacy - safety within the RCT stage III The price is about 10 times higher than for generic medicines

Biological drugs in a broader context

- Gene therapy
- Anti-sense therapy
- Immunization with vaccines

Biological drugs in a broader context

Gene therapy

- Incorporation of a gene sequence into a target tissue by an appropriate vector approach
- treating or preventing gene-related illnesses by changing the expression human genes

Gene therapy - vectors

- biological vectors of viral origin
  - the most effective method of therapy
  - retroviruses , lentiviruses , adenoviruses

- injection of naked DNA directly into the tumor
- genetic cannon - DNA wraps around gold particles and scored into the epidermis - strong helium gun
- lipofections of DNA -coated liposome and delivered into the tissue
- intravascular , intratracheal , oral…

Vectors for plasmids

Table 59.3 Characteristics of some delivery systems for gene therapy

Vector	Advantages	Disadvantages
Liposomes	Virus-free, cheap to produce	Low efficiency, sometimes cytotoxic
DNA cassettes	Virus-free	Low efficiency, expression temporary
Herpes simplex virus type I	Highly infective, persistent expression	No integration with host DNA, cytotoxic, difficult to handle
Adenovirus	Highly infective in epithelia	Immunogenic and transient, requires readministration
Adeno-associated virus	Stable	Low capacity
Retrovirus	Efficient, permanent	Low capacity, unstable, must integrate into host DNA, requires dividing cells

After Wolf & Jenkins, 2002.

Gene therapy SCID

- SCID severe combined immunodeficiency
- 1990 my first attempt at gene therapy on 4-year girl Ashanti DeSilva
- the T cells have been modified ex vivo
- normal ADA (adenosine deaminase) by a vector derived from MoMLV (Moloney murine leukemia virus).

- The girl is still alive .

- 2002 -5 boys with severe X-linked SCID underwent gene therapy ex vivo, with four times a year the state has improved significantly, with two of them unfortunately died leukemia .
- Attempts suspended and perfecting the methodology

Gene therapy - the risks

- Adverse immune response
- Infections vector - natural activation of virus
- Genetic influence on gametes
- Risk of malignity- activation of protooncogenes , suppression of regulatory genes

Biological drugs in a broader context

Anti-sense therapy

- Incorporation of complementary oligonuleotides to the initiation codon / promoter to DNA
- block the effects of action of proteins that are not transcribed

- **Olimersen** - lowering expression of Bcl -2 (overexpressed in many cancer) - withdrawn form registration

The antisense and gene therapy in practice

- **Fomivirsen** - antisense sequences to the mRNA of human CMV - Ophthalmic applications for pac . HIV + to reduce CMV infection
- **Pegaptanib** - oligonucleotide binding to the VEGF protein - for the treatment of wet AMD
- **Gencidin** - adenovirus carrying the gene for p53 - From r . 2004 registered in China
- **Glybera** - 3 x 1012 genome copies of human lipoprotein lipase in a viral vector (adeno- associated virus serotype 1 (AAV1) to treat hyperlipoproteinemia I

Clinical use of biological drugs

(selected examples)

Recombinant hormones

Insulin the first biological drug (1982)

- S. cerevisiae , E. coli - modified insulins (aspart, glulisine detemir, glargin)

Glucagon - peptide, 29 AMK, *E. coli i S. cerevisieae*

GH - 191 AMK, 2x S-S bridge

- before biotechnological synthesis it was isolated from hypophysis of dead people

- I: Turner sy. (caryotype 45, XO)

- 1977 (Nutropin, P. Seeburg, Genentech, UCSF)

IGF – growth failure

Recombinant hormones

Parathyroid hormone - 115 AA

Calcitonin - originally isolated from salmon

Gonadotropins - for IVF (RG Edwards , Nobel. Prize , 2010)

FSH - follitropin α (CHO cells) - hyperovulation

LH - maturation of oocytes, together with FSH

hCG - (CHO) cells - follicular maturation, support for ovulation

Biological treatment of autoimmune diseases

1. rheumatic diseases
2. psoriasis
3. inflammatory bowel disease
4. asthma bronchiale
5. multiple sclerosis
6. ophtalmology

1. Biological Treatment of rheumatic diseases

Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis , ankylosing spondylitis

Early intervention prevents irreversible changes;

Some of patients stay in sustained remission even after treatment has stopped !

1. Biological Treatment of rheumatic diseases

Anti-TNF drugs

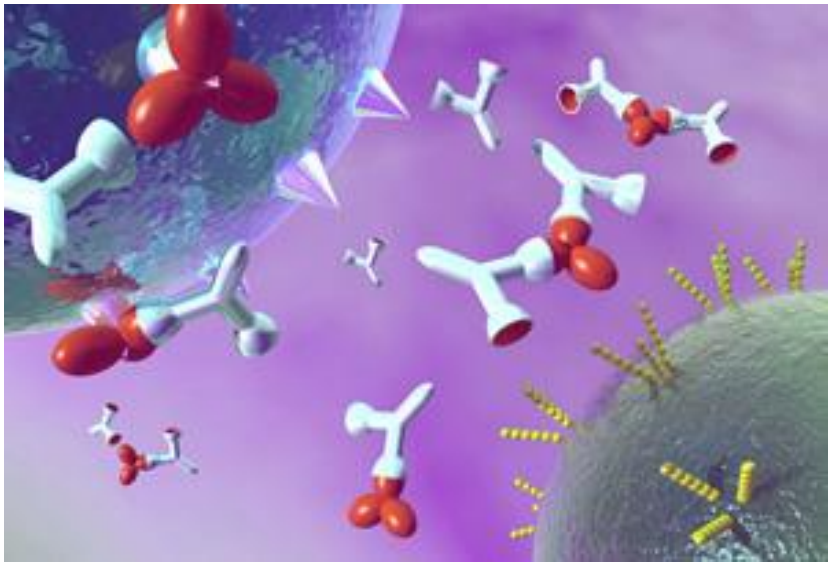
Infliximab – chimeric mAbs, IgG, 75 % of human,

25% of the murine antibody

high affinity binding to human TNFα

formation of stable complexes which bind complement

induction of apoptosis and lysis of the cells that produce TNFα , the disintegration of granulomas



1. Biological Treatment of rheumatic diseases

Anti-TNF drugs

Adalimumab

- human MAB binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors

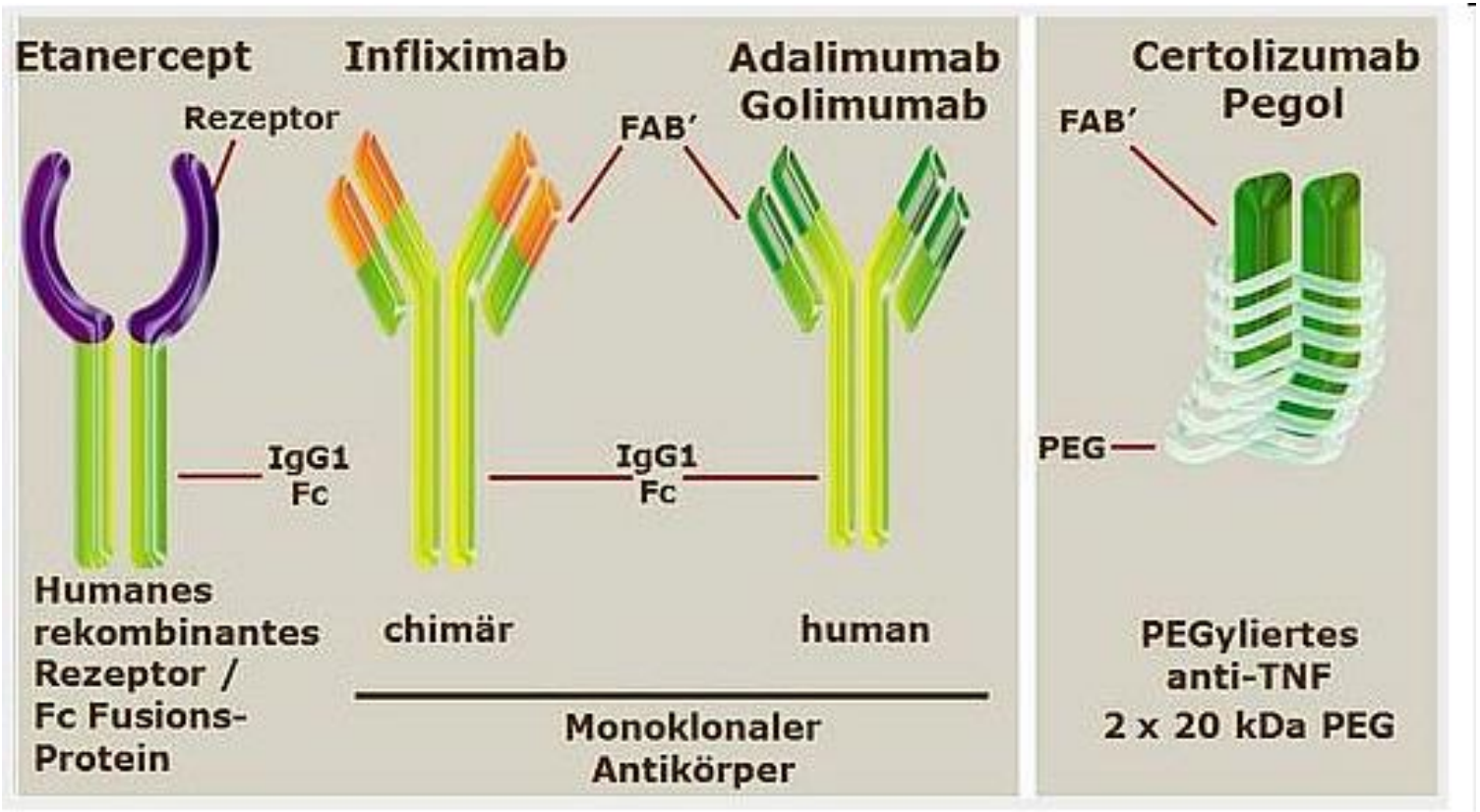
Golimumab

– human MAB wich bind to both soluble and membrane bounbd TNFα

- the same mechanism action as infliximab

1. Biological Treatment of rheumatic diseases

Certolizumab – humanized Fab fragment of TNFα antibody, konjugated with PEG



1. Biological Treatment of rheumatic diseases

Etanercept – binds TNFα

= soluble dimeric fusion protein – extracelulár domain of receptor for TNFα and Fc chain of human IgG_1

Mechanism of action: competitive inhibition of TNFα, decreased effect of TNFβ

does not bind complement, but leads to the disintegration of granulomas

1. Biological Treatment of rheumatic diseases

Anakinra – IL1 receptor antagonist („IL-1 RA“)

weaker effect than anti-TNF drugs

Rituximab - binds to the transmembrane antigen CD20

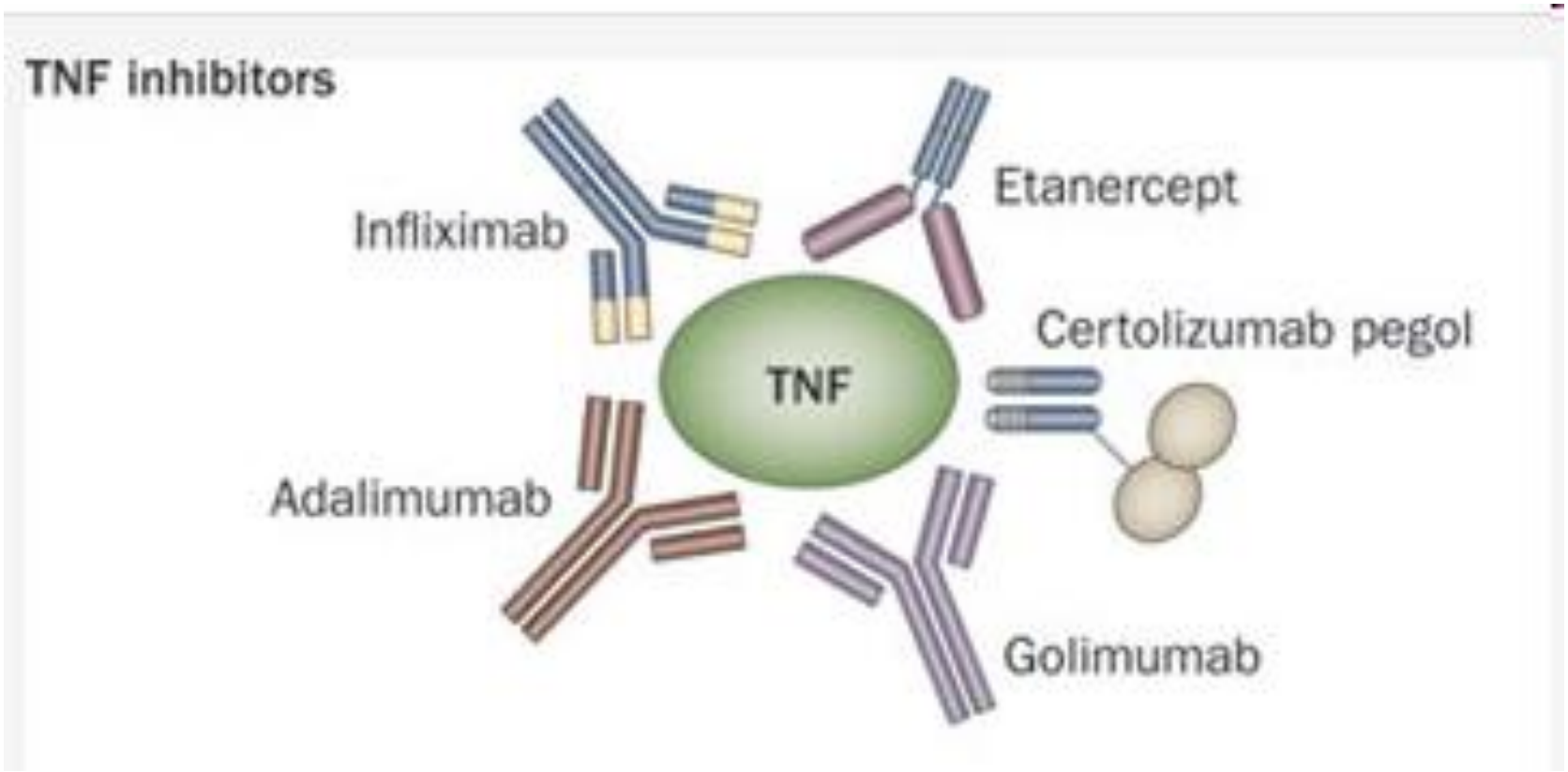
(on pre-B and mature B lymphocytes)

expressed on> 95% of all non-Hodgkin lymphomas of B cell origin.

in combination with MTX , cyclophosphamide

Biological treatment of rheumatic diseases

anti-TNF drugs



Adverse effects of anti -TNF agents

opportunistic infections –

higher risk for: combination of immunosuppressive drugs (with 2 - combined to 14x !)

malnutrition

Age > 50 years

mycobacteria , listeria , fungal , viral infections

Adverse effects of anti -TNF agents

Paradoxical autoimmune reactions

anti-idiotypic antibodies (in addition prevents binding of the antibody to TNF)

TB –activation of latent forms

Late carcinogenicity - lymphoproliferative disease (2-3 times higher versus the healthy population) , inconsistent data

Others - specific ADR for specific substances

1. Biological Treatment of rheumatic diseases

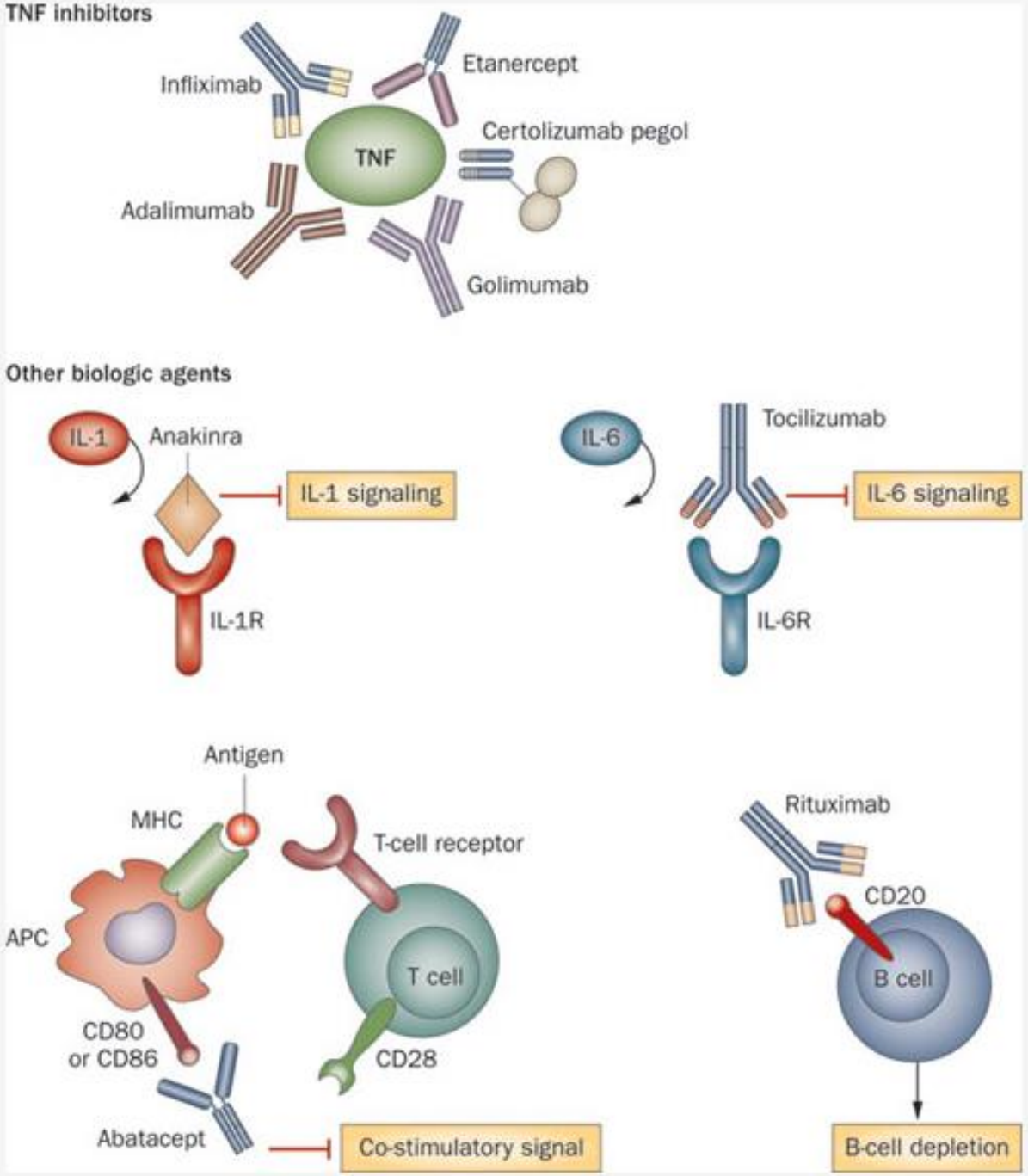
Abatacept - recombinant fusion protein from the extracellular CTLA4 (Cytotoxic T - lymphocyte - assoc . Antigen 4) ;

competitively binds to CD80 , thereby preventing T cell proliferation –

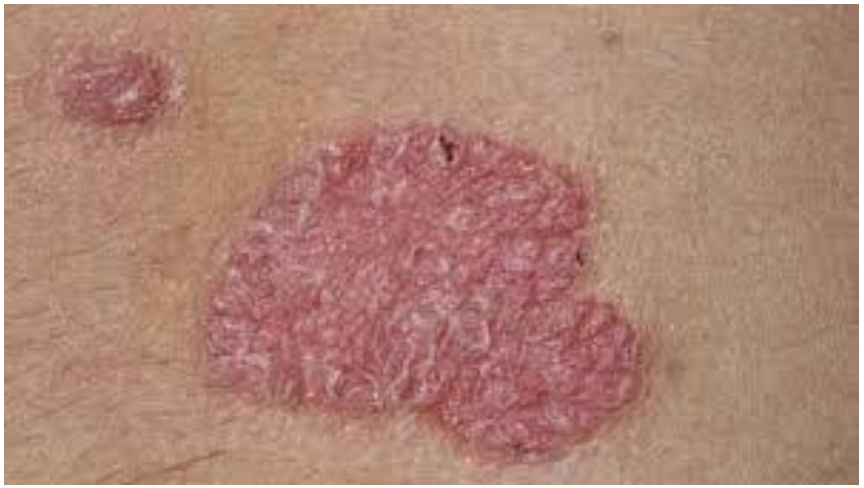
in children not to be combined with anti-TNF therapy (infectious complications)

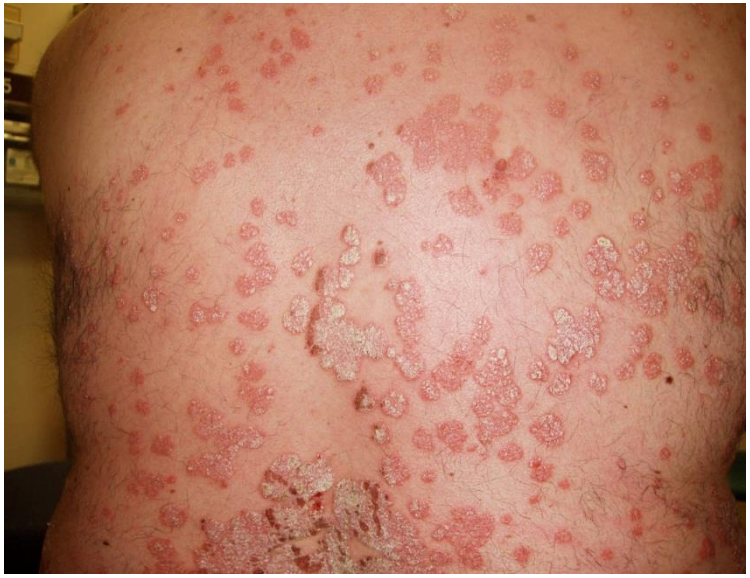
Tocilizumab - humanized mAb against conventional IL6

AE: (infection) + lipids increase (CHOL , LDL, TAG)


TNF inhibitors
Infliximab
Etanercept
TNF
Certolizumab pegol
Adalimumab
Golimumab
Other biologic agents
IL-1
Anakinra
IL-1 signaling
IL-1R
IL-6
Tocilizumab
IL-6 signaling
IL-6R
Antigen
MHC
T-cell receptor
APC
T cell
CD80
or CD86
CD28
Abatacept
Co-stimulatory signal
Rituximab
CD20
B cell
B-cell depletion

2. The biological treatment of psoriasis





2. The biological treatment of psoriasis

Etanercept - see above

- Only one biological treatment of psoriasis for children 8-18 years

Infliximab - see above – s.c. admin 0th , 2nd, 6th week , then after 8 weeks

Ustekinumab - MAB fully human IgG1 anti-IL -12/ 23 (important in the pathogenesis of psoriasis) inhibition of cytokine cascade sc at 0, 4 weeks, 12 weeks

AE : nasopharyngitis, headache, arthralgia, local irritation at the injection site

3. Biological treatment of inflammatory bowel disease

inflammatory bowel disease

Crohn's disease

ulcerative colitis

Anti-TNF drugs (see above)

infliximab

adalimumab

certolizumab

3. Biological treatment of inflammatory bowel disease

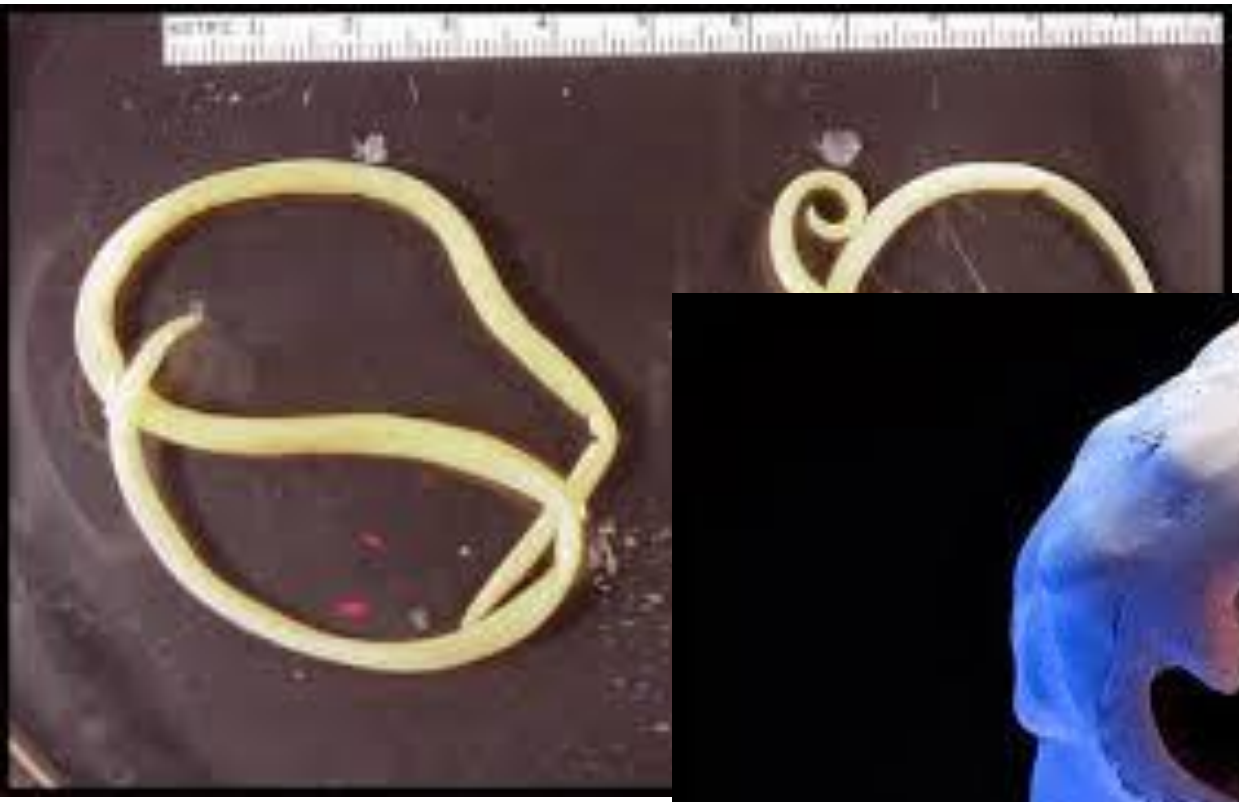
Natalizumab - IgG4 humanized MAB against integrin α (on the surface of leukocytes, ensures migration across the capillary wall)

Rescue treatment in Crohn D. (only in the US , in Czech Republic registered for MS)

Vedolizumab - humanized mAb IgG1 against α4β1 integrin (on activated leukocytes , provides adhesion to the endothelium and the penetration into the circulation from the gastrointestinal tract)

3. Biological treatment of inflammatory bowel disease

trichuris suis ova



3. Biological treatment of inflammatory bowel disease

trichuris suis ova

15 clinical studies :

ulcerative colitis

Crohn's disease

psoriasis

celiac disease

diseases of the autism spectrum

INFLAMMATORY BOWEL DISEASE

Trichuris suis therapy in Crohn's disease

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Background: Crohn's disease is common in highly industrialised Western countries where helminths are rare and uncommon in less developed areas of the world where most people carry worms. Helminths diminish immune responsiveness in naturally colonised humans and reduce inflammation in experimental colitis. Thus exposure to helminths may help prevent or even ameliorate Crohn's disease.
Aims: The aim of the study was to determine the safety and possible efficacy of the intestinal helminth *Trichuris suis* in the treatment of patients with active Crohn's disease.
Patients: Twenty nine patients with active Crohn's disease, defined by a Crohn's disease activity index (CDAI) ⩾220 were enrolled in this open label study.
Methods: All patients ingested 2500 live *T suis* ova every three weeks for 24 weeks, and disease activity was monitored by CDAI. Remission was defined as a decrease in CDAI to less than 150 while a response was defined as a decrease in CDAI of greater than 100.
Results: At week 24, 23 patients (79.3%) responded (decrease in CDAI >100 points or CDAI <150) and 21/29 (72.4%) remitted (CDAI <150). Mean CDAI of responders decreased 177.1 points below baseline. Analysis at week 12 yielded similar results. There were no adverse events.
Conclusions: This new therapy may offer a unique, safe, and efficacious alternative for Crohn's disease management. These findings also support the premise that natural exposure to helminths such as *T suis*

15 studies found for: trichuris suis

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Rank	Status	Study
1	Recruiting	**Trichuris Suis Ova (TSO)in Recurrent Remittent Multiple Sclerosis and Clinically Isolated Syndrome** **Condition:** Multiple Sclerosis **Intervention:** Drug: Trichuris suis ova
2	Active, not recruiting	**Trichuris Suis Ova in Autism Spectrum Disorders** **Condition:** Autism **Intervention:** Drug: Trichuris Suis Ova
3	Recruiting	**Mucosal Immunity of Ulcerative Colitis Patients Undergoing Therapy With Trichuris Suis Ova** **Condition:** Ulcerative Colitis **Intervention:** Drug: Trichuris suis ova
4	Completed	**Trichuris Suis Ova Therapy for Relapsing Multiple Sclerosis - a Safety Study** **Condition:** Relapsing Multiple Sclerosis **Intervention:** Biological: Trichuris suis ova
5	Completed	**Trichuris Suis Ova in Peanut and Tree Nut Allergy** **Condition:** Food Allergy

4. Biological treatment of bronchial asthma

Adjunctive/supplementary treatment in patients with more serious desease which do not respond to other treatments

–Omalizumab – humanized anti ab, bis IgE , s.c.

AE: malignancies?, parasitoses ... data not convincing

Mepolizumab - anti IL5 antibody

Infliximab/Golimumab/etanercept – anti TNFα

Off label, clinical benefit not convincing

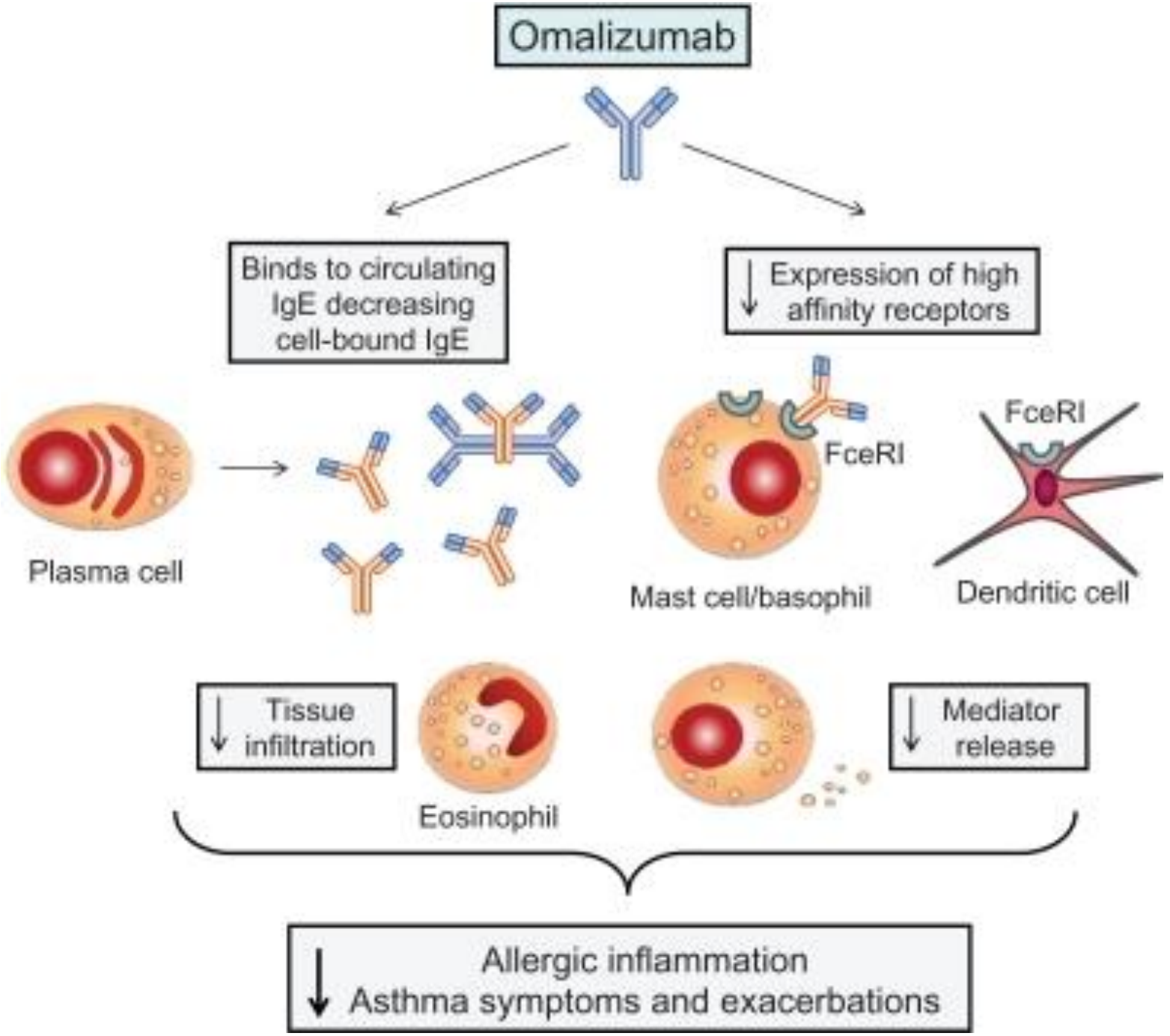
4. Biological treatment of bronchial asthma

Other „problematic“ treatment

keliximab – MAB anti- CD4 , smaller study demonstrated effect on pulmonary parameters (PEF) ; studies have been stopped because of concerns about the reduction in the number of CD4 cells

pitrakinra - inhibits the binding of IL- 4 and IL -13 to IL- 4Rα subunit; may prevent worsening of FEV1 after allergen exposure ; tested also in EA; requires further study

daclizumab - binds to CD25 inhibits the binding of IL- 2 receptor; may decrease T-cell activation , improves FEV1 , in one study alleviate symptoms ; 3 patients had serious adverse reactions


Omalizumab
Binds to circulating IgE decreasing cell-bound IgE
↓ Expression of high affinity receptors
Plasma cell
FceRI
Mast cell/basophil
FceRI
Dendritic cell
↓ Tissue infiltration
Eosinophil
↓ Mediator release
↓ Allergic inflammation
↓ Asthma symptoms and exacerbations

5. Biological treatment of multiple sclerosis

- demyelinating disease
- onset 20-40 yrs of age, women more frequently
- usually begins first clinical event (clinically isolated syndrome , CIS) includes visual, sensory or motor symptoms

Relaps-remitent form

Progresive form

- If untreated - after 10-20 years swithes in secondary progression - ↑ neurological disability in about 50 % after 15 years of physical disability and cognitive dysfunction with serious socioeconomic consequences

Total direct + indirect costs of invalidized is 3 times higher than biol. treatment

5. Biological treatment of multiple sclerosis

Natalizumab - AB binds to α4β1 integrin of lymphocytes which allow them to enter into the CNS (bind integrin subunit on endothelial adhesion molecules before penetratvasion of vascular wall)

It has a preventive effect on relapses and reduce the symptoms of ongoing relapse

Adverse reactions: Serious opportunistic infections , rare (1 : 1000) progressive multifocal leukoencephalopathy (**PML**) – risk factors- JCV viral infection/antibodies, imunosupressant treatment

iv at intervals of 4 weeks

5. Biological treatment of multiple sclerosis

Glatiramer acetate – a mixture of synthetic polypeptides derived from four AA (Glu, Ala , Tyr , Lys)

- Peptide analog of myelin basic protein - suppresses inflammation and also has neuroprotective properties .

influences lymphocyte populations in the circulation by induction of immunoregulatory Th2 lymphocytes

5. Biological treatment of multiple sclerosis

Anti-CD20 MAB (CD 20 lymphocytes)

rituximab

ocrelizumab

ofatumumab

alemtuzumab

Anti CD 25 MAB

daclizumab – humanized monoclonal antibody of IgG1 subtype that binds to the Tac epitope on the interleukin-2 (IL-2) receptor α-chain (CD25), thus, effectively blocking the formation of the high-affinity IL-2 receptor.

For severe attacks of MS

6. the treatment of viral hepatitis

IFNα, IFNβ –chronic infection HBV, HCV

Antivirotics - tenofovir, entecavir, adefovir, lamivudin

IFNα – „conventional“ is already not used

CIFN – consensual IFN - prim . structure according to the most frequently occurring AAs in the sequence of all the known IFN

PEGylated – PolyEthylenGlycol – polymer of ethylene oxide - prolongs the half (7-10x) , increases the plasma concentrations do not change the absorption rate

- Protection against proteases

6. the treatment of viral hepatitis

PEG-IFNα2a – substituted monomethoxyPEG + IFN α2a

PEGylated – PolyEthylenGlycol – polymeric etylendioxid – prolong halflife (upo to 100x)

PEG-IFNα2b – linear PEG + IFNα2b

Albumin-IFNα2b - recombinant protein, a fusion of two genes ; efficiency , NA similar to the previous one,

1 application every 14 days (longer half-life of albumin) , higher price

6. the treatment of viral hepatitis

General ADRs IFN

- **Frequent** - flu-like syndrome . , chronic fatigue syndrome

- myelosuppression

- dysthymia , depression, anorexia

- weight loss, diarrhea

- **Rare** - inflammation at the injection site

- psychotic disorder , suicidal tendencies

- disorders of sex . functions

- acute heart failure

- Interstcial nephritis

The use of targeted/biological therapy in ophthalmology

- used primarily substances with ***antiangiogenic activity*** (ie. block of neovascularization)
- most importance for the process of angiogenesis , VEGF = **vascular endothelial growth factor**
  - important physiological functions
  - located on the lining of blood and lymph vessels in the body
  - regulates the proliferation and vascular permeability
  - several types (A - E)
- **drugs used**
  - monoclonal antibodies (bevacizumab, ranibizumab)
  - small drugs (pegaptanib, vortepofin)
  - aflibercept= fusion protein

The use of targeted/biological therapy in ophthalmology

- Bevacizumab - was developed for the treatment of colorectal cancer, indication AMD is used off-label

MA : monoclonal antibody against VEGF (binds VEGF1 and VEGF2 , blocks the interaction of DP.)

AE: acceleration of hypertension, proteinuria, thromboembolic events, poor wound healing...

- ranibizumab
  - Indications : AMD , CNV (chorioidal neovascularization)
  - MA : fragment of a monoclonal antibody against VEGF - A
  - short plasma half-life
  - Administration 1x per month until the patient's visual acuity is stable (three consecutive monthly assessments)

Targeted therapy

- pegaptanib
  - synthetic oligonucleotide
  - the indication wet AMD
  - MA : binds to receptor VEGF - A_{165}
- vorteporfin
  - as a single infusion is administered systemically
  - always in combination with photodynamic therapy
- aflibercept
  - MA : recombinant fusion protein; false receptor binds VEGF-A and PlGF

Thank you for attention

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