TOLL-U PODOBNI RECEPTORJI

Seminarska naloga pri predmetu Biološke membrane

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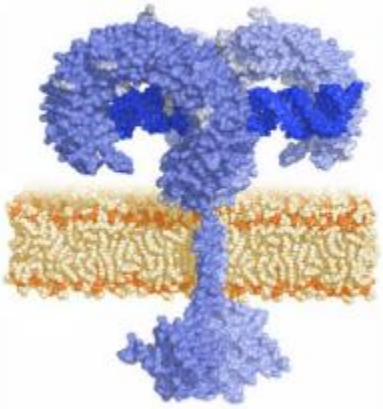
Ljubljana, januar 2015

TLR receptorji

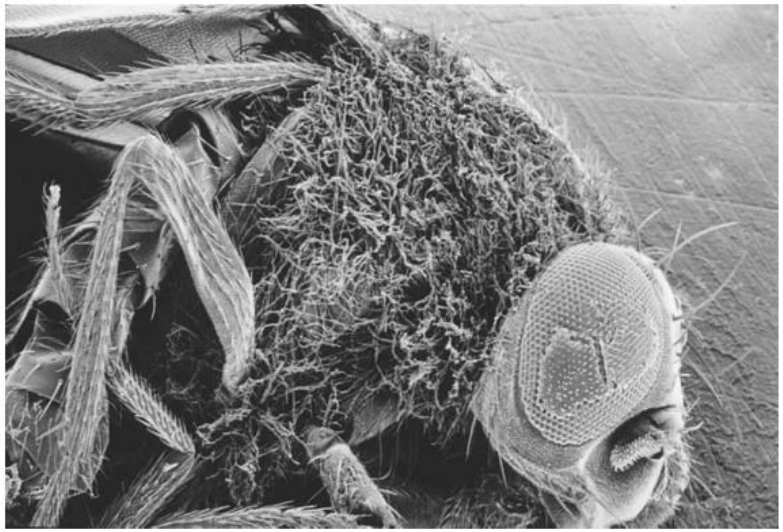
- Membranski proteini
  - Vranica, periferni levkociti
  - Pljuča, prebavni trakt
- Prirojena imunost
  - Nespecifični imunski odgovor
    - Naravne pregrade
    - Fagocitne celice
  - Specifični imunski odgovor
    - Tollu podobnimi receptorji (TLR)
      - PAMPi
      - DAMPi
      - Proizvodnja interferonov, proinflamatornih citokinov in efektorskih citokinov



Odkritje TLR

- Družina receptorjev Toll
  - Christiane Nüsslein-Volhard (1985)
    - Das ist ja toll!

- Jules Hoffmann (1996)
- Bruce Beutler (1997)
- Ralph Steinman

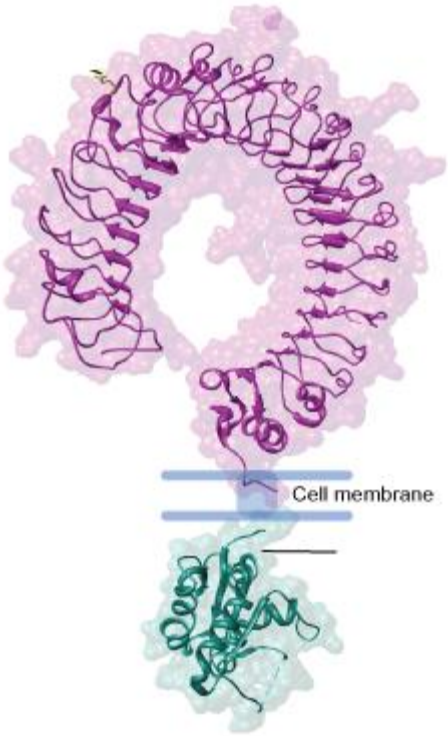


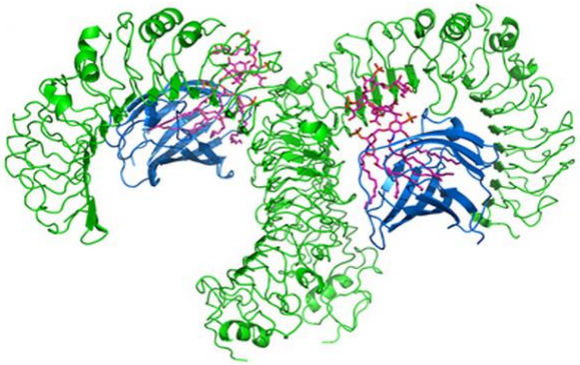
TLR receptorji

- Poznanih
  - 10 receptorjev TLR pri človeku
  - 13 pri miših: ~~TLR10~~, TLR11, TLR12 in TLR13
- Lokalizacija:
    - receptorje, ki se nahajajo na površini celice (TLR1, TLR2, TLR4, TLR5, TLR6 in TLR11)
    - receptorje, ki se nahajajo v membranah celičnih veziklov (TLR3, TLR7, TLR8 in TLR9)
- Ligandi: lipidi, lipoproteini, peptidoglikani, proteini ter nukleinske kisline

Struktura TLR

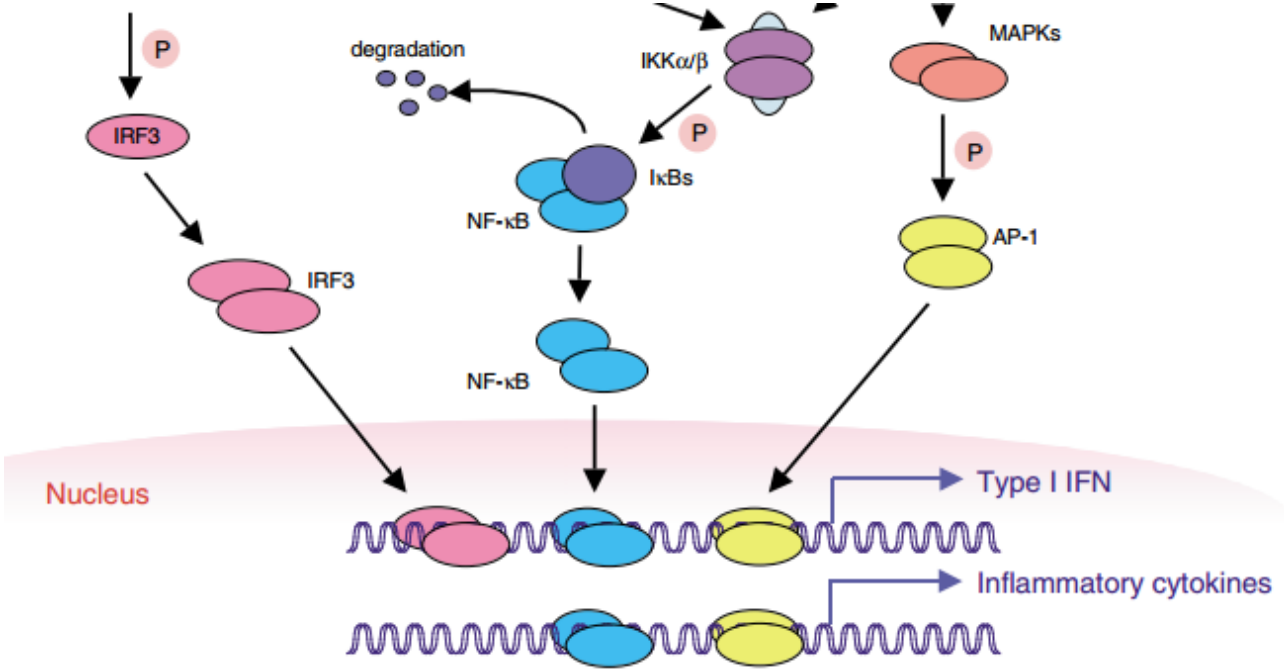
- Transmembranski protein tipa I
  - Ekstracelularna domena (N-konec)
    - podkvasta ektodomena (19-25 z levcinom bogatih ponovitev)
  - Transmembranska domena
  - Citoplazemska domena (C-konec)
    - Toll-interlevkin 1 receptorske (TIR)





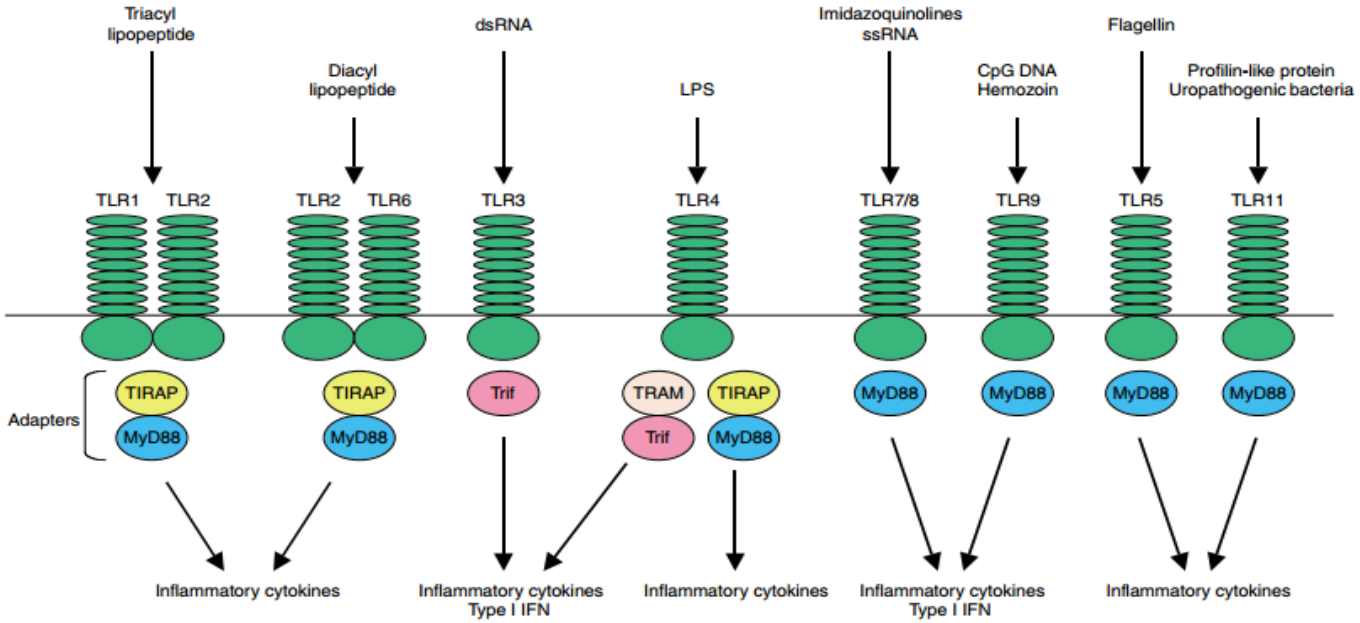
Signalizacija preko TLR

- Vezava mikrobnih ligandov
- Vpliv na izražanje genov (imunski odgovor)
- Izzid signalizacije: aktivacija transkripcijskih faktorjev NF-κB, IRF-jev ali AP-1 preko MAP-kinaz



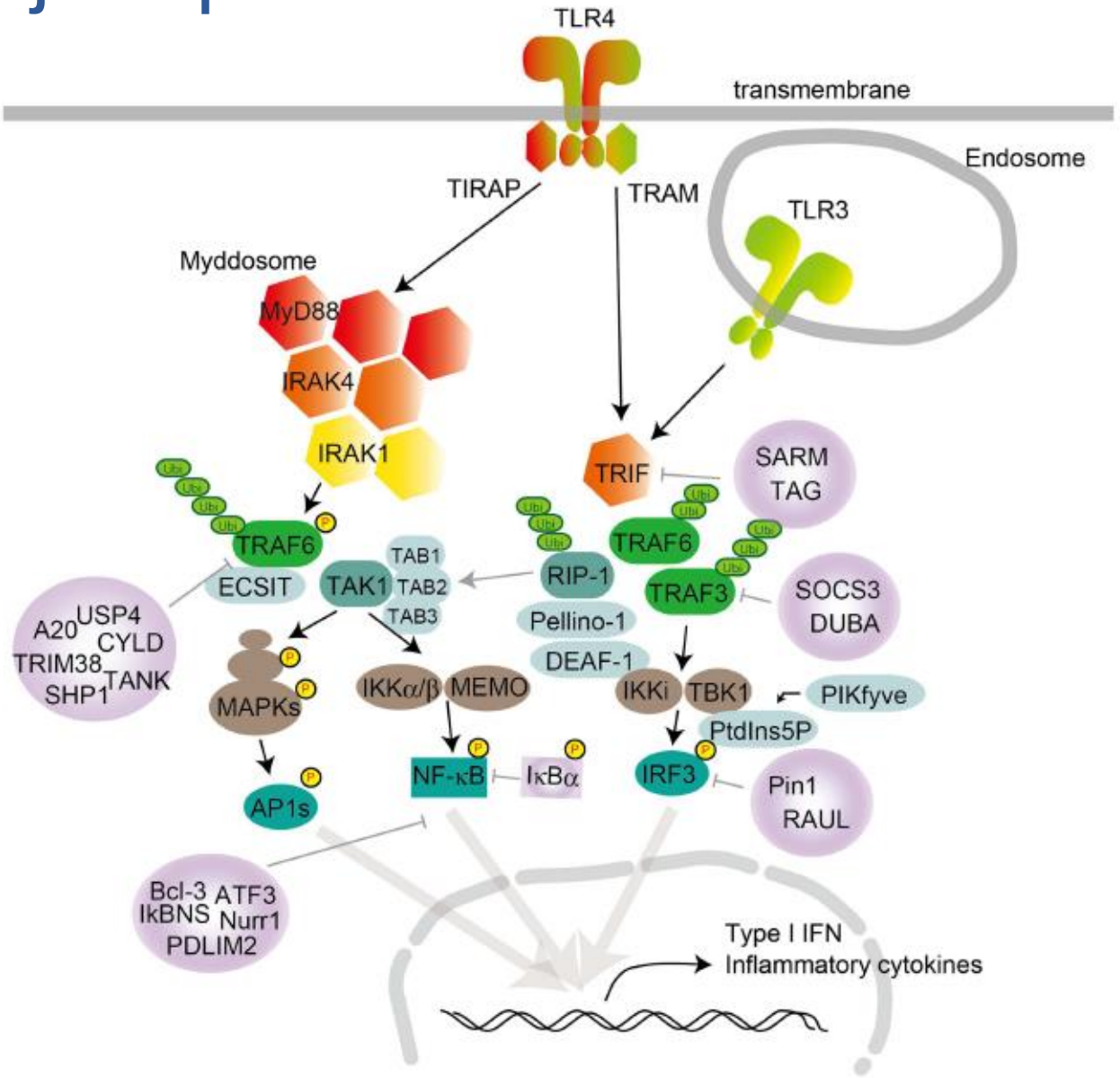
Signalizacija preko TLR

- Vezava liganda, dimerizacija receptorja
- Aktivacija signalne kaskade preko adapterskih proteinov s TIR domeno; MyD88, TRIF, TIRAP/MAL in TRAM.
- Vsi TLR-ji izkoriščajo MyD88, ki je odgovoren za aktivacijo NF-κB in MAPK, kar povzroči produkcijo vnetnih citokinov
- TRIF – alternativna pot, produkcija tudi IFN tipa I

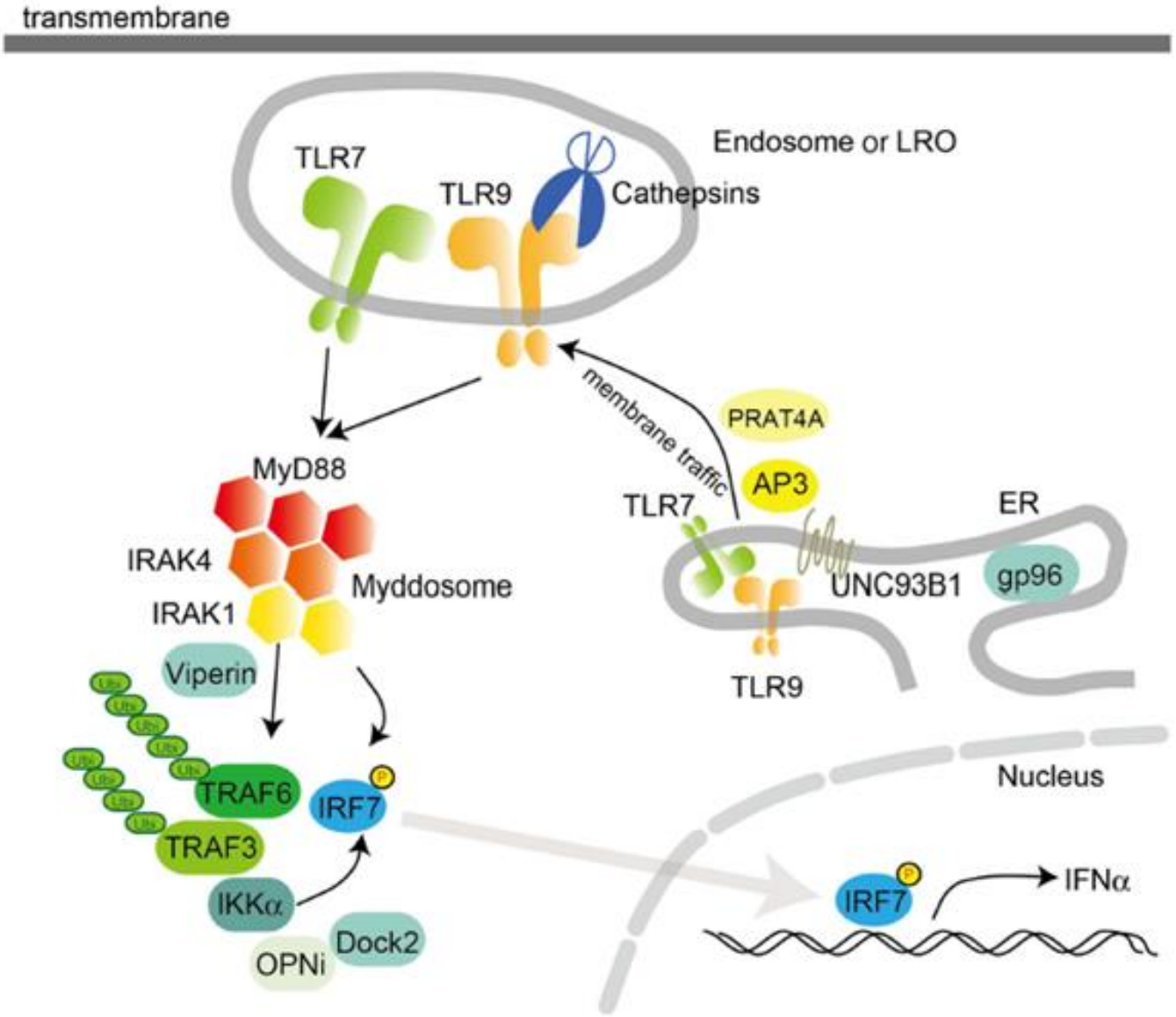


Signalizacijske poti

- **MyD88**
- **TRIF**

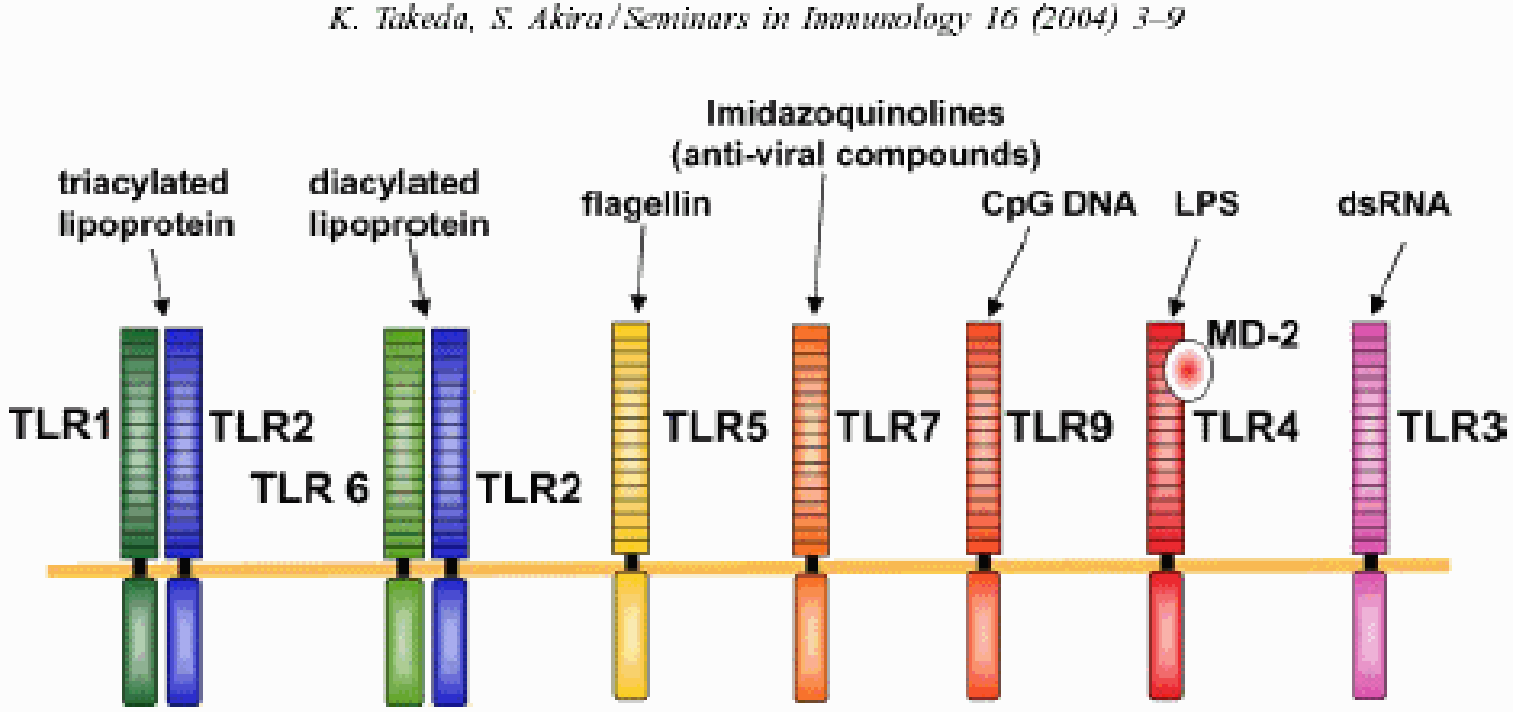


Signalizacija TLR3 in TLR9 v plazmacitoidnih deneritskih celicah



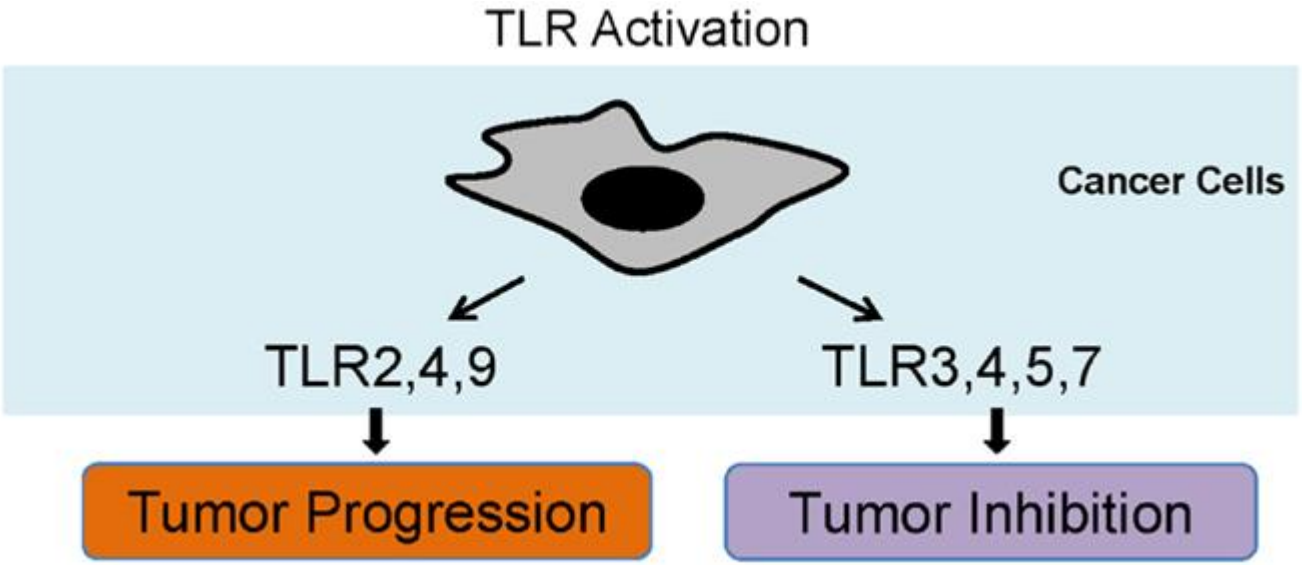
BOLEZNI, POVEZANE S TLR RECEPTORJI

- Pod določenimi pogoji lahko TLR-ji zaznajo tudi gostitelju lastne molekule



BOLEZNI, POVEZANE S TLR RECEPTORJI

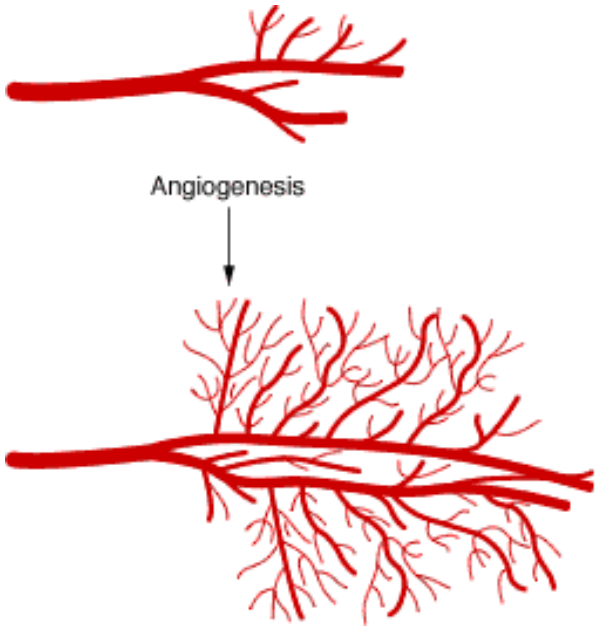
- Alzheimerjeva bolezen (TLR4 in TLR6)
- Avtoimunske bolezni (TLR7 in TLR9)
- Rak (več TLR-jev)



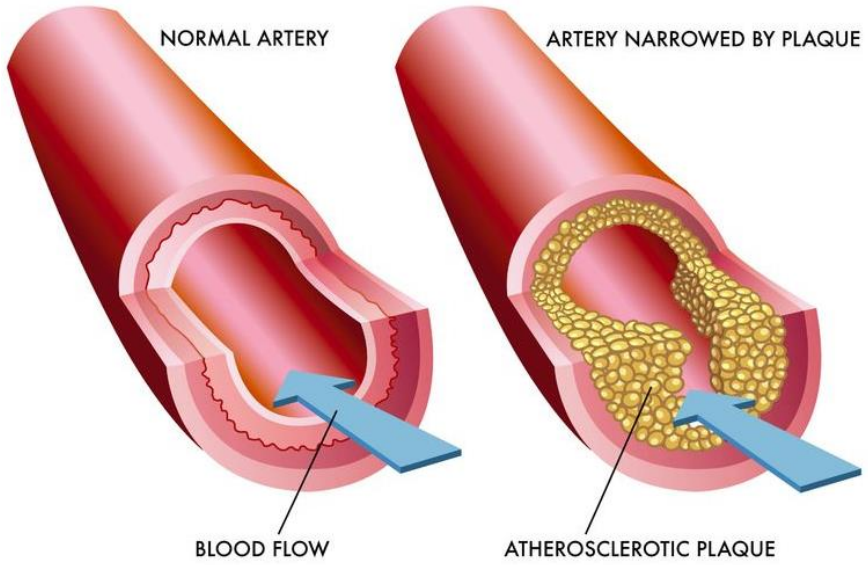
BOLEZNI, POVEZANE S TLR RECEPTORJI

- Miokardne bolezni (TLR4: septična kardiomiopatija, ishemija, srčno popuščanje, srčna hipertrofija, toksična kardiomiopatija)

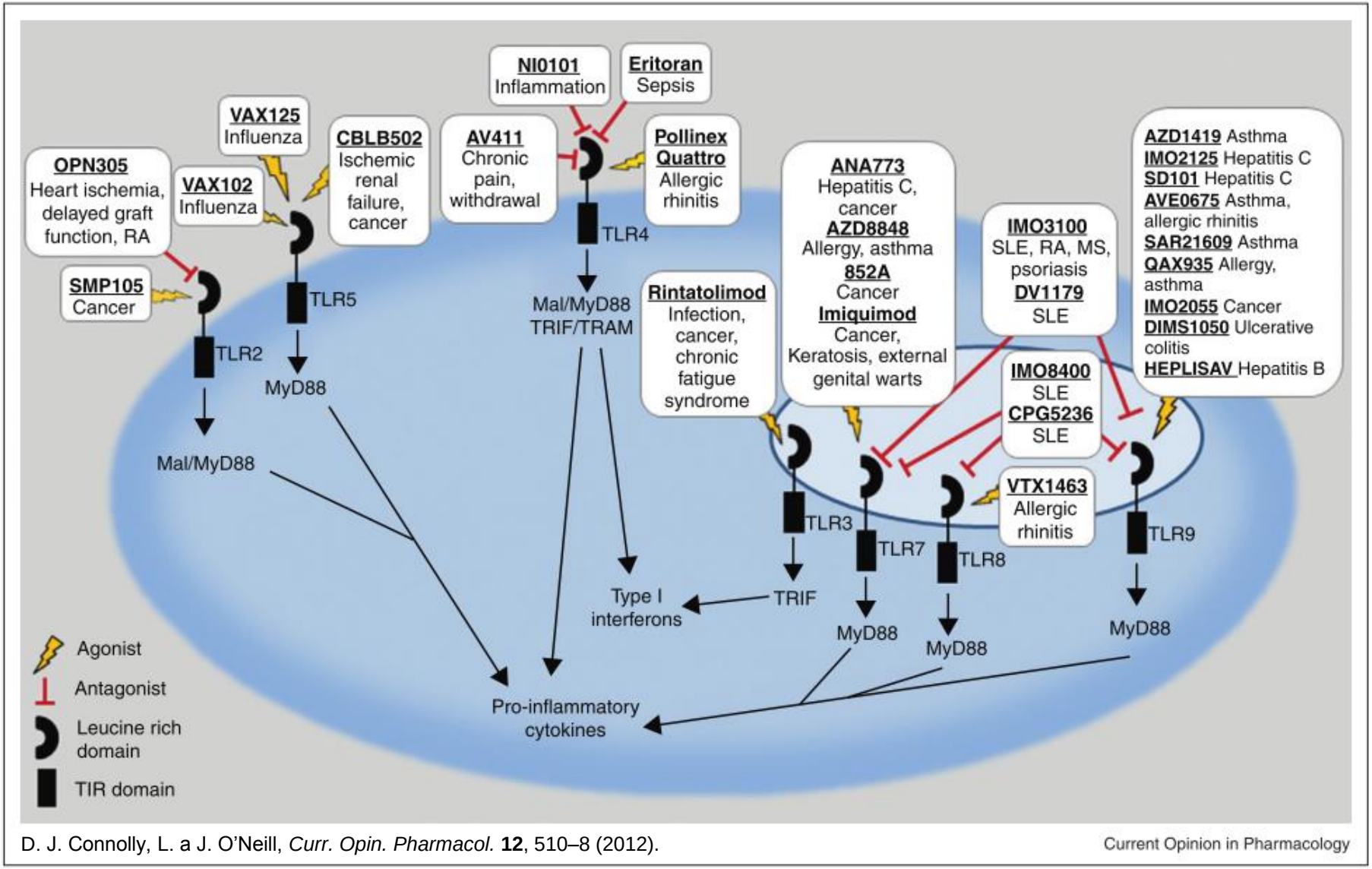
- Angiogeneza (TLR2, 4, 7 in 9)



- Ateroskleroza (TLR4 in 2)



CILJANJE TLR ZA TERAPIJO



D. J. Connolly, L. a J. O'Neill, *Curr. Opin. Pharmacol.* **12**, 510–8 (2012).

Current Opinion in Pharmacology

CILJANJE TLR ZA TERAPIJO

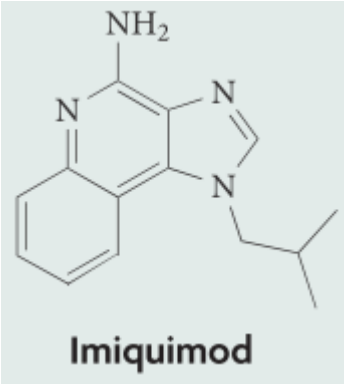
Table 1

Developmental status of TLR targeted therapeutics

Compound	Company	Target	Indications	Drug class	Clinical phase
SMP105	Dainippon Sumitomo Pharma	TLR2 agonist	Cancer	Autoclaved mycobacteria	Preclinical
NI0101	NovImmune	TLR4 antagonist	Acute and chronic inflammation	Antibody	Preclinical
IMO8400	Idera Pharmaceuticals	TLR7/8/9 antagonist	Systemic lupus erythematosus	CpG oligonucleotide	Preclinical
CBLB502	Cleveland BioLabs	TLR5 agonist	Ischemic renal failure, Cancer	Flagellin	Preclinical Phase I
IMO3100	Idera Pharmaceuticals	TLR7/9 antagonist	Systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis Psoriasis	CpG oligonucleotide	Preclinical Phase II
AZD1419	Astra Zeneca	TLR9 agonist	Asthma	CpG oligonucleotide	Preclinical
OPN305	Opsona Therapeutics	TLR2 antagonist	Heart ischemia, delayed graft function, rheumatoid arthritis	Antibody	Phase I
ANA773	Anadys Pharmaceuticals	TLR7 agonist	Hepatitis C, cancer	Small molecule ssRNA	Phase I
IMO2125	Idera Pharmaceuticals	TLR9 agonist	Hepatitis C	CpG oligonucleotide	Phase I
SD101	Dynavax Technologies	TLR9 agonist	Hepatitis C	CpG oligonucleotide	Phase I
VTX1463	VentiRx Pharmaceuticals	TLR8 agonist	Allergic rhinitis	ssRNA-based molecule	Phase I
AVE0675	Sanofi Aventis/Coley Pharmaceuticals	TLR9 agonist	Asthma, allergic rhinitis	CpG oligonucleotide	Phase I
SAR21609	Sanofi Aventis/Coley Pharmaceuticals	TLR9 agonist	Asthma	CpG oligonucleotide	Phase I
QAX935	Idera Pharmaceuticals	TLR9 agonist	Allergy, asthma	CpG oligonucleotide	Phase I
DV1179 (IRS954)	Dynavax Technologies	TLR7/9 antagonist	Systemic lupus erythematosus	CpG oligonucleotide	Phase I
VAX125	VaxInnate	TLR5 agonist	Influenza	Flagellin and Hemagglutinin	Phase I
CPG52364	Pfizer	TLR7/8/9 antagonist	Systemic lupus erythematosus	Quinazoline derivative	Phase I
IMO2055	Idera Pharmaceuticals	TLR9 agonist	Cancer	CpG oligonucleotide	Phase I/II
AV411	Avigen	TLR4 antagonist	Chronic pain, withdrawal	Small molecule phosphodiesterase (PDE) inhibitor	Phase II
VAX102	VaxInnate	TLR5 agonist	Influenza	Flagellin and M2e	Phase II
852A	3M Pharmaceuticals	TLR7 agonist	Cancer	Small molecule ssRNA	Phase II
AZD8848	Astra Zeneca	TLR7 agonist	Allergy, asthma	ssRNA based molecule	Phase II
Rintatolimod	Hemispherx Biopharma	TLR3 agonist	Infection, cancer, chronic fatigue syndrome	dsRNA molecule	Phase II Phase III
DIMS1050 (Kappaproct)	InDex Pharmaceuticals	TLR9 agonist	Ulcerative colitis	CpG oligonucleotide	Phase III
Pollinex Quattro	Allergy therapeutics	TLR4 agonist	Allergic rhinitis	MPL, L-tyrosine and allergens	Phase III
HEPLISAV	Dynavax Technologies	TLR9 agonist	Hepatitis B	Hepatitis B antigen and CpG DNA	Phase III
Eritoran	Eisai Pharmaceuticals	TLR4 antagonist	Sepsis	Synthetic lipodisaccharide	Suspended in Phase III
Imiquimod (Aldara)	3M Pharmaceuticals	TLR7 agonist	Cancer, Keratosis, external genital warts, small superficial basal cell carcinoma	Small molecule ssRNA	Phase II Approved

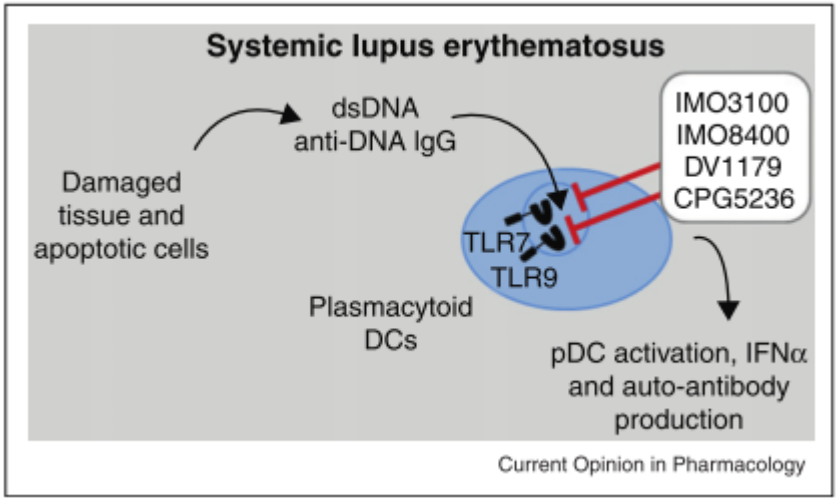
CILJANJE TLR ZA TERAPIJO

- imiquimod (Aldara)
  - agonist TLR7 → IFNα, TNFα,…
  - HPV, keratoza, bazalnocelični karcinom



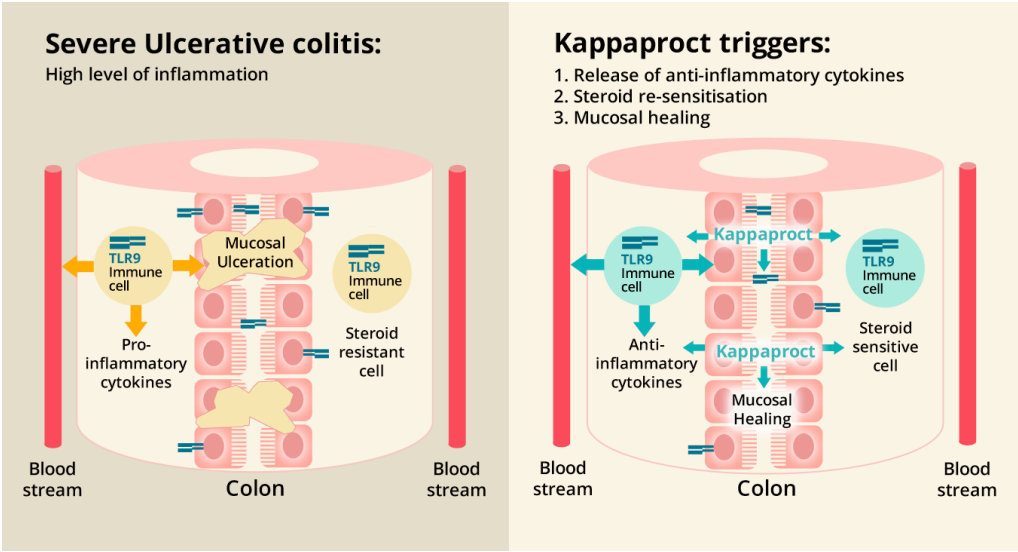
- HELPISAV
  - HBsAg + CpG DNA
  - agonist TLR9
  - cepljenje proti HBV
  - III. faza

- DV1179
  - CpG DNA
  - antagonist TLR7 in TLR9
  - sistemski lupus eritematozus
  - I. faza



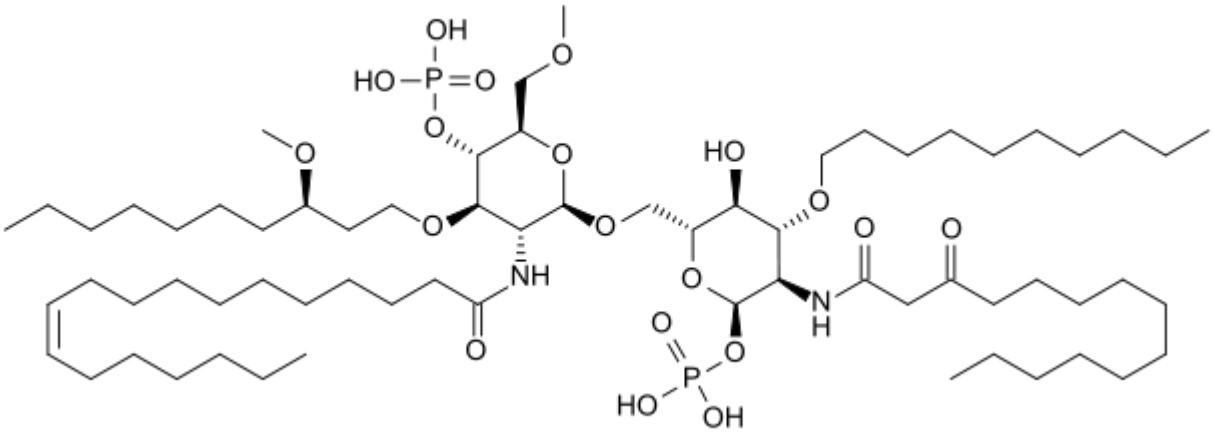
CILJANJE TLR ZA TERAPIJO

- DIMS0150 (Kappaproct)
  - CpG DNA
  - agonist TLR9
  - ulcerozni kolitis
  - III. faza



- OPN305
  - mAb anti-TLR2
  - preprečuje aktivacijo TLR2/1 in TLR2/6
  - ishemija
  - II. faza

- Eritoran
  - antagonist TLR4
  - sepsa (LPS)
  - III. faza †

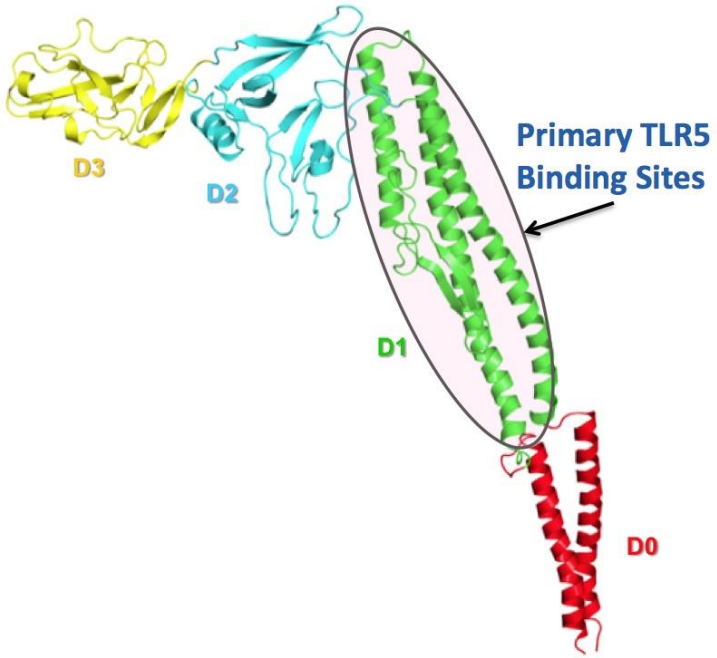


CILJANJE TLR ZA TERAPIJO

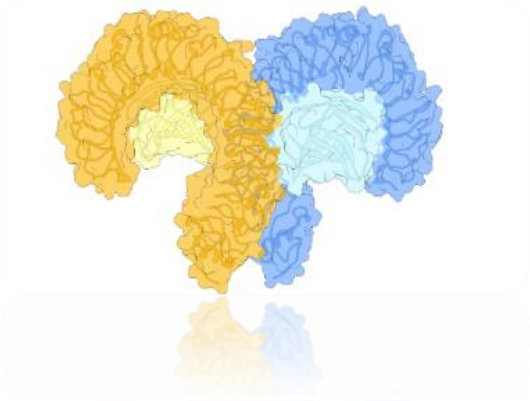
- Pollinex Quattro
  - agonist TLR4 MPL + ekstrakt peloda ambrozije
  - cepivo za sezonski alergijski rinitis
  - III. faza

- VAX102
  - fuzija M2e-flagelin
  - TLR5
  - cepivo proti gripi
  - II. faza

- VAX125
  - fuzija H1 HA-flagelin
  - TLR5
  - cepivo proti gripi
  - II. faza



POVZETEK



- prirojena imunost
- prva obrambna linija pred tujki
- prepoznavajo ohranjene molekulske vzorce patogenov
- podkvasta oblika z LRR
- signaliziranje do vnetnih citokinov in IFN
- aktivacija pridobljene imunosti
- vpliv pri številnih obolenjih
- tarče za zdravljenje

HVALA ZA POZORNOST!

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