Immunostimulation and Immunomodulation - Vaccination, Biological Treatment, Current Possibilities of Immunological Intervention

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Pharmacotherapy in immunology

Allergy therapy - antihistamines, cromoglycans, corticoids, local alpha and betamimetics, biological therapy, specific immunotherapy

Immunosuppression - NSAIDs, corticosteroids, calcineurin inhibitors, mTOR inhibitors, cyclophosphamide, azathioprine, mycophenolate, methotrexate

Immunostimulation
- non-specific - levamizole, isoprinosine
- specific - vaccination
- substitution - immunoglobulins
Therapy of allergic diseases
Antihistamines used to treat allergic diseases

1. First generation Antihistaminics
   - Highly sedative: Diphenhydramine, Dimenhydrinate, Promethazine, Hydroxyzine
   - Moderately sedative: Pheniramine, Cyproheptadine, Meclizine, Buclizine, Cinnarazine
   - Mild sedative: Chlorpheniramine, Dexchlorphenhiranme, Dimethindene, Triprolidine...
   - Only injectable antihistaminic in the Czech republic – Bisulepin (Dithiaden).

2. Second generation Antihistaminics
   - Fexofenadine, Loratadine, Desloratadine, Cetrizine, Levocetrizine, Azelastine, Mizolastine, Rupatadine....
Sodium cromoglycate

Derivative of Khellin, substance conained in corrot like plant Khella (Ammi visnaga), for centuries used as myorelaxans (Egypt).

Stabilizes membrane of basophiles - prevents degranulation and release of mediators of allergic reaction. Acts „a step earlier“ than antihistamines. Application in nasal sprays, nebulizers, drops but also orally. Commercial preparations - local - Allergocrom, Cromohexal, oral Nalcrom Few side effects, mild effects, but short half-life – 4 x daily application - reduced usability. Longer acting is another cromon - Nedocromil. Nowadays largely replaced by topical corticosteroids, but are important for pediatric patients due to the safety of treatment.
Mechanisms of allergen immunotherapy

Monocytes
- ↑ IL-10

Specific allergen immunotherapy
- T lymphocytes
  - ↓ allergen specific proliferation
  - ↓ quantity in tissues
  - ↓ cytokines in blood stream
  - ↓ Th2 cytokines
  - ↑ Th1 cytokines
  - ↑ Treg, IL-10, TGF-β

Eosinophiles
- Mastocytes
- ↓ quantity in tissues
- ↓ release of mediators

B lymphocytes
- ↓ allergen specific IgE
- ↓ seasonal increase of IgE
- ↑ blocking antibodies IgG1, IgG4 and IgA
- ↓ IL-10
Allergens for diagnosis and treatment

Purified extracts or recombinant proteins
Anti-inflammatory and immunosuppressive therapy
Nonsteroidal anti-inflammatory drugs, NSAID

Suppress pain and inflammation. Effect - inhibition of cyclooxygenase (COX, mainly required inhibition of COX-2) - suppression of arachidonic acid metabolites (prostaglandins, thromboxanes, prostacyclins)

Heterogeneous group of drugs - Salicylates (aspirin), propionic acid derivatives (Ibuprofen, Ketoprofen, Naproxen ...), acetic acid derivatives (Indometacin, Diclofenac ...), Sulfoanilides (Nimesulid) ...

Coxibs (cyclooxygenase-2 inhibitors) - selective COX-2 inhibitors - fewer side effects in the digestive tract.. There is information about adverse effects on the cardiovascular system. Celecoxib, valdecoxib, etoricoxib, lumiracoxib.

Side effects - dyspepsia, gastr. ulcer (unwanted COX-1 inhibition), nephrotoxicity, hepatotoxicity
Disease Modifying Antirheumatic Drugs" (DMARDs) in the treatment of rheumatoid arthritis

A heterogeneous group of drugs slowing the course of the disease. They contain drugs not belonging to steroidal or non-steroidal anti-inflammatory drugs.

A) Antimalarics - Chlorochin and Hydroxychlorochin
B) Gold salts
C) Sulphonamide Sulfasalazine
D) Penicillamine
E) Immunosuppressants - methotrexate, azathioprine, cyclophosphamide, leflunomide
F) Biological therapy

Different levels of undesirable effects - retinopathy (antimalarial), leucopenia (sulfasalazine), nephrotoxicity, myelotoxicity (gold salts) ...

The exact mechanism of action is not always known (A-D). Different application schemes according to severity of RA.
Molecular targets of Immunosuppressive drugs

Antigen presenting cell

CD4 → CD3 → MHC II → TCR → Steroid

Anti-CD3

T-lymphocyte

Cyclosporin A

Anti-IL-2R

Steroid

Calcineurin

Sirolimus

Everolimus

NFAT

TOR

Cyclin C/D

S

G1

M

Azathioprin

Cyklofosfamid

Mykofenolát

mRNA

G2
Serum and immunoglobulin preparations
Immunoglobulin preparations

Since the 1940s, they have been prepared using the so-called Cohn fractionation based of precipitation of plasma proteins using ethanol and freezing (fraction II). The preparation for intramuscular administration containing aggregated globulins would cause anaphylactoid reaction during intravenous administration. Useful for the treatment of mild deficits and infections. There are insufficient doses for agammaglobulinaemia.

Intravenous gamaglobulins - since the 1970s. Highly purified IgG not containing aggregates and IgA or IgM antibodies. Originally intended for treatment of agamoglobulinaemia, "accidentally" discovered immunomodulatory effects.

Exact mechanism of immunomodulatory action is unknown, presumed mechanisms are blockade of Fc receptors, anti-idiotypic effects, reduction of complement activation ...

Nowadays a wide range of indications (including off-label)
Intravenous gammaglobulins (IVIG)

FDA guidelines:
- prepared from mixed serum from at least 1,000 donors
- contains all 4 subclasses IgG (IgG1 - IgG4)
- biological activity for at least 21 days
- does not contain serum of patients positive for HIV and hepatitis B and C
- treatment inactivating viruses

Indication:
Antibody immunodeficiencies
CVID, hypogammaglobulinaemia, X-linked agammaglobulinaemia, acquired antibody deficits

Autoimmune diseases
Vaskulitis (Kawasaki's disease - 1st choice medicine), thrombocytopenic purpura, autoimmune thrombocytopenia, Pemphigus, Myasthenia gravis, Lupus erythematosus, Guillan-Barré syndrome, multiple sclerosis ...

Hematological diseases
chronic lymphocytic leukemia

Transplantation
management of complications in kidney transplantation, GVHR

Infections and septic states
effectiveness has not been sufficiently demonstrated, nevertheless sometimes used
Passive immunization

By the thirties of the 20th century, serum therapy was the main therapeutic procedure for infectious diseases. Used before the invention of antibiotics.

Initially infusion of unmodified serum aseptically collected from an immunized animal. Complications - urticaria, fever, arthritis, peripheral neuritis, or even anaphylactic shock - type I and II hypersensitivity reactions (according to Coombs and Gell)

Later – precipitated IgG from animal sera digested with pepsin (resulting in Fc and bivalent F (ab ')$_2$), purified by chromatography. Inactivation of viruses is ensured by heat treatment for 10 hours at 60 °C

Nowadays - therapeutically used serum against botulism, tetanus, rabies and diphtheria. The use of serum against viper venom has been abandoned in the Czech republic.
Immunostimulation
Isoprinosine

Synthetic purine derivative (inosine + dimethylaminoisopropanol and acetaminobenzoic acid) immunostimulatory and antiviral activity.

Indications: Persistent viral infections, mainly caused by herpesviruses, in the past also used in HIV infection therapy. In therapy of HIV is largely replaced by highly active antiretroviral therapy (HAART), in herpes infections with specific antiviral drugs (Zovirax, Herpesin ...)

Currently used in recurrent infections caused by a weakened immune system (eg EBV). Only chemically defined immunostimulant drug available currently.
Levamisole

Originally a veterinary antihelmintic, effective only against nematodes. Immunostimulatory effects, particularly cellular immunity, were detected later. Tested as an adjuvant in combination with 5-fluorouracil in colorectal cancer - results unconvincing. Good efficacy has been reported for poorly healing wounds. Side effects - agranulocytosis, vasculitis. Released from the market, currently available only for veterinary use.
Levamisole contaminated cocaine

More than 70% of samples of cocaine detained in the US contained Levamisole. In most users with no negative effect, in part caused agranulocytosis and vasculitis, sometimes necrotizing. It was originally considered to be an additive for weight gain and gain. Now a new theory: Levamisol is in many ways similar to nicotine, acts on acetylcholine receptors and increases activity of the nervous system. Cocaine increases the production of dopamine and serotonin in the short term and acts as a stimulant of the central nervous system. The effects of cocaine and levamisol are likely to be mutually supportive!
Necrotizing vaskulitis
„Flash eating cocaine“
Bacterial immunomodulators

Inactivated lysates of various bacterial species. Preparations primarily stimulating non-specific immunity by binding PAMP's to appropriate PRRs. The participation of antigen-specific mechanisms has not yet been fully clarified. Effect - increased secretion of IgA, mucus, lysozyme, activation of monocyte-macrophage cell lines, cytokines IFN-γ, IL-12 …
Indications: primarily recurrent infections affecting mucosal surfaces - respiratory tract, urogenital tract.
Preparations proven by a number of studies, drugs on prescription or food supplements.
Clinical experience is mostly very positive.
<table>
<thead>
<tr>
<th>název přípravku</th>
<th>složení přípravku</th>
<th>léková forma</th>
<th>způsob aplikace</th>
<th>indikace</th>
<th>vlastní zkušenosti</th>
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</thead>
<tbody>
<tr>
<td>Broncho-Vaxom</td>
<td><em>Haemophilus influenzae</em>&lt;br&gt;<em>Streptococcus pneumoniae</em>&lt;br&gt;<em>Klebsiella pneumoniae</em>&lt;br&gt;<em>Klebsiella ozaenae</em>&lt;br&gt;<em>Staphylococcus aureus</em>&lt;br&gt;<em>Streptococcus pyogenes</em>&lt;br&gt;<em>Streptococcus viridans</em>&lt;br&gt;<em>Neisseria catarrhalis</em></td>
<td>tobolky obsahující lizy něm 10&lt;sup&gt;9&lt;/sup&gt; bakteriálních těl jednotlivých druhů, celkem 7 mg; pro děti poloviční dávka</td>
<td>10–30denní kúra s následnou 3týdenní pauzou, 1 tobolka ráno nalačněno</td>
<td>prevence a léčba chronických a recidivujících infekcí dýchacích cest</td>
<td>po ukončení základního 10denního kúry možno další kúry a pauzy upravit dle individuální odpovědnosti pacienta na léčbu</td>
</tr>
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<td>Luivac</td>
<td><em>Staphylococcus aureus</em>&lt;br&gt;<em>Streptococcus mitis</em>&lt;br&gt;<em>Streptococcus pyogenes</em>&lt;br&gt;<em>Klebsiella pneumoniae</em>&lt;br&gt;<em>Moraxella catarrhalis</em>&lt;br&gt;<em>Haemophilus influenzae</em> mechanická destrukce bakterií</td>
<td>tablety obsahující lizy něm 10&lt;sup&gt;9&lt;/sup&gt; bakteriálních těl jednotlivých druhů, celkem 3 mg; pro děti i dospělé stejná dávka</td>
<td>1 tableta denně ráno nalačněno ve 28denních kúrach s 28denními pauzami</td>
<td>prevence a léčba recidivujících a chronických infekcí dýchacích cest a středouší</td>
<td>po ukončení základního 28denního kúry možno další kúry a pauzy volit dle individuální odpovědnosti pacienta na léčbu</td>
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<tr>
<td>Ribomunyl</td>
<td>směs glykoproteinů bakteriální stény&lt;br&gt;<em>Klebsiella pneumoniae</em> a směs purifikovaných ribozomů bakteriálních druhů&lt;br&gt;<em>Streptococcus pyogenes</em>&lt;br&gt;<em>Klebsiella pneumoniae</em>&lt;br&gt;<em>Haemophilus influenzae</em>&lt;br&gt;<em>Streptococcus pneumoniae</em></td>
<td>sáčky nebo tablety, celkem 2 mg; pro děti i dospělé stejná dávka</td>
<td>1 tableta či sáček ráno nalačno po 4 dny v týdnu v prvních 3 týdnech, následné týdenní pauza a pokračování 1krát měsíčně 4denní kúrou</td>
<td>prevence a léčba recidivujících a chronických infekcí dýchacích cest a středouší</td>
<td>tablety možno též rozpuštět v ústech – nejlépe na noc před spaním</td>
</tr>
<tr>
<td>Uro-Vaxom</td>
<td>purifikovaný extrakt <em>Escherichia coli</em></td>
<td>kapsle 6 mg</td>
<td>1 kapsle po 10–30 dnu ráno nalačněno</td>
<td>doplňková léčba opakovaných močových infekcí</td>
<td>u chronických infekcí možno podávat 90 dnů</td>
</tr>
<tr>
<td>Název přípravku</td>
<td>Složení přípravku</td>
<td>Léková forma</td>
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<tr>
<td><strong>Imunostim GS</strong></td>
<td><em>Staphylococcus aureus</em>&lt;br&gt;<em>Escherichia coli</em>&lt;br&gt;<em>Streptococcus pneumoniae</em>&lt;br&gt;+ 10 mg vitaminu C</td>
<td>směs lýzátů jako pastilky k rozpuštění v ústech 50 mg</td>
<td>3krát denně po 10 dnů rozpuštění v ústech, 2 týdny pauza, pak další 10 denní kúra</td>
<td>prevence a léčba infekcí horních dýchacích cest a dutiny ústní</td>
<td>autor nemá dostatečné zkušenosti s tímto preparátem</td>
</tr>
<tr>
<td><strong>Olimumovac</strong></td>
<td><em>Klebsiella pneumoniae</em>&lt;br&gt;<em>Staphylococcus aureus</em>&lt;br&gt;<em>Propionibacterium acnes</em></td>
<td>lýzát ve formě kapslí 9 mg</td>
<td>1 kapsle ráno nalačno po 5 dnů, pak 5 dnů pauza – opakovat 4krát, následně 1krát měsíčně 5 denní kúra</td>
<td>prevence a léčba recidivujících infekcí hlavně dýchacích cest</td>
<td>základní léčebná kúra 4 měsíce, dle potřeby možno prodloužit na 6 měsíců</td>
</tr>
<tr>
<td><strong>Candidac</strong></td>
<td>bakteriální lýzát&lt;br&gt;<em>Candida albicans</em>&lt;br&gt;<em>Candida krusei</em>&lt;br&gt;<em>Candida glabrata</em>&lt;br&gt;<em>Propionibacterium acnes</em></td>
<td>lýzát ve formě kapslí 5 mg</td>
<td>1 kapsle ráno nalačno po 10 dnů, pak 20 dnů pauza</td>
<td>prevence a léčba recidivující kvasinkové infekce</td>
<td>základní kúra 3–6 měsíců, případně i delší</td>
</tr>
<tr>
<td><strong>Acnevac</strong></td>
<td><em>Propionibacterium acnes</em>&lt;br&gt;<em>Staphylococcus aureus</em>&lt;br&gt;<em>Staphylococcus epidermidis</em></td>
<td>lýzát ve formě kapslí 5 mg</td>
<td>1 kapsle ráno nalačno po 10 dnů, pak 20 dnů pauza</td>
<td>léčba nehojící se akné a jiných bakteriálních kožních infekcí</td>
<td>základní kúra 3–6 měsíců, případně i delší</td>
</tr>
<tr>
<td><strong>Urovac</strong></td>
<td><em>Klebsiella pneumoniae</em>&lt;br&gt;<em>Pseudomonas aeruginosa</em>&lt;br&gt;<em>Enterococcus taecalis</em>&lt;br&gt;<em>Escherichia coli</em>&lt;br&gt;<em>Proteus mirabilis</em>&lt;br&gt;<em>Propionibacterium acnes</em></td>
<td>lýzát ve formě kapslí 5 mg</td>
<td>1 kapsle ráno nalačno po 10 dnů, pak 20 dnů pauza</td>
<td>recidivující močové infekce</td>
<td>základní kúra 3–6 měsíců, případně i delší</td>
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</table>

Chewing gum SEVAK

Chewing gum containing diluted bacteria lysates - one of the first „dietary supplements„ in Czech market.

Product of the Czechoslovak State Institute of Serum and Vaccines. In the 1980s production stopped. The idea has never been revived.
Thymic hormones

Bovine thymus extract - Thymostimulin (TP-1 by Serono)
A mixture of polypeptides (molecular weight 1000-12000 Da) is used as a stimulant T lymphocyte factor.
Indications: secondary cellular immunodeficiency, DiGeorg syndrome, adjuvant therapy in oncology
High costs (1 dose approximately 20,000 CZK), risk of transmission of diseases (BSE - end of the production in 1990s

ZADAXIN® (thymosin alpha 1)
Synthetic polypeptide, registered in Asia, Eastern Europe and South America, Europe and the US in the II. to III. phase of clinical testing.

Ac-Ser-Asp-Ala-Ala-Val-Asp-Thr-Ser-Ser-Glu-Ile-Thr-Thr

Lys

Val-Val-Glu-Lys-Lys-Glu-Lys-Leu-Asp

Glu

Glu-Ala-Glu-Asn-OH
Transfer factor

Modified lysates of human or animal leukocytes contain various substances (peptides, nucleoproteins) - a complex, detailed, non-characterized composition. Stimulation of cellular immunity - activation of lymphocytes, increase of their proliferation and cytokine formation, activation of phagocytic and chemotactic activity of PMN and monocyte / macrophage line. Some studies suggest a homeostatic effect, ie the normalization of immune status. syst. The mechanism is not described in detail, and the effect is rather empirical.

Indications: diseases with laboratory impairment of cellular immunity (reduction of number of T-lymphocytes) - relapsing chronic infections, CVID, septic states, psoriasis, fatigue syndrome on immune deficiency, severe conditions of allergic origin with cellular defect, adjuvant therapy after chemotherapy or radiotherapy ...

The term "transfer factor", especially abroad, is understood in the broader sense, often at the border of homeopathy. The FDA has issued a warning that TF has not been properly proven to be effective or safe for any disease, in United States, TF are administered as a dietary supplement.
Transfer factor

Imunor
ImunomedicA, Ústí nad Labem
Transferendi factor suillus 10 mg.
Soluble ultrafiltered extract prepared from peripheral blood leukocytes for oral use contains molecules of less than 12 kDa. Prescription drug.

Immodin
Sevapharma, Praha
(původně Transfer factor SEVAC)
Leucocyti dialysatum lyophilisatum  200 x 10⁶
Soluble dialysed extract prepared from peripheral blood leukocytes of healthy donors for subcutaneous injections contains molecules less than 10 kDa. Medication on prescription, without registration in the Czech Republic.
Vakcination
Mandatory vaccination in the Czech Republic (Decree No. 299/2010 Coll.)

**Infanrix hexa (hexavaccine)**
Subunit and recombinant antigens, safe for immunosuppressed people and recommended in secondary immunodeficiencies.
- poliomyelitis (infantile paralysis)
- whooping cough (pertussis – *Bordetela pertussis*)
- *Haemophilus influenzae* infection (epiglotitis, meningitis)
- hepatitis B
- tetanus (*Clostridium tetani*)
- diphtheria (*Corynebacterium diphteriae*)

**Priorix (trivaccine)**
Attenuated but still live viruses, contraindications for severe immunodeficiencies !!!
- mumps
- measles
- rubella

**Bacillus Calmette-Guerin (BCG)**
Vaccine against tuberculosis, currently only in children at increased risk
Optional (not funded) vaccines

Rotavirus - children's diarrhea
Varicella – chickenpox
Meningococcal diseases - *Neisseria meningitidis* – meningitis, sepsis
Human papilloma virus infection – cervical cancer
Pneumococcal diseases – pneumonia, meningitis, sepsis
Tick borne encephalitis - in small children is not useful due to low sensitivity to virus
## Czech Republic: Recommended vaccinations

### Vaccination calendar

<table>
<thead>
<tr>
<th>Disease</th>
<th>Weeks</th>
<th>Months</th>
<th>Years</th>
<th>Months</th>
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<tbody>
<tr>
<td>tuberculosis</td>
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<td>rotavirus infection</td>
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<td>diphtheria</td>
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<tr>
<td>tetanus</td>
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<td>pertussis</td>
<td>acP</td>
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<tr>
<td>polomyelitis</td>
<td>IPV</td>
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<tr>
<td>Haemophilus influenza type b infection</td>
<td>Hib</td>
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<tr>
<td>hepatitis B</td>
<td>HepB</td>
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<tr>
<td>pneumococcal disease</td>
<td>PCV10</td>
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<td>meningococcal disease</td>
<td>MenB</td>
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<td>measles</td>
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<td>mumps</td>
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<tr>
<td>rubella</td>
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<tr>
<td>varicella</td>
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</table>

### Vaccination Schedule

- **General recommendation**
- **Recommendation for specific groups only**
- **Catch-up** (e.g., if previous doses missed)
- **Vaccination not funded by the National Health system**
- **Mandatory vaccination**
Vaccination risks

Mostly, a mild reaction at the application site or a short-term increase in temperature or nodal swelling.
Allergic reactions - vaccines may contain egg proteins or antibiotics!!!
Rarely described encephalopathy, Guillain-Barré syndrome, apnea. More serious reactions are subject to reporting under Act No. 378/2007 Coll.

Speculation between vaccination and the development of autism - the relationship is not supported statistically.

Vaccination and allergies - an unclear role, speculating about the undesirable direction of immunity towards Th2.

Immunodeficient patients - careful consideration should be given to the administration of vaccines, particularly attenuated live micro-organisms.
Biological treatment
Monoclonal antibodies in human medicine
Recombinant cytokines

Recombinant IFNα - hepatitis B, hepatitis C, haematoomcology (chronic myeloid leukemia, hairy cell leukemia ...), PEG-conjugated or albumin-conjugated preparations - longer retention in circulation. Commercial preparations - Roferon, Pegasys, PegIntron, Albinerferon alfa ...


Recombinant IL-2 - Aldesleukin (Proleukin) - Metastatic melanoma therapy and metastatic renal cell carcinoma. Responsibility about 15%.

Recombinant G-CSF - Neupogen - chemotherapy-induced neutropenia therapy
Anti-TNF therapy

The goal is to block the pathological action of TNF-α, a pro-inflammatory cytokine taking part in the pathogenesis of autoimmune diseases.

Remicade - Infliximab
The recombinant chimeric monoclonal antibody against TNF is produced in mouse myeloma cell culture. In 2003, the total sale was about 2 billion USD.
Indications: Rheumatoid arthritis, Crohn's disease, severe forms of psoriasis.

Humira - Adalimumab
The first recombinant fully human antibody is produced in the human cell line. An effect analogous to Infliximab.

Enbrel - Etanercept
Soluble receptor fusion protein for the TNF and Fc portion of human IgG1 - a structure similar to the antibody - two TNF binding sites. Function - competitive inhibition of TNF activity.
Thank for your attention