



Immunology and therapy

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Immunotherapy?



= treatment of disease by **inducing, enhancing or suppressing** the **immune response**

Activation of IS:

- ✓ cancer (biological therapy)
- ✓ vaccination (immunization)
- ✓ immunostimulation therapy



Suppression of IS:

- ✓ autoimmune disease
- ✓ transplantations
- ✓ allergies

Immunomodulation:

- ✓ thalidomide

Immunization (vaccination)



- **Active:** induction of specific immunity against a antigen (after infection or vaccination) = body itself *forms* the Ab
- **Passive:** administration of Ab (body *si not forming* them) – either natural (IgG from mother) or artificial way



Edward Jenner – May 14th 1796

- farmers do not suffer from smallpox
- transfer of material from cowpox
- 8 yrs old James Phipps
- lat. *vacca* = cow

- 1980 – WHO - eradication

pic.: © <https://commons.wikimedia.org/wiki/File:E.Jenner.jpg>

Active immunization

Types of vaccine:

1. **attenuated**: alive and weakened by passaging (it loses pathogenicity) – e.g. measles, rubella, mumps,...
2. **dead**: dead viruses or bacteria, conserved antigen structure (flu, pertussis, hepatitis A,...)
3. **toxoids**: bacterial toxins with reduced toxicity, but with conserved antigens – tetanus, diphtheria
4. **subunits**: digested and purified viral particles (fewer AE flu e.g.)
5. **conjugated**: polysaccharide antigen bound with immunogenic protein (carrier) – suitable for children – e.g. pneumococcus, meningococcus, *Haemophilus influenzae* type B
6. **recombinant**: production in a yeast clone
7. **synthetic**



Passive immunization

Types of antibodies:

- animal: heterologous, xenogenic globulins
- human: homologous globulins – normal or hyperimmune (from donors with high titer of Ab)

Examples:

- ✓ botulism immune globulin
- ✓ antitetanic globulin
- ✓ antirabies globulin – in case of bite or injury from animal suspected of being infected



Types of vaccination in CZ

1. **regular** – decree no. 355/2017 Coll. – vaccination calendar – compulsory for children: **hexavaccine** (diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, *Haemophilus infl. B*), **MMR** (measles, rubella, mumps)
2. **special** – for people with higher risks at work
3. **exceptional** – e.g. in flooded areas
4. **travelling** into/from several countries
5. **injury** – tetanus, rabies
6. **on request:**
 - ❖ tick-borne encephalitis, flu, rotavirus, hepatitis A (recommended = not reimbursed)
 - ❖ *pneumococcus*, *papillomavirus* (voluntary = non-compulsory, but reimbursed)




Adverse effects

- **local** reaction: edema, redness, painfullness
- **general**: higher temperature, fever, headache, joint and muscle ache

Unusual AE must be reproted to SUKL – data from 2017: total 794 reports (mainly hexa; most cases higher temperature, fever, painfullness; minor neurological symptoms)



Antivax

- non-compliance with obligation: 10 000 CZK fee (400 €)
- Jan 2016 decision of CC – can be refused due to freedom of conscience (certain conditions!)
- cca 1% of parents refuse vacc. totally
- public health protection  parent's right for upbringing
- herd immunity – spread of a disease (at least 95% vacc.)

MMR vaccine and autism
– article retracted
in 2010 pro dishonesty and
ethical issues



THE LANCET

EARLY REPORT | VOLUME 351, ISSUE 9103, P637-641, FEBRUARY 28, 1998

RETRACTED: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children

Dr AJ Wakefield, FRCS,  SH Murch, MB, A Anthony, MB, J Linnell, PhD, DM Casson, MRCP, M Malik, MRCP, et al

Show all authors

DOI: [https://doi.org/10.1016/S0140-6736\(97\)11096-0](https://doi.org/10.1016/S0140-6736(97)11096-0)

Summary

References

Article info

Linked Article

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Summary

Background

We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder.

Methods

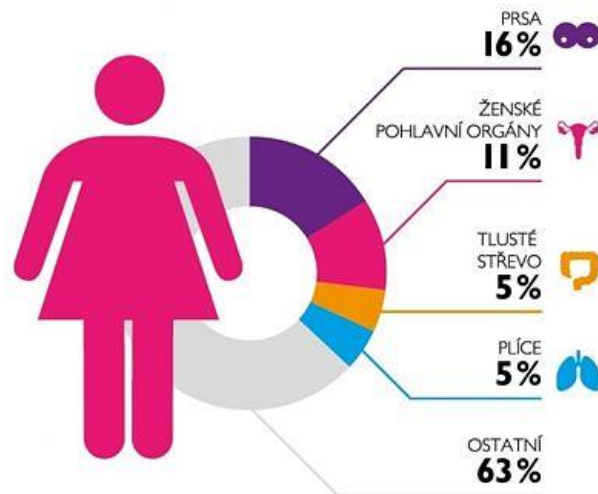
12 children (mean age 6 years [range 3–10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records, ileocolonoscopy and biopsy sampling, magnetic resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined.

Cancer – targeted therapy

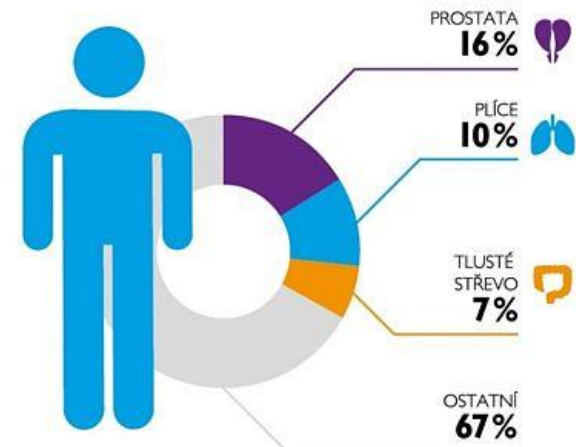


cancer = variable group of diseases caused by malignant tumor (uncontrolled growth)

1. cellular
2. antibody
3. cytokine



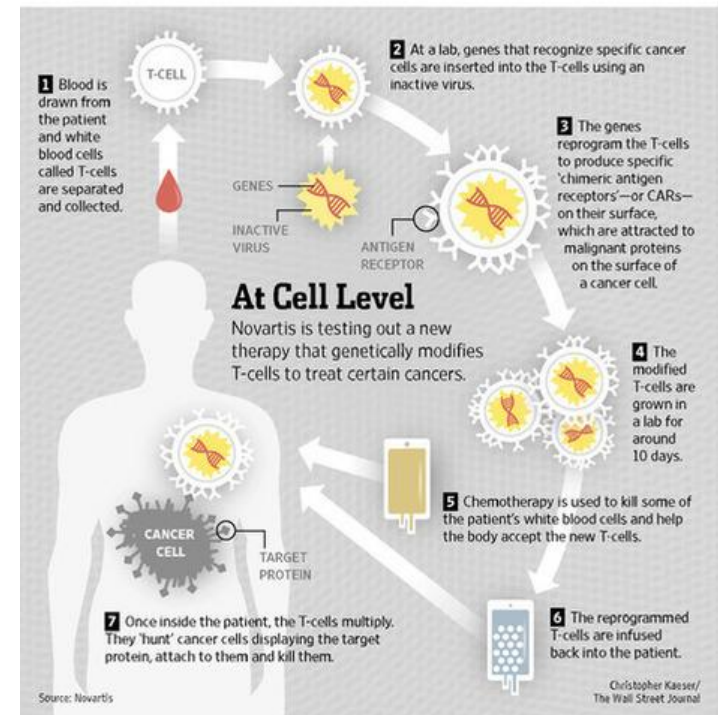
NEJČASTĚJŠÍ ZHOUBNÉ NÁDORY



Cellular immunotherapy

Tisagenlecleucel (Kymriah®):

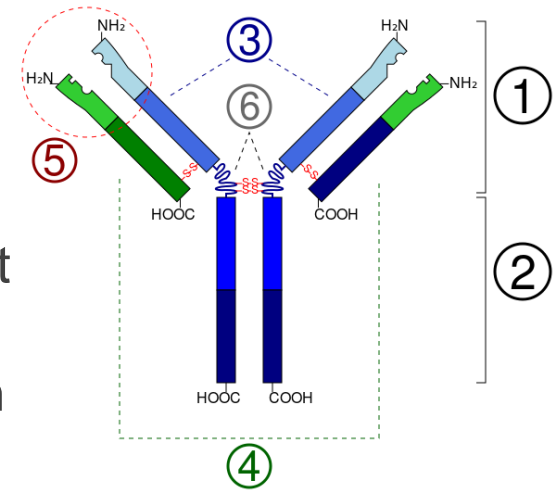
- th. of acute lymphoblastic leukemia (ALL) non-responsive to standard treatment
- Aug 2017 – first gene therapy approved by FDA
- single treatment = 550 000 \$
- technique CAR-T (chimeric antigen receptor) to CD19



Antibody immunotherapy

Types (monoclonal **-mab**):

- **conjugated**: MAB + cytotoxic or radioactive compound (*trastuzumab-emtansin* = against HER2 pos. breast cancer; inh. microtubules)
(*ibritumomab-tiuxetan* = non-Hodgkin lymphoma + yttrium-90)



- **naked**:

- against surface antigens - Fc region (complement or cytotoxic reaction) – e.g. CD20
- immune checkpoint blockers – receptor PD-1
- inhibitors of angiogenesis

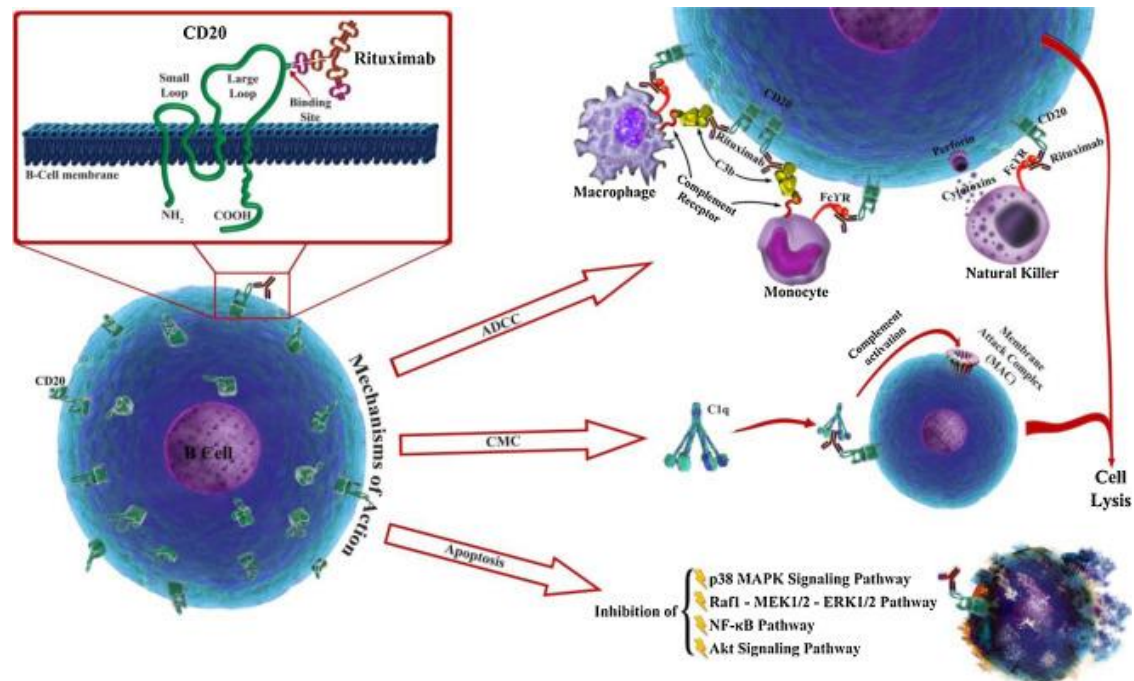
Immunogenicity: mAb (human), zmAb (humanized), chAb (chimeric)



Rituximab

Rituximab (MabThera, Rituxan, Zytux):

- ✓ chimeric MAB against CD20 (B lymphocytes)
- ✓ reg. 1997, patent protection expired in 2016, now biosimilars (cost per patient = cca 18 000 \$)
- ✓ I: cancer of WBC (leukemia, lymphomas), + autoimmunities (reumatoid arthritis)



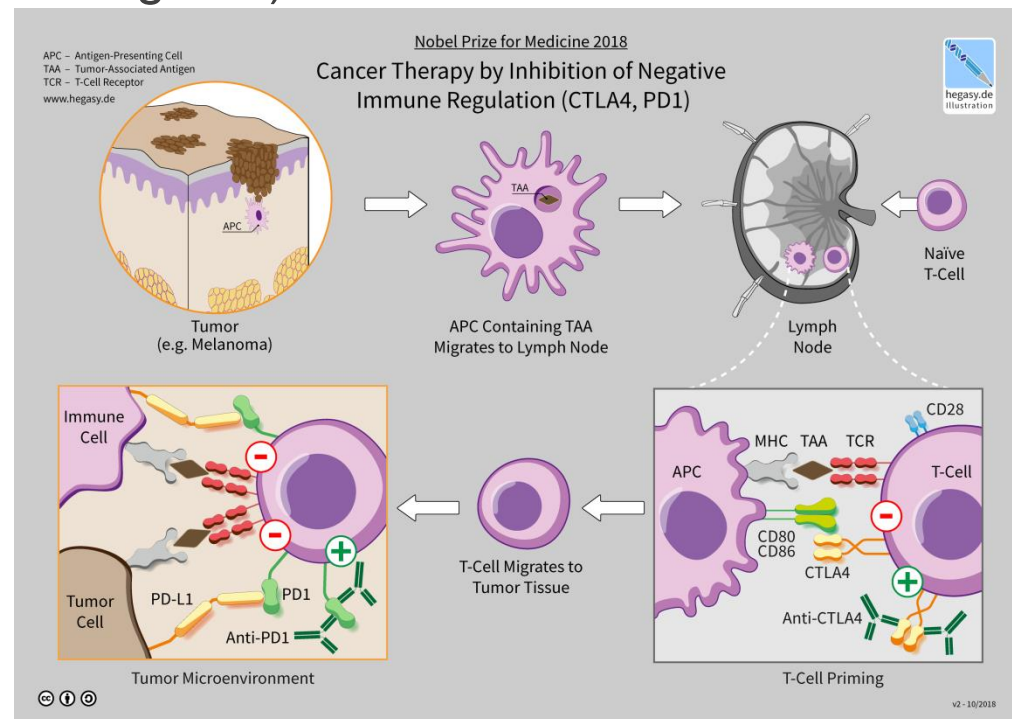
Immune checkpoint blockers

(Nobel Prize in Phys/Med 2018 – James P. Allison, Tasuku Honjo)

Checkpoints – negative or positive – important

Ipilimumab (Yervoy):

- ✓ I: inoperable or metastatic melanoma
- ✓ human MAB against CTLA-4 (cytotoxic T lymphocyte-associated antigen 4)



Author: Guido4



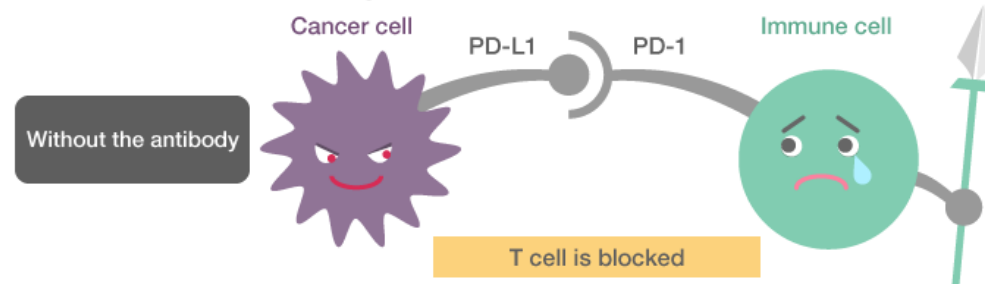
Immune checkpoint blockers

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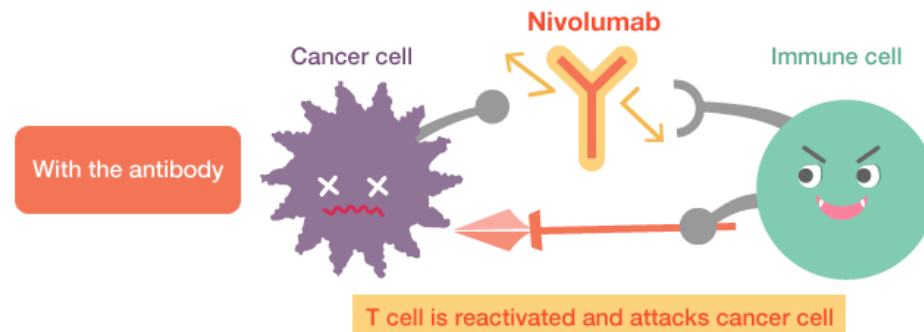
Nivolumab (Opdivo):

- ✓ I: inoperable or metastatic melanoma
- ✓ human MAB against PD-1 (programmed cell death protein 1)

How the Anti-PD-1 Antibody Works



When PD-L1 binds with PD-1, the cancer puts the brakes on immune cells (T cells) and blocks attacks on cancer cells.



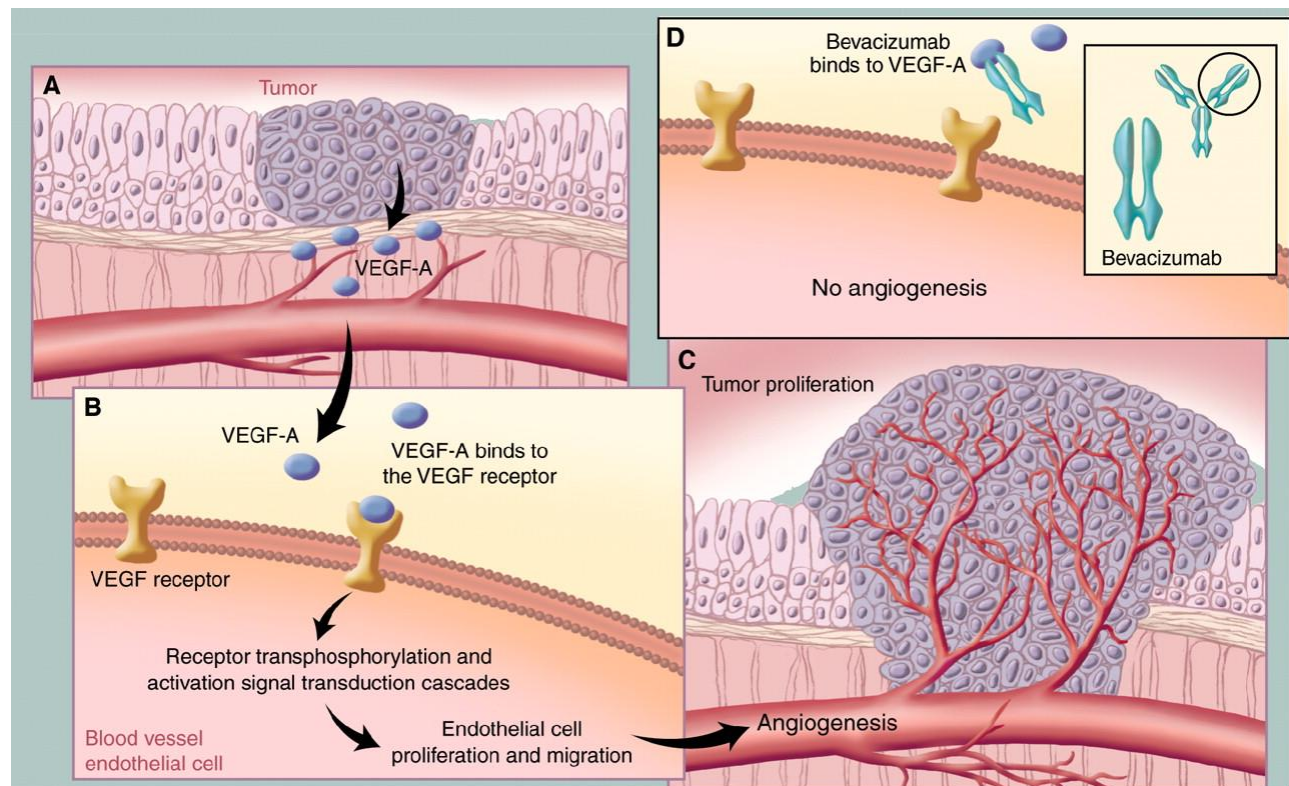
Nivolumab removes the brakes on T cells by preventing PD-L1 from binding with PD-1, thereby reactivating T cells and allowing them to attack cancer cells.



Inhibitors of angiogenesis

Bevacizumab (Avastin):

- ✓ humanized MAB against VEGF-A (vascular endothelial growth factor)
- ✓ I: th. of colon, breast, lung, etc. cancer



Cytokine therapy

Signal proteins of immune system.

Interleukin 2: recombinant form = aldesleukin

✓ Th.: malignant melanoma, kidney cancer

Interferon α :

✓ Th.: hairy cells leukemia, Kaposi's sarcoma HIV+, chronic myeloid leukemia, etc.



Immunostimulators



= compounds increasing activity of immune system
(*great offer; reliable effect?*)

Beta- glucans:

- **pleuran** from saprotroph *Pleurotus ostreatus* (Oyster mushroom)
- insoluble polysacharid (β -1,3/1,6-D-glc)
- RCT: preventively, signif. reduced incidence of flu and other respir. diseases in children

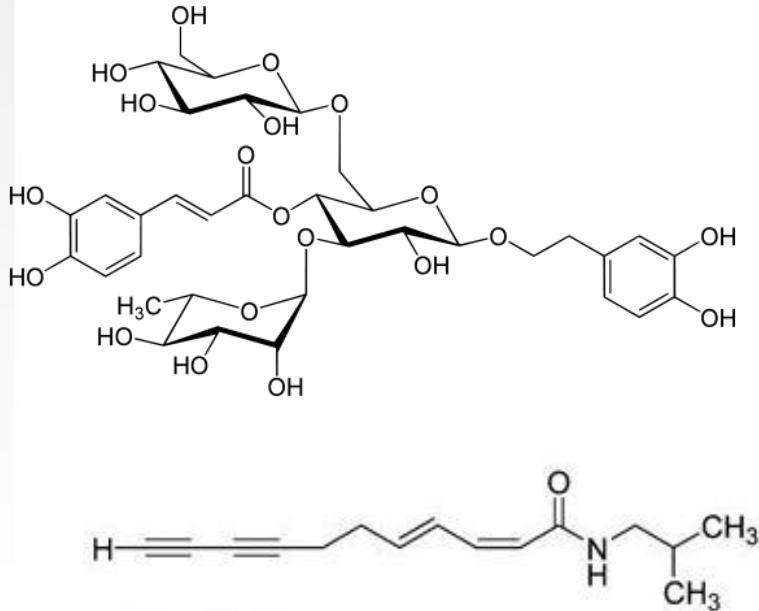


Jesenak M., Sanislo L., Kuniakova R., Rennerova Z., Buchanec J., Banovcin P. Imunoglukan P4H[®] in the prevention of recurrent respiratory infections in childhood. *Cesk Pediatra*. 2010;73:639–647.

Immunostimulators

Echinacea purpurea, Asteraceae:

- ethanolic extract (95% herb, 5% root) – RCT reduced incidence of cold
- alkamides, derivatives of caffeic acid, echinacosides



Jawad M et al. Safety and Efficacy Profile of *Echinacea purpurea* to Prevent Common Cold Episodes: A Randomized, Double-Blind, Placebo-Controlled Trial. *Evidence-based Complementary and Alternative Medicine* : eCAM. 2012;2012:841315. doi:10.1155/2012/841315.



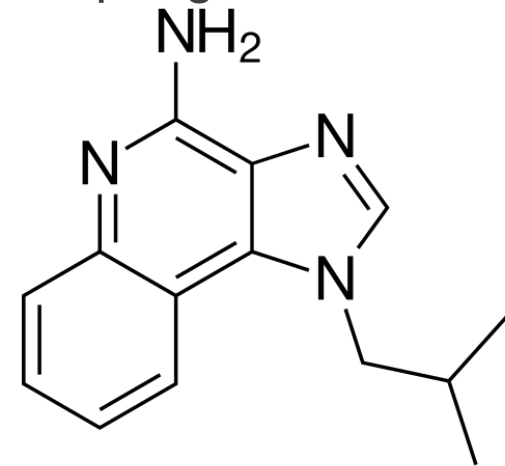
Stimulation of non-specific IS

Filgrastim:

- ✓ recombinant G-CSF (granulocyte - colony stimulating factor) - glycoprotein
- ✓ stimulates production of neutrophils – stimulation of IS
- ✓ neutropenia after chemotherapy and bone marrow transplantation

Imiquimod:

- ✓ binds to toll-like receptor 7 – activation of cytokines (INF- α and TNF- α) and by that NK cells and macrophages
- ✓ locally on genital warts

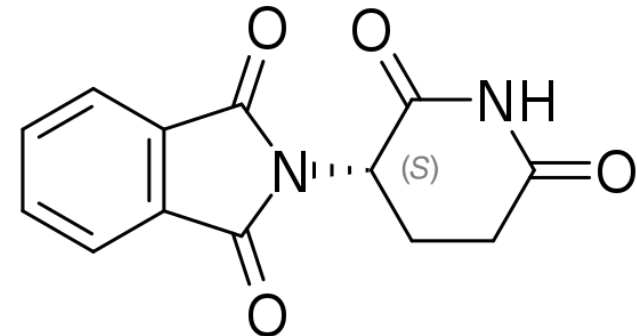
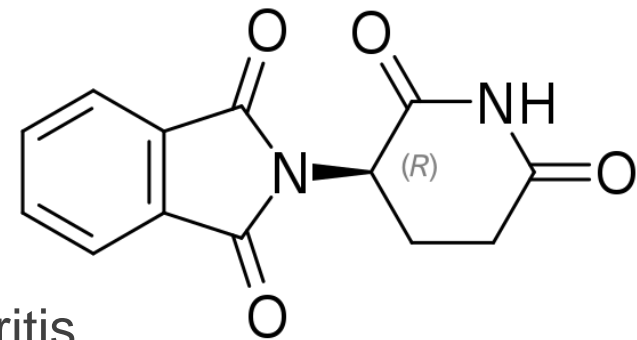


Immunomodulation (↓↑)



Thalidomid:

- ✓ Contergan[®]: 1957 West Germany; morning sickness in pregnancy
- ✓ 1961: teratogen – worldwide cca 10 000 cases of phocomelia
- ✓ stricter approval of new drugs! (R-nausea; S-teratogen)
- ✓ 1998: new th.: multiple myeloma (+dexa); erythema nodosum leprosum (inflam.)
- ✓ other derivatives MM:
 - 2001: **lenalidomid**
 - 2009: **pomalidomid**
- ✓ **apremilast**: th. of psoriasis and psoriatic arthritis (inh. PDE4 a TNF α – against inflam.)



Imunoterapie?



= léčba onemocnění **vyvoláním**, **posílením** nebo **potlačením** imunitní odpovědi

Aktivace IS:

- ✓ rakovina
(biologická léčba nádorových onemocnění)
- ✓ očkování
(imunizace)
- ✓ imunostimulancia



Imunomodulancia:

- ✓ thalidomid

Suprese IS:

- ✓ autoimunitní onemocnění
- ✓ transplantace
- ✓ alergie

Imunosupresivní léčba



proč podáváme?

- ✓ prevence odmítnutí transplantovaného orgánu (kostní dřeň,...)
- ✓ autoimunitní choroba (revmatoidní artritida, roztroušená skleróza, psoriáza, IBD,...)

dělení:

1. cytostatika
2. glukokortikoidy
3. protilátky
4. látky vázající se na imunofiliny
5. další látky



Cytostatika

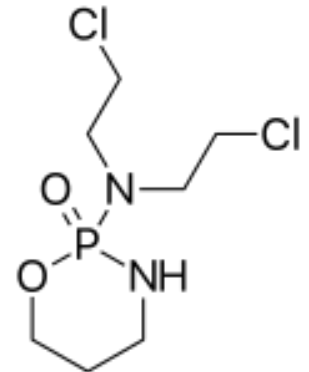
= látky inhibující dělení buněk – uplatňuje se působení na T a B buňky

Cyklofosfamid:

- MÚ: alkylační činidlo (prodrug – metabolizuje se v játrech) – váže se na N7 v G – crosslinking – narušení dělení bb.
- I: rakovina, autoimunity (systémový lupus erythematoses)
- léčba závažných stavů, má NÚ (nauzea, útlum kostní dřeně, alopecie)



motýlovitý exantém



Cytostatika

Metotrexát:

- MÚ: antimetabolit – inh. dihydrofolát reduktázy (DHFR) = inhibice syntézy DNA, RNA, proteinů

