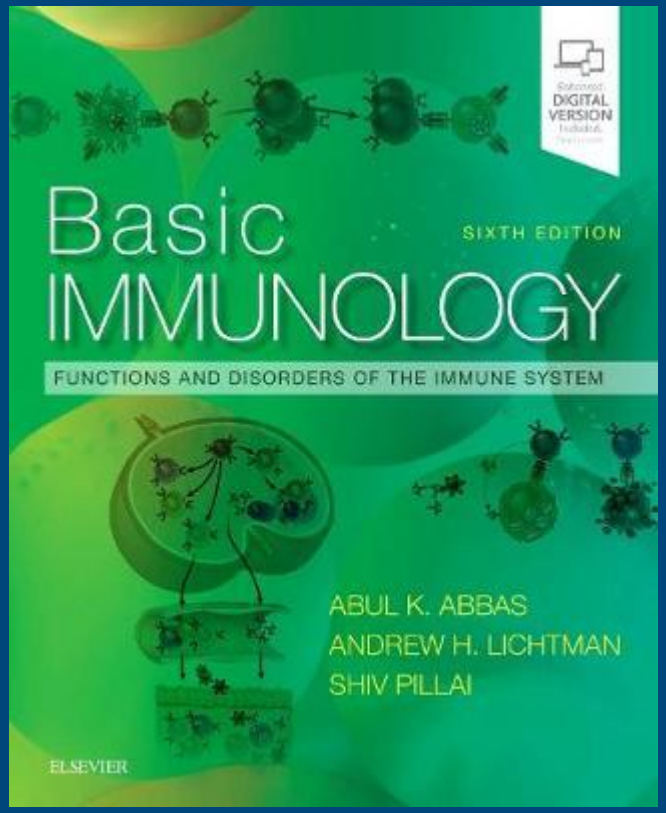
Afweer 3



Boek: Abbas, Basic Immunology.
Aanrader, maar niet noodzakelijk

1. **Onderdelen van het afweersysteem**
   Cellen, signaalstoffen

2. **Hoe leert het afweersysteem**
   Tolerantie, memory

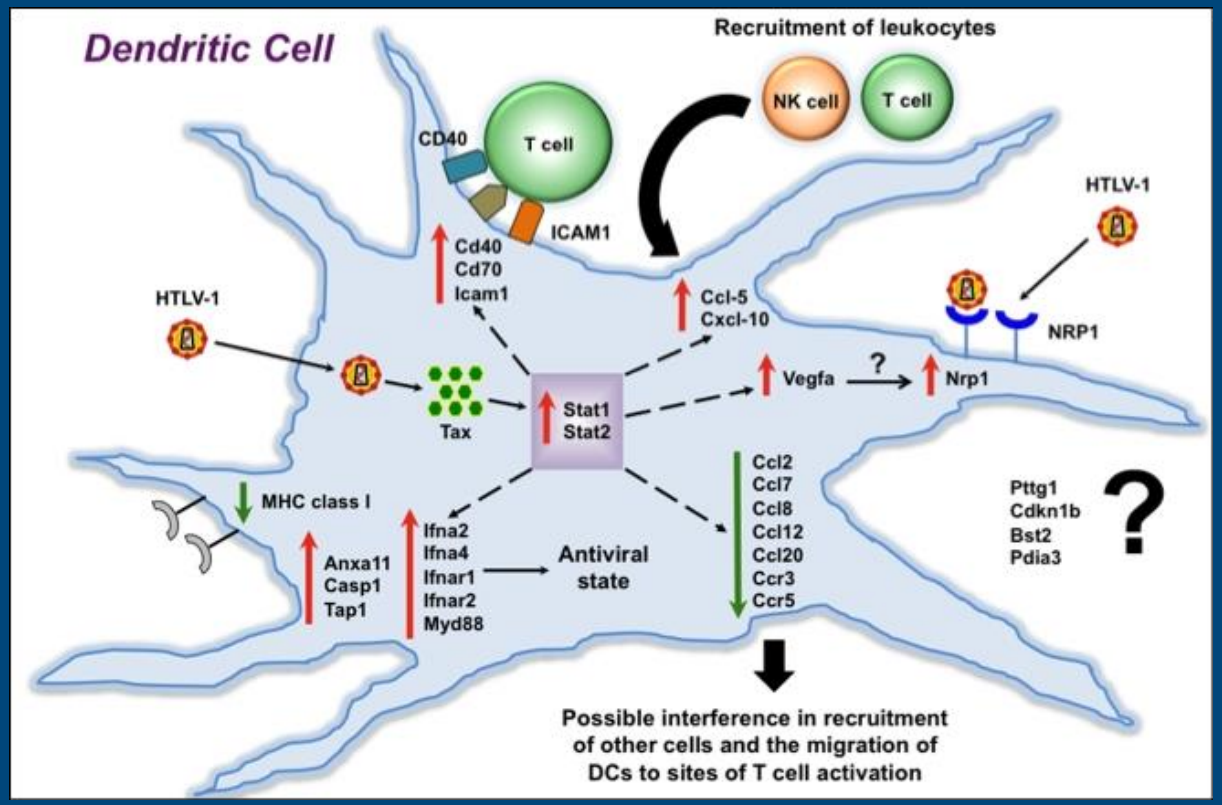
3. **Huidige kennis**
   (RNA-)vaccins, antilichamen

4. **Intracellulaire afweer**
   RNA detectie, PCR (mol.biol.)

5. **Afweer en veroudering**
   Symbiose, ethiek

https://www.youtube.com/watch?v=zQGOcOUBi6s

Van a-specifiek naar specifieke afweer:
De dendritische cel (professionele APC)



https://www.youtube.com/watch?v=MI-BLaj5nFk

https://www.youtube.com/watch?v=9DMsGNvVGfI

DC's fagocyteren ziekmakers en breken deze af. Een klein onderdeel van de ziekmaker (antigeen) wordt gepresenteerd aan de specifieke afweer => vgl met macrofaag

Sommige DC's zitten in het weefsels en gaan na activatie naar de lymfeklier

DC in huid = Langerhans cel

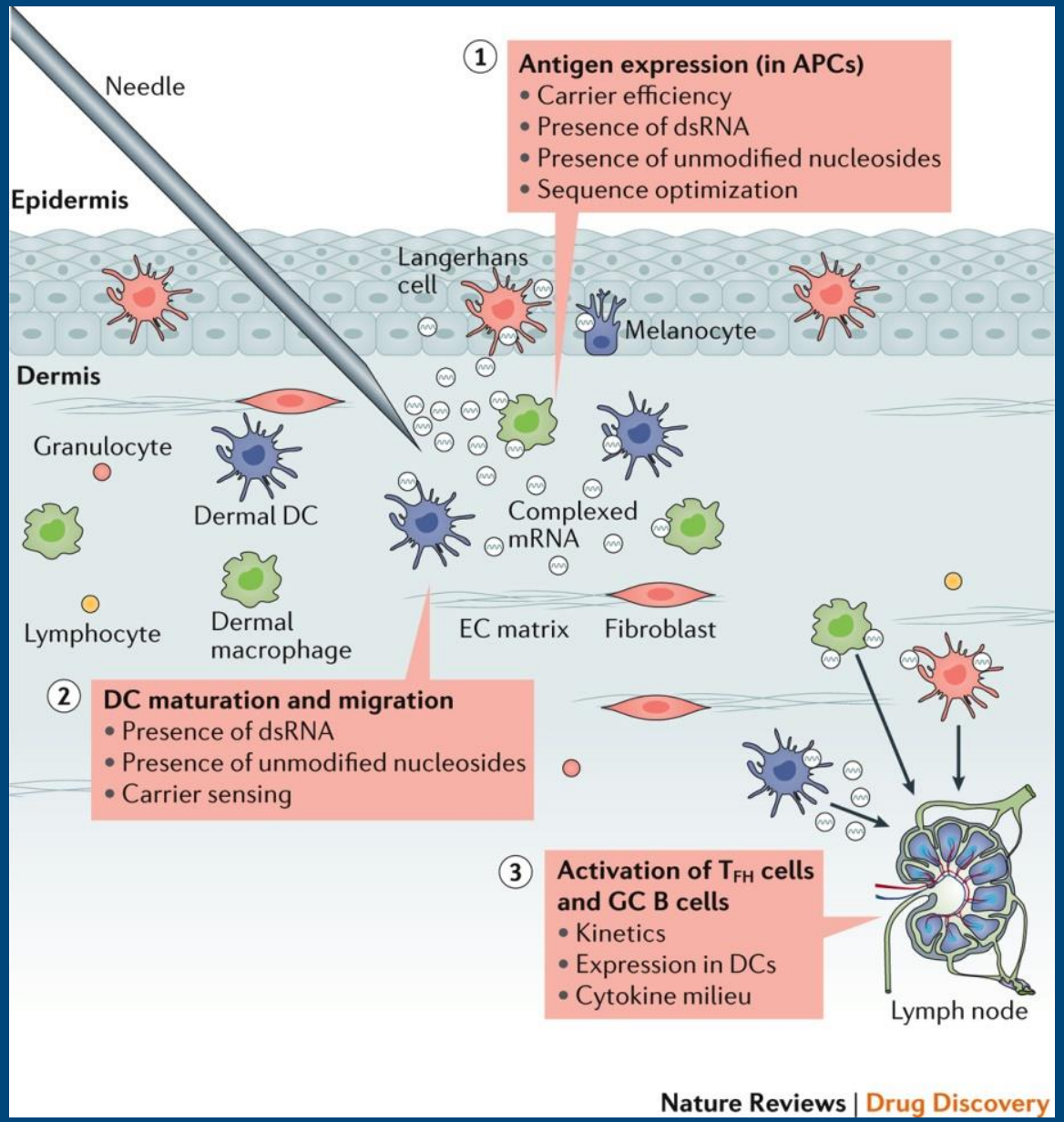
Maar meeste zitten al in LK = Lymphoid DC

=> Target van mRNA vaccin!

DC in Thymus

=> Centrale tolerantie

The delivery problem, solved



mRNA vaccins
(Moderna, BioNtech)

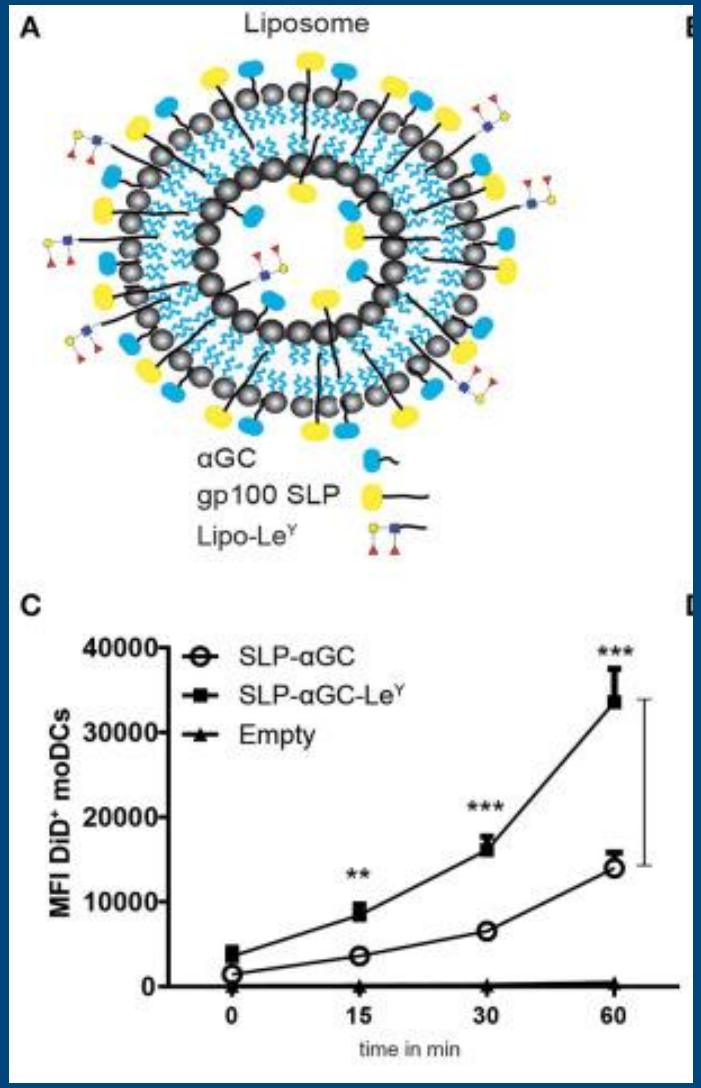
Zijn verpakt in liposomen die specifiek worden opgenomen door DC's in LK, die ze ziet als ziekmaker
=> presentatie in lymfeklier

mRNA zijn zo aangepast (modified nucleosides) dat ze heel efficient worden afgelezen (translatie)
⇒ Expressie van corona eiwit (alleen spike, dus geen volledig virus

Targeting DC's with liposomes => delivery

Dendritic cells (DC) are an attractive target for the initiation of strong immune responses as they possess the capability of capturing antigens and presenting them to specific T-cells for their activation. The skin harbors different types of antigen presenting cells, such as dermal DC (dDC) and Langerhans cells (LC) and is therefore an attractive site for delivery of vaccines. Delivery of vaccines to DC and LC can be addressed by targeting e.g., C-type lectin receptors such as Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) and Langerin. This can be easily done using their natural glycan ligands, including Lewis Y (Le^Y)

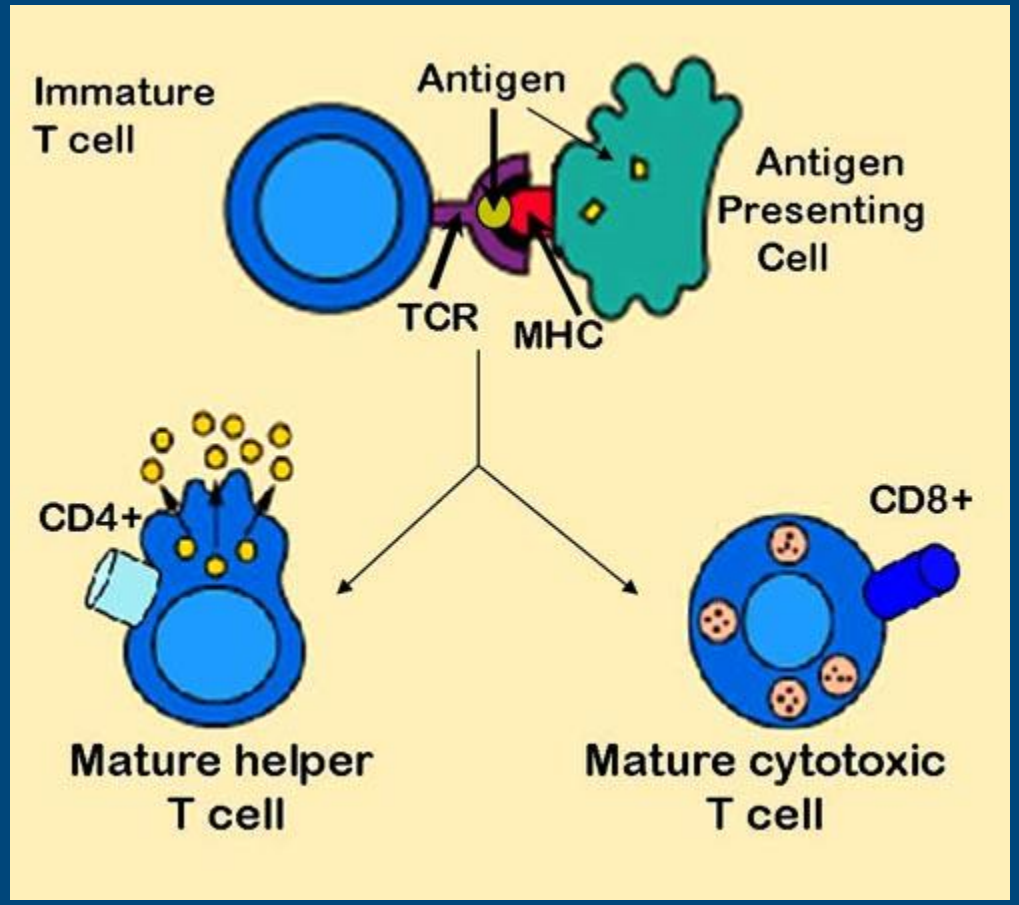
=> MHC-II loading?

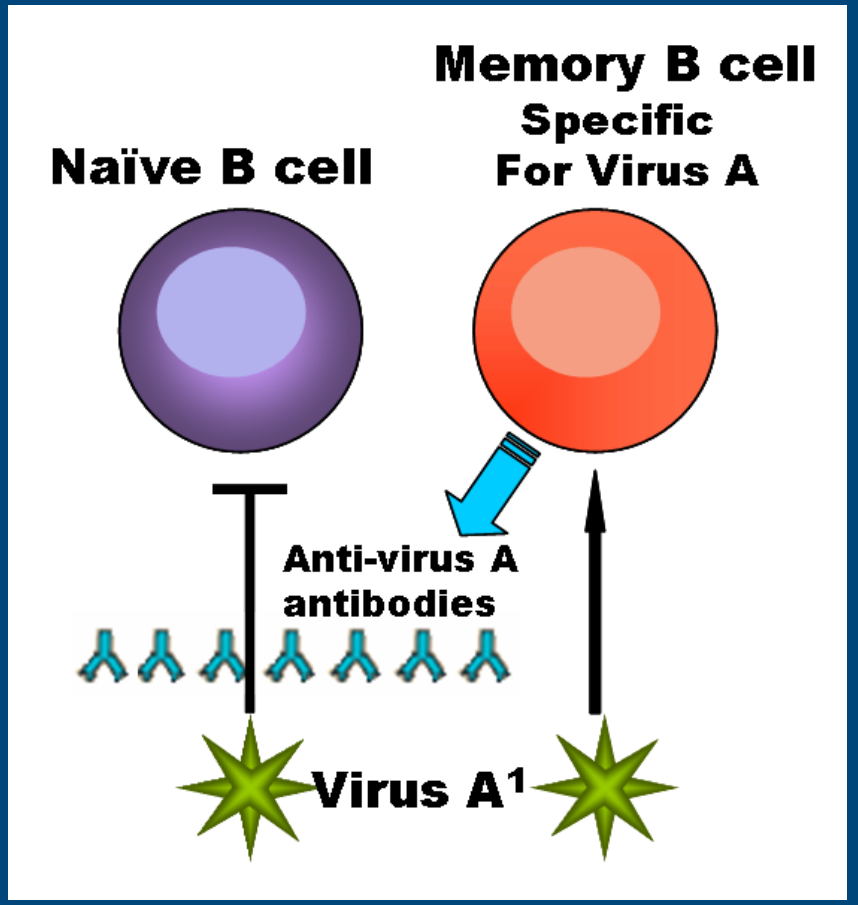


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7267035/

https://www.frontiersin.org/articles/10.3389/fimmu.2018.00590/full

Specifiek: T en B cellen, CTL, T-helper, antilichamen en memory





Alles nodig voor volledige bescherming / opruiming

Erg ingewikkeld => complexity!

https://www.youtube.com/watch?v=dTb0iEUS1oA
https://en.wikipedia.org/wiki/Clonal_selection

T Cellen
T Lymfocyte

- Worden gemaakt in het beenmerg
- Rijpen in de Thymus en Lymfeklieren

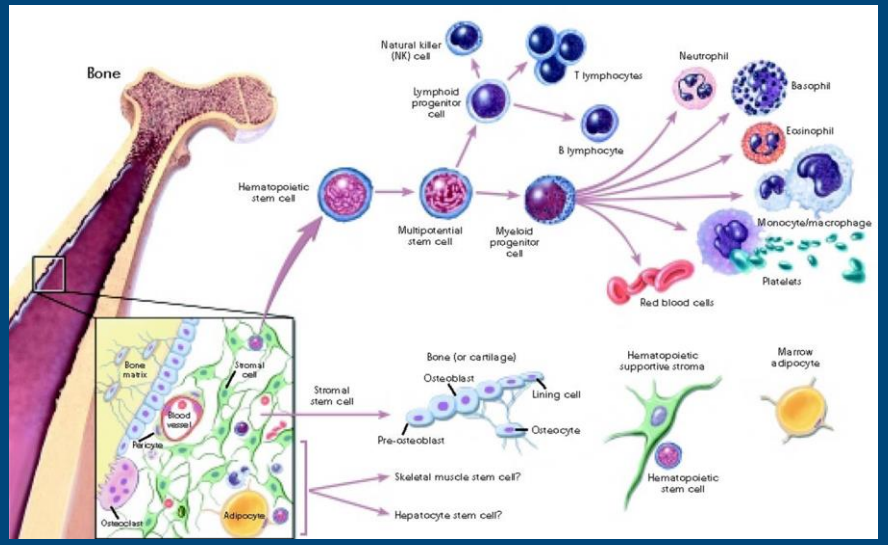
- Hulp functie (T helper)

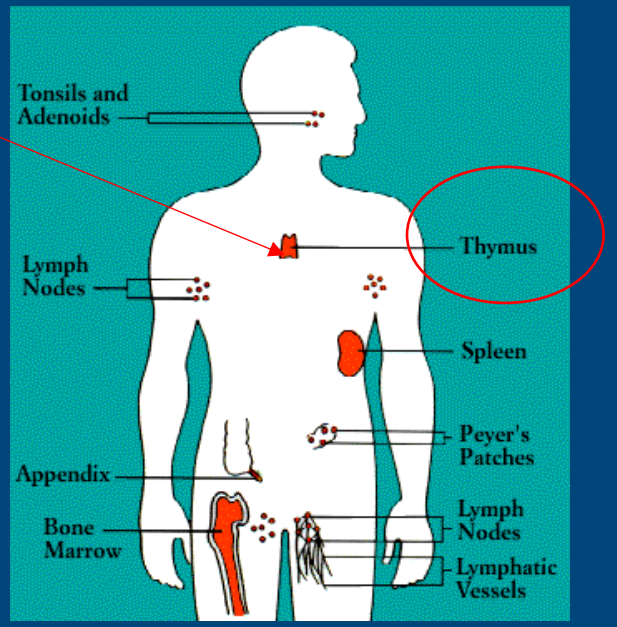
=> Th

- Cel dodende functie (Cytotoxic T Lymphocyte)

=> CTL

=> Cellulaire immuniteit





B Cellen
B Lymfocyte

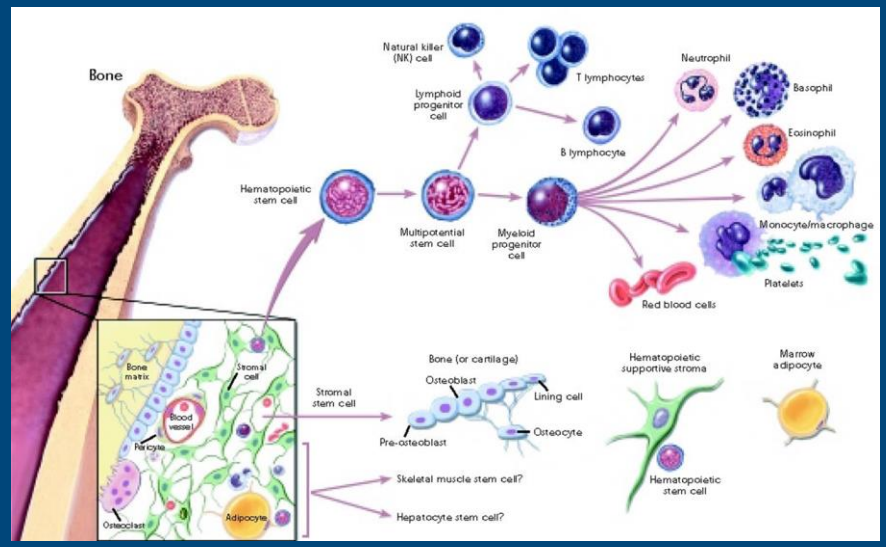
- Worden gemaakt in het beenmerg
- Rijpen in het Beenmerg, Lymfeklieren en Milt

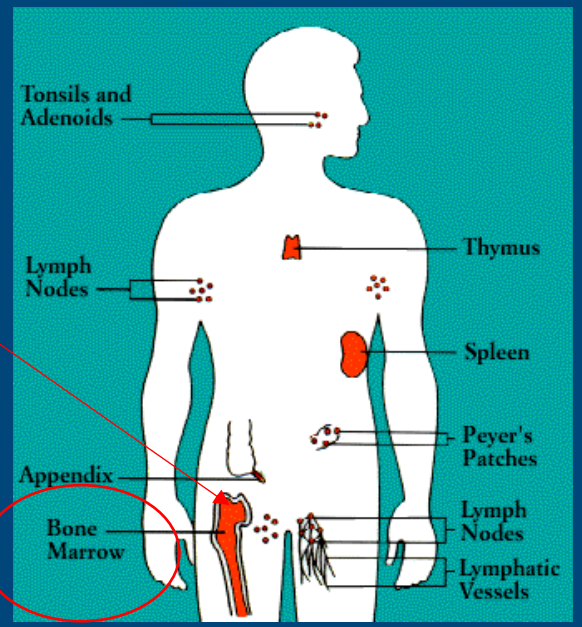
- Produceren antilichamen

⇒Humorale (bloed) immuniteit

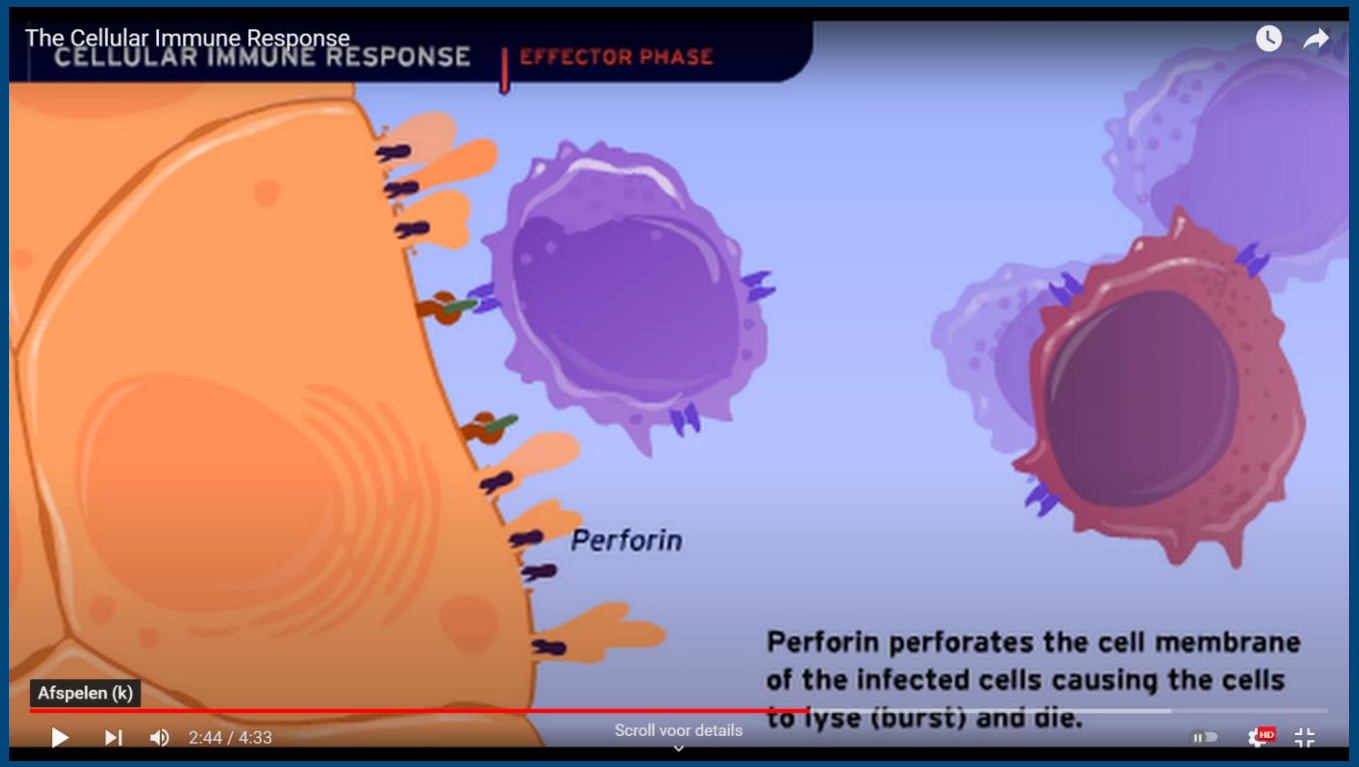
NB: B cellen zijn in eerste instantie gevonden in de Bursa bij vogels

NB De milt is eigenlijk een grote lymfeklier gespecialiseerd in het beschermen van het bloed





Cytotoxische T-Lymfocyt
Doodt met virus geinfecteerde cellen



https://youtu.be/oUpcRfpEh3c

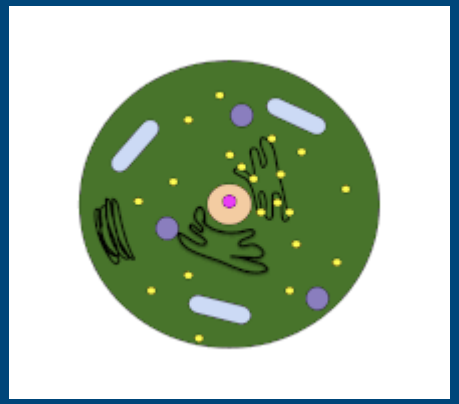
https://youtu.be/dTb0iEUS1oA

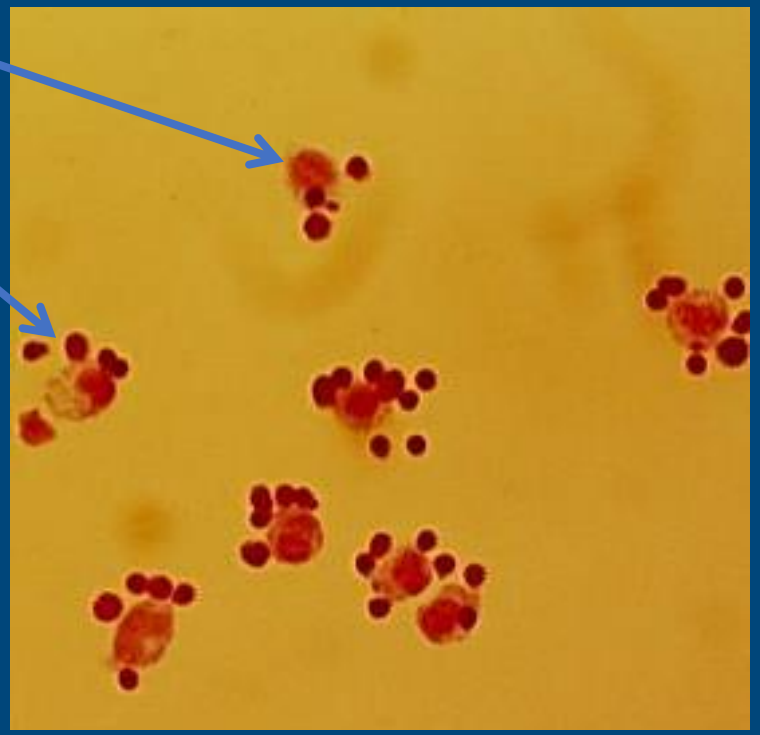
Activatie en werking is ingewikkelder dan voor de B-cel (die antilichamen produceert).

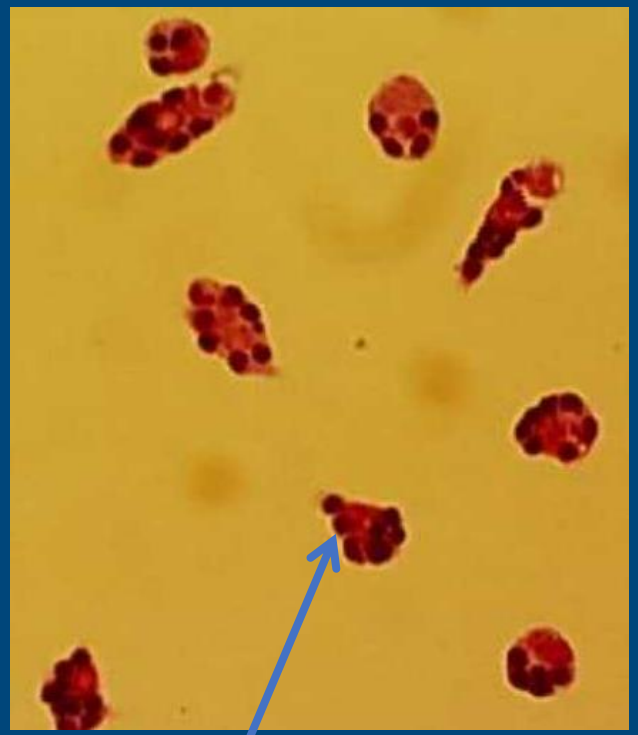
Maar voor het bestrijden van virussen is de CTL-respons belangrijker dan de B-cel respons

Celbio: Cellen gaan standaard dood via apoptose
=> en worden netjes opgeruimd (fagocytose)

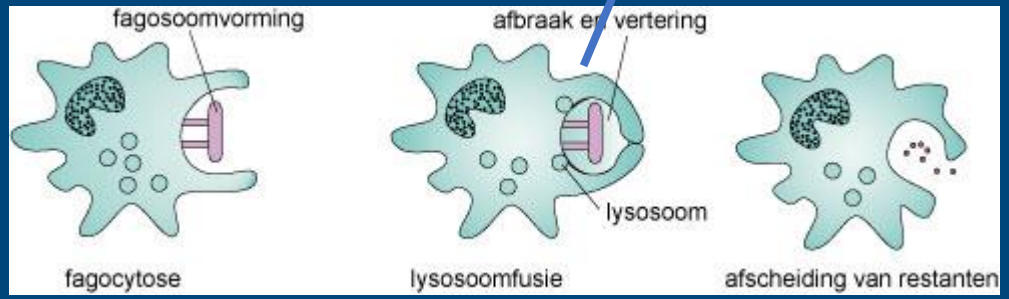
Macrofagen ruimen dode (apoptotische) cellen op via fagocytose







Apoptose is een georganiseerd proces waarbij een cel zich geschikt maakt voor ordentelijke opruiming



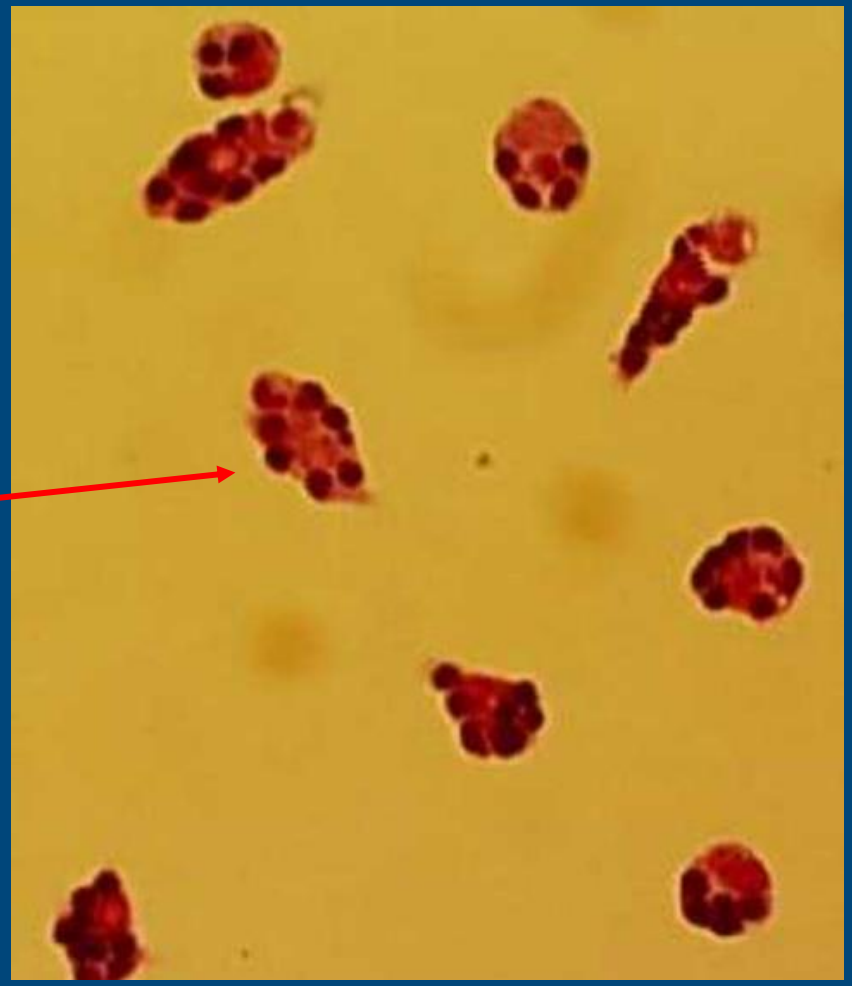
Halfwaardetijd cellen

- Rode bloedcel 110 dagen
- Huidcel 21 dagen
- Darm epitheel 2 dagen => hans cleevers
- Long epitheelcel 2 jaar

⇒Vrijwel elke cel in het lichaam is vervangen na ~10 jaar

NB Meeste cellen gaan ordelijk dood via apoptose,

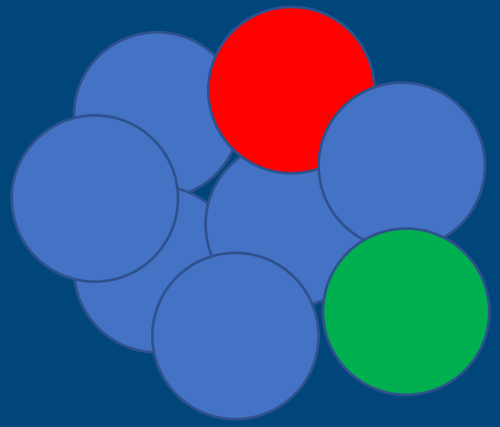
en worden verwijderd door macrofagen

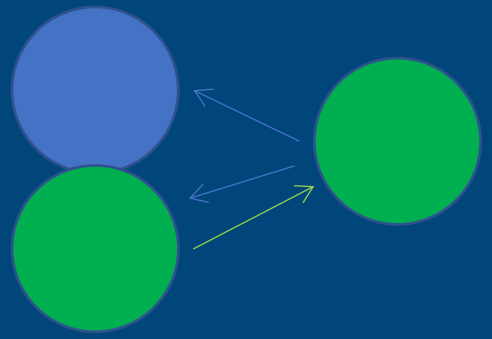


https://www.timeshighereducation.com/news/life-span-of-human-cells-defined-most-cells-are-younger-than-the-individual/198208.article

http://www.uptodate.com/contents/red-blood-cell-survival-normal-values-and-measurement

Celbio: Leven is een fluide verzameling
Atomen / Cellen / Organismen

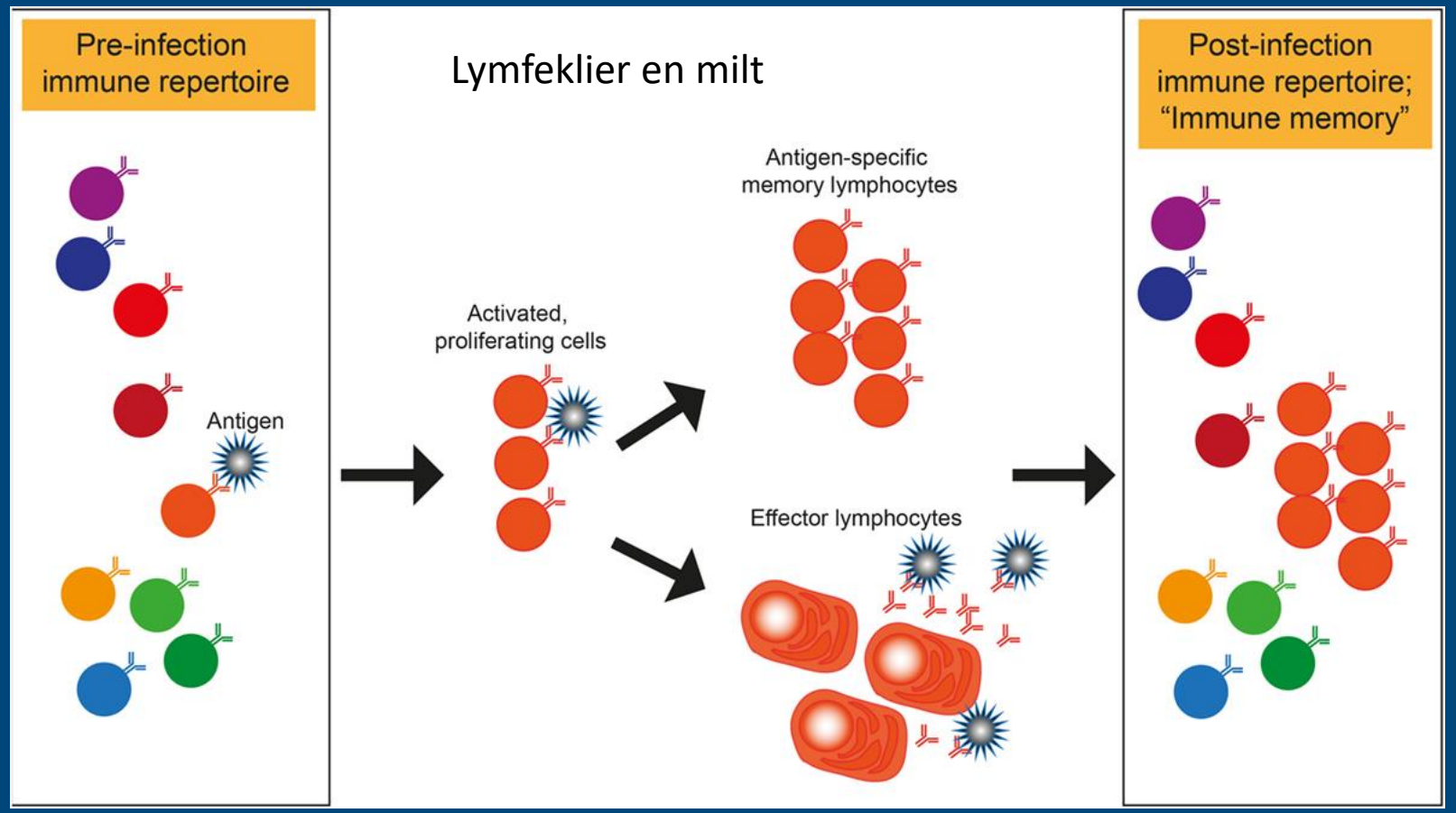




Dode cel
stamcel

Elke cel wordt op termijn vervangen.
En uit een stamcel die deelt ontstaan 2 nieuwe cellen (1 wordt de nieuwe stamcel)
=> Leven is modulair

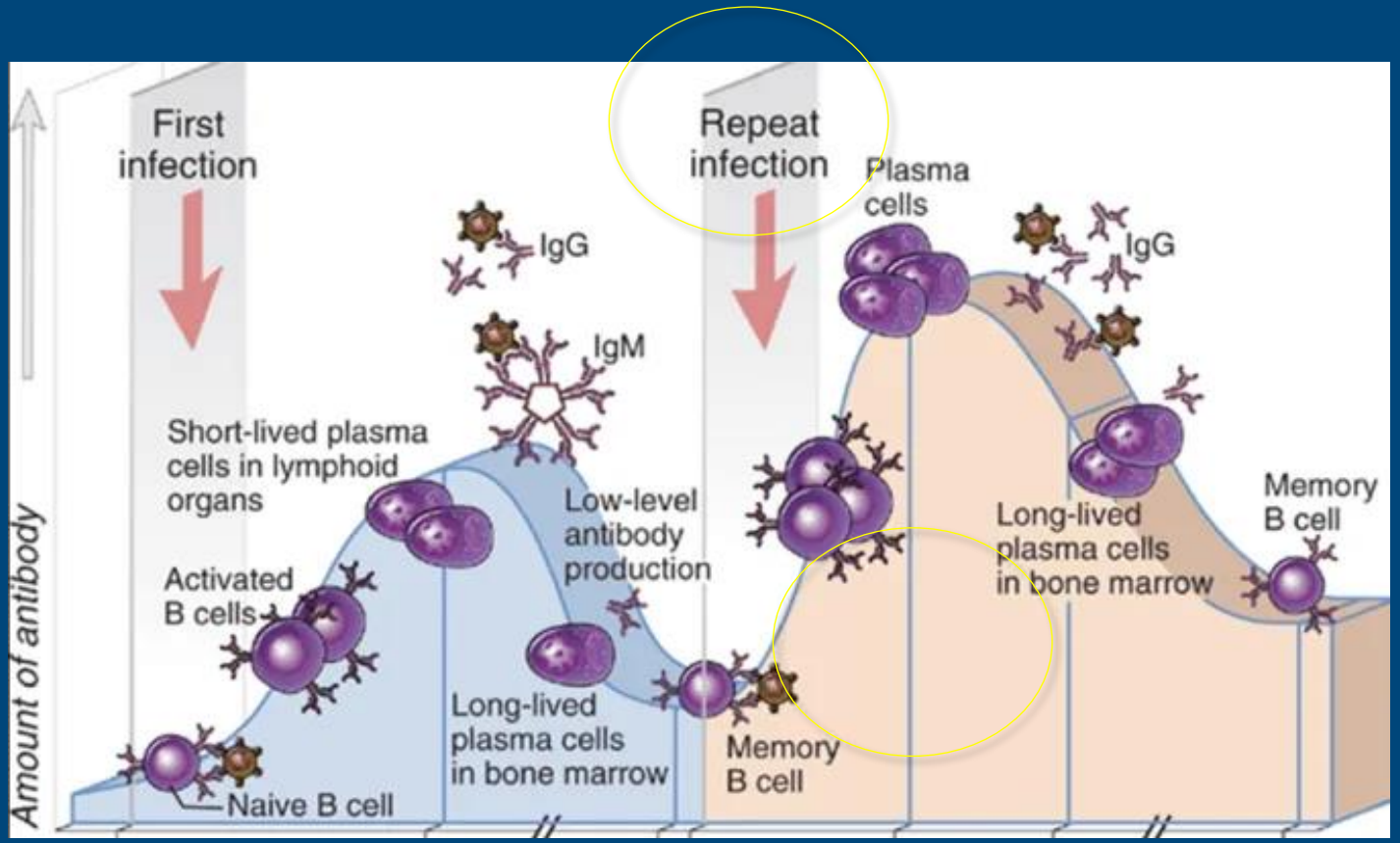
Het leerproces van de specifieke afweer: Repertoire en memory



An immune system that produces a wide variety, will likely have one or two subtypes that recognise any germ we are exposed to
https://en.wikipedia.org/wiki/Immune_repertoire

Afgelopen jaar, ook bij de HOVO
Memory (geheugen) => basis van vaccinatie

After a first encounter with an antigen special T and B cells — the so called memory T and B cells are formed => faster and stronger response to a 2nd challenge



Bron: Abbas, Basic Immunology.

Vaccin
Verzwakte ziekmaker, of delen hiervan

- Voorkomt niet de infectie
- Maakt memory T en B cellen

=> Snelle, en vaak subklinische, reactie

=> Elk jaar miljoenen mensen niet dood

- Heel kosteneffectief
- Heel weinig bijwerkingen, al zijn die niet nul (autisme? allergien?)

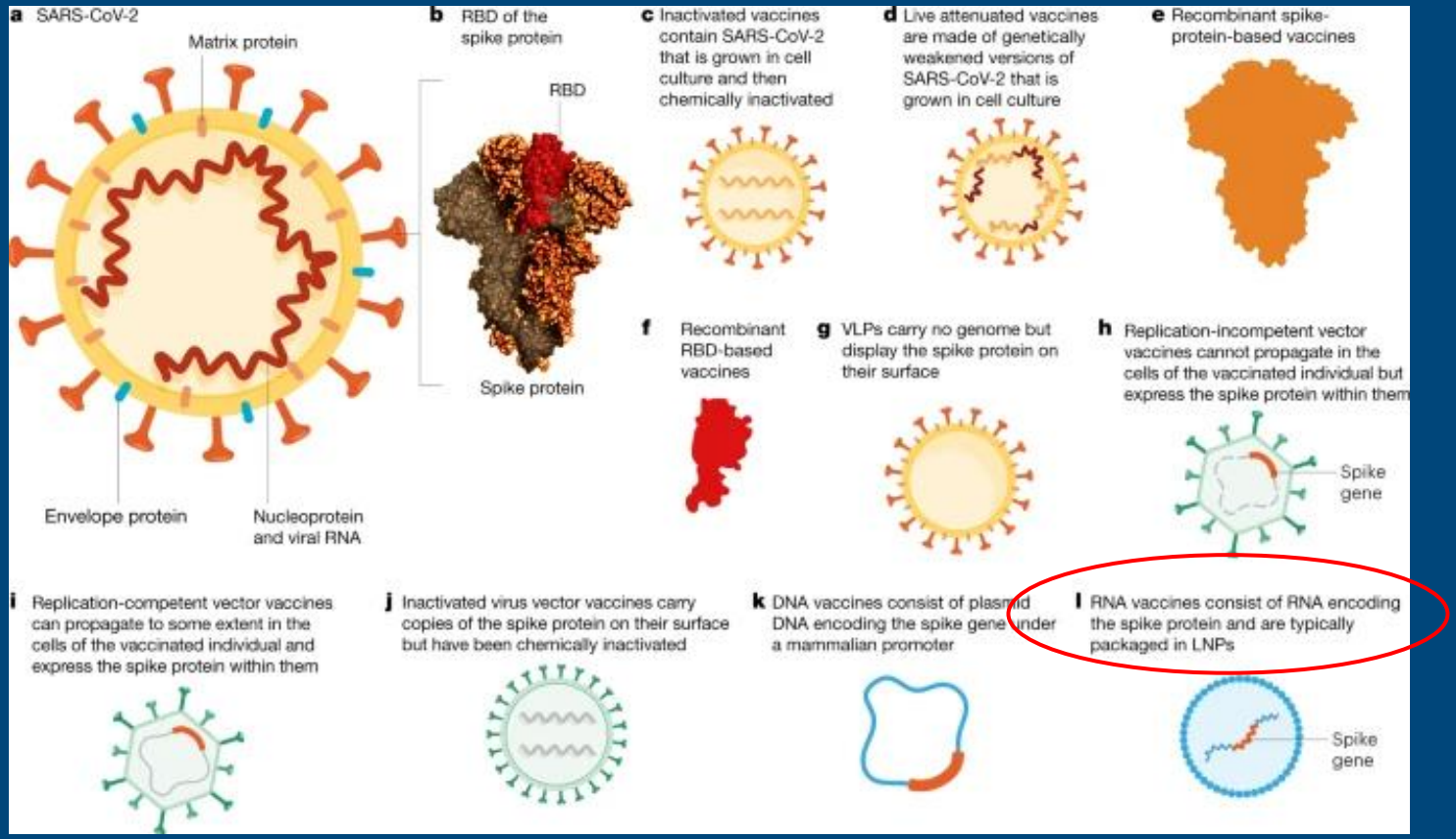
- Ook voor risicogroepen verstandig (ouderen, zieken) => griepprik
- Normaal is ziek worden niet zo'n probleem, en voor jonge kinderen zelfs nuttig (minder allergie)

Effectiveness of Vaccines for Some Common Infectious Diseases

Disease	Maximum number of cases (year)	Number of cases in 2004	Percent change
Diphtheria	206,939 (1921)	0	-99.99
Measles	894,134 (1941)	37	-99.99
Mumps	152,209 (1968)	236	-99.90
Pertussis	265,269 (1934)	18,957	-96.84
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	12	-99.98
Tetanus	1,560 (1923)	26	-98.33
Haemophilus influenzae type B	~20,000 (1984)	16	-99.92
Hepatitis B	26,611 (1985)	6,632	-75.08

Abbas et al. *Cellular and Molecular Immunology* (2007, 6th ed.) Page:4

(SARS-CoV-2) vaccines



https://www.nature.com/articles/s41586-020-2798-3
https://www.nature.com/nature/volumes/586/issues/7830

Versie 1.0
Jenner (volledig virus, maar koe ipv mens)

Versie 2.0
Geinactiveerd (c) mazelen

Versie 3.0
Uitgekleed (h)

Versie 4.0
Geen virus meer (i)
⇒ Alleen informatie
⇒ Plug and play

Intracellulaire afweer (tegen virussen)
De interferon respons

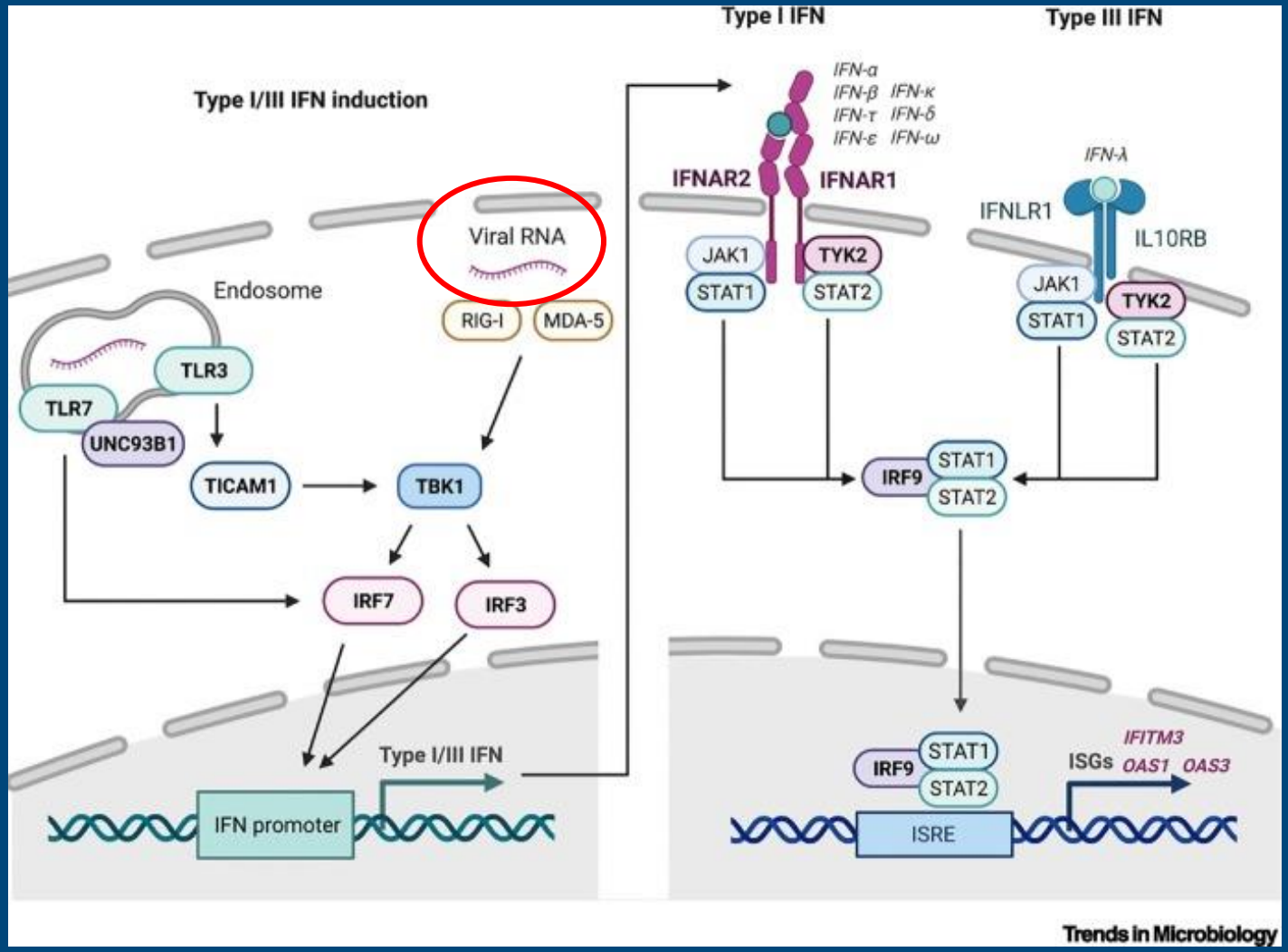
Simplified signaling cascades leading to transcription of type I/III interferon genes following infection with an RNA virus (*left panel*).

Simplified signaling cascades leading to transcription of interferon-stimulated genes (ISGs) following type I/III interferon stimulation (*right panel*).

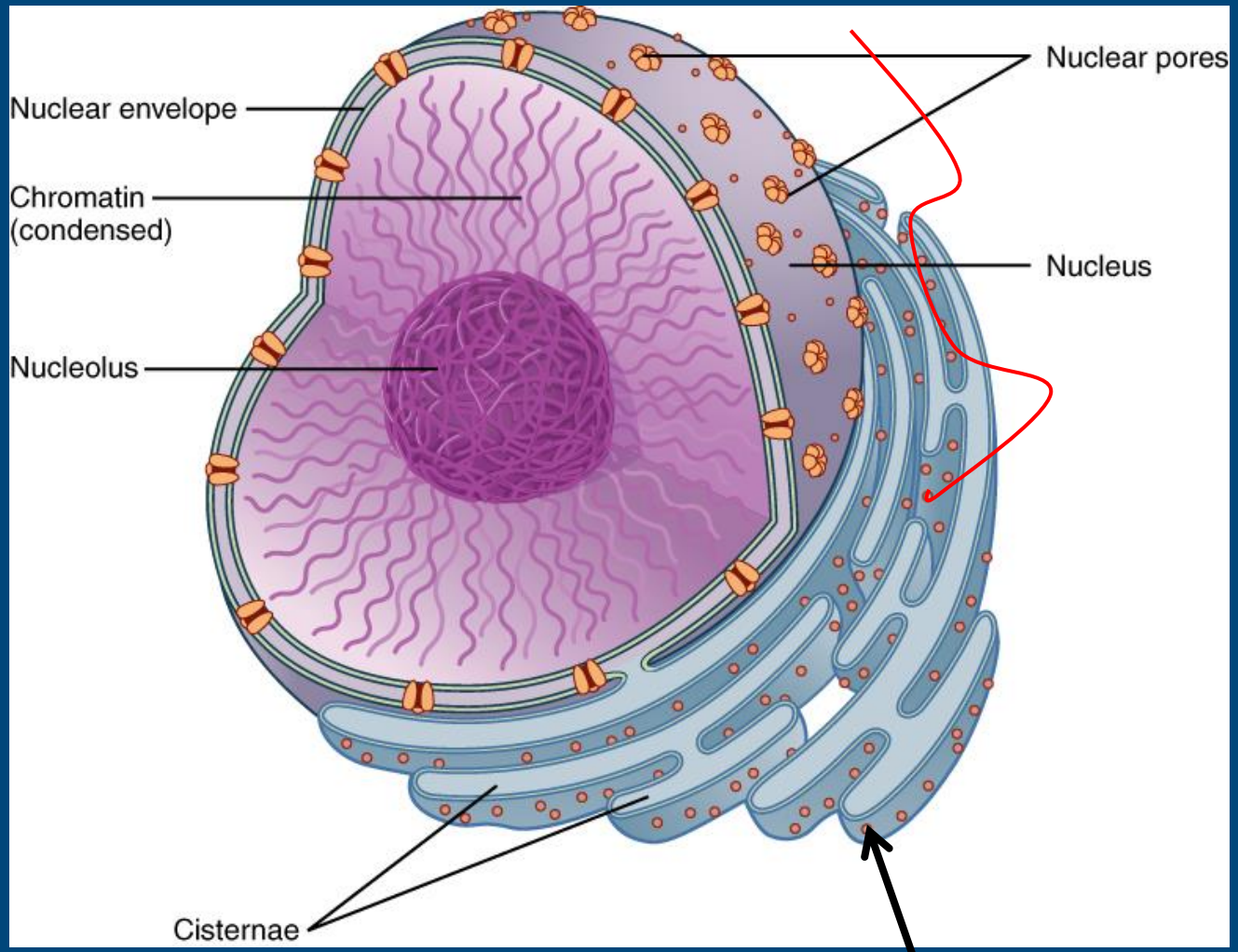
⇒Meer MHC

⇒Pro-inflammatoire cytokines

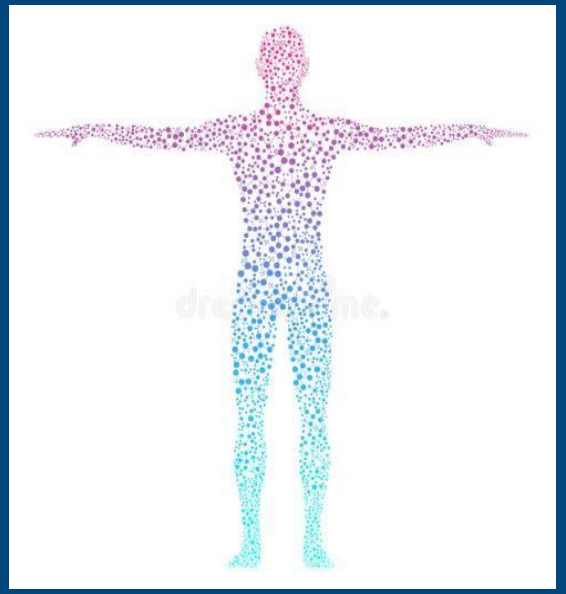
=> gevaar



De celkern, met daarin DNA

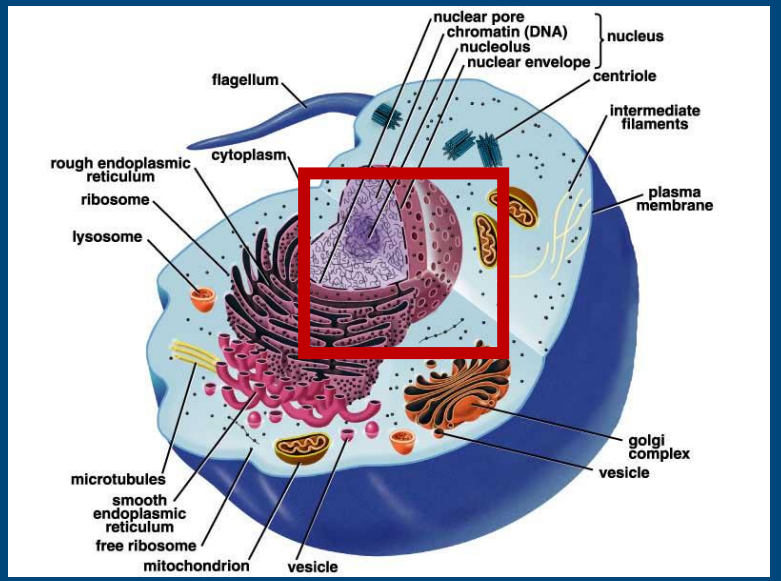


Ruw Endoplasmatisch Reticulum met ribosomen
(mRNA => eiwit)

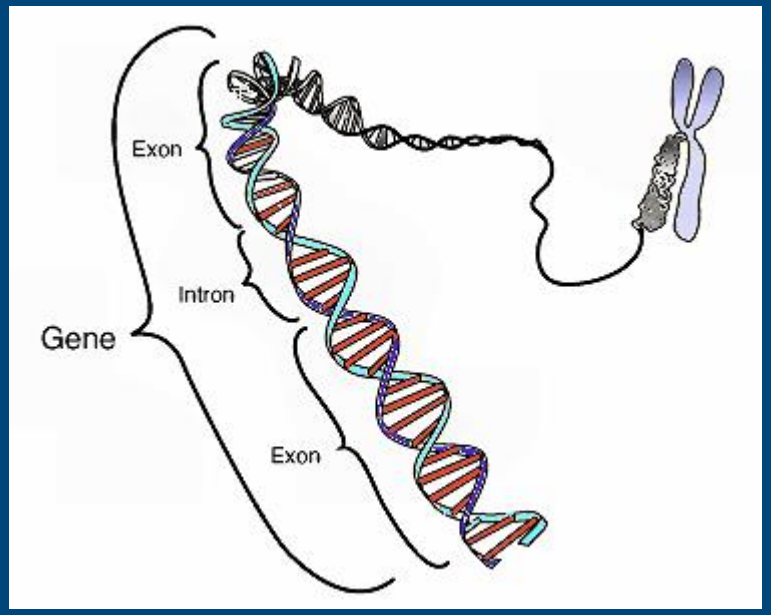


Leven bestaat uit cellen https://youtu.be/SEejivHRIbE

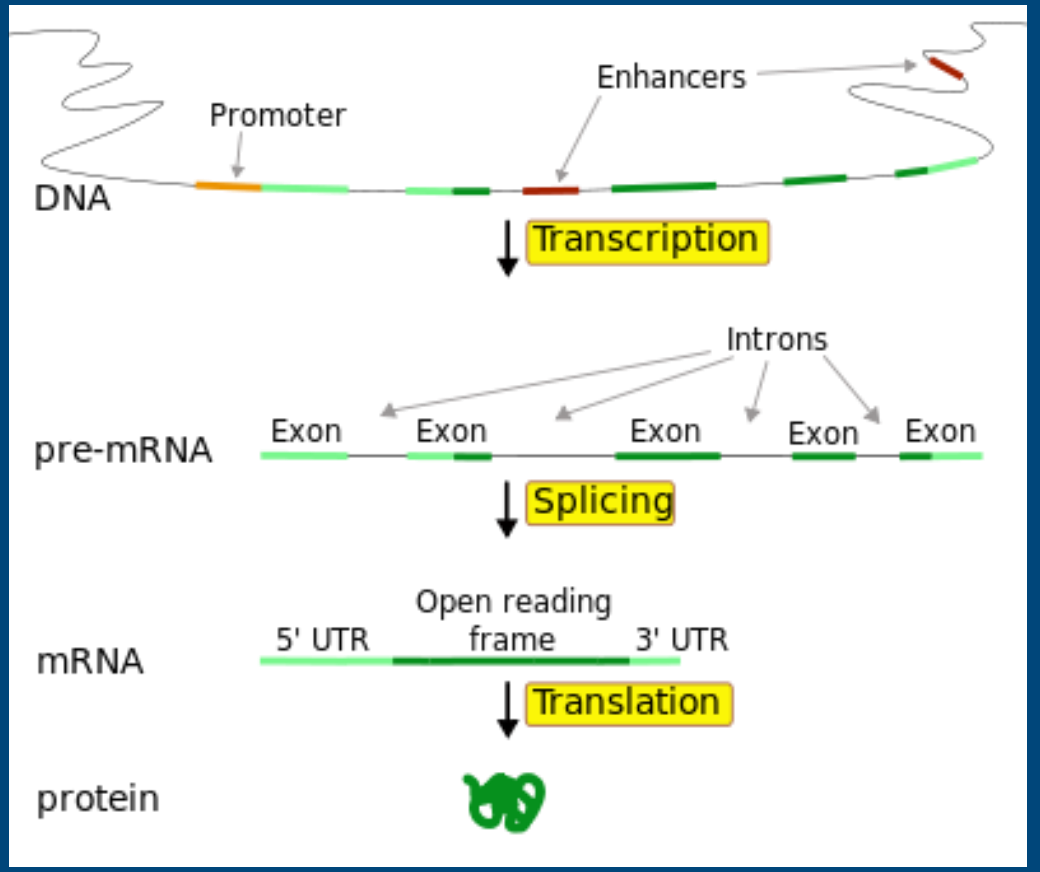
Een (eukaryote) cel met celkern



Gen => RNA => Eiwit



Een gen produceert 2-30 mRNAs/uur



Gen

RNA

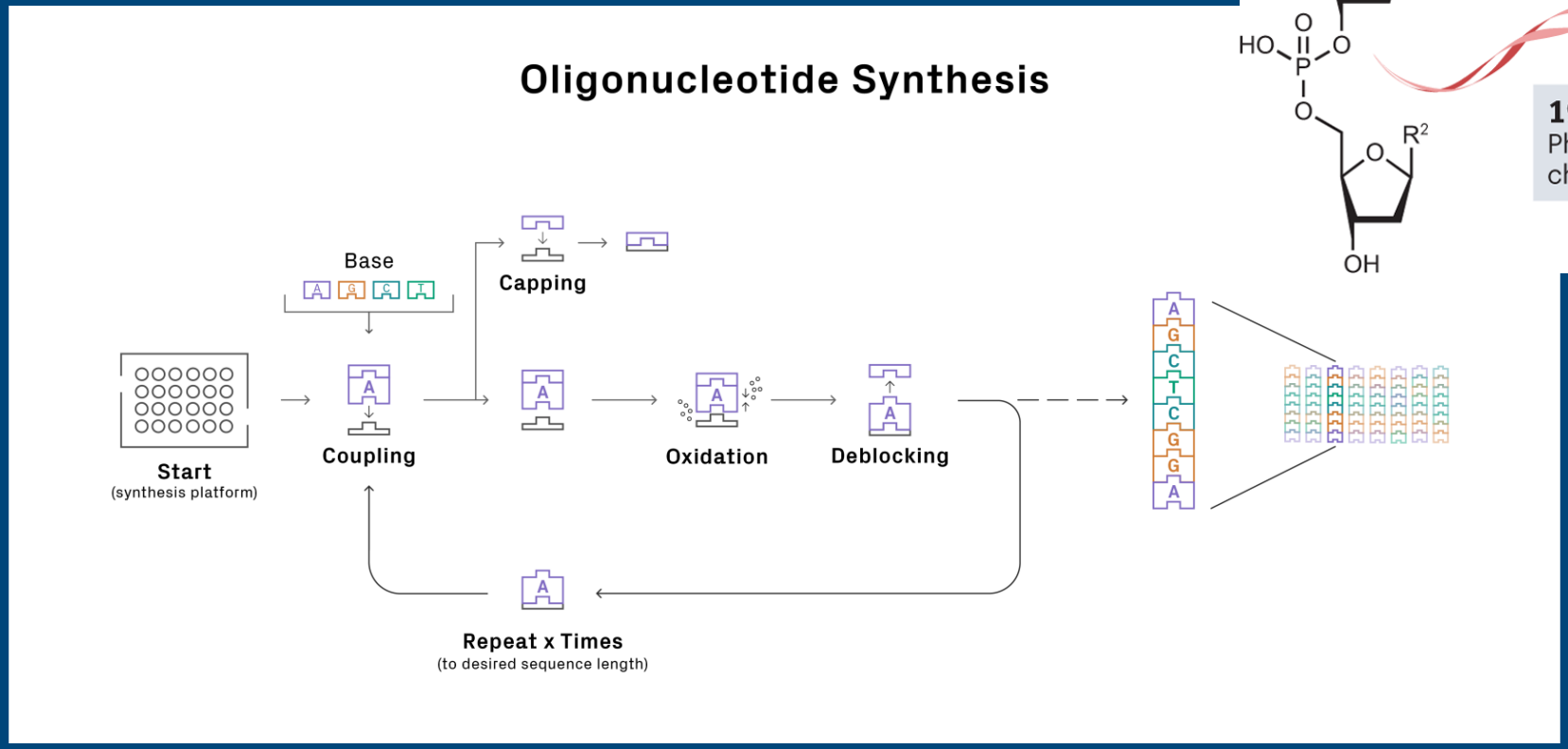
Eiwit

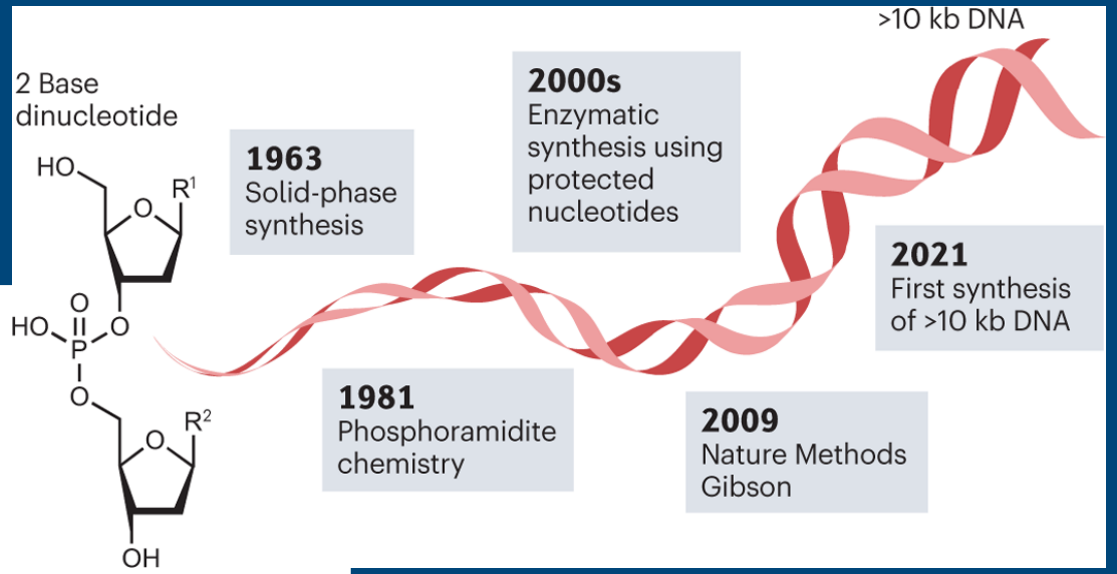
Watson, Crick, Franklin, Wilkins.

Central dogma of molecular biology

DNA/RNA synthese (schrijven)

- Oligonucleotide synthesis cycle





10kb = 10.000 nucleotiden
=1 gen

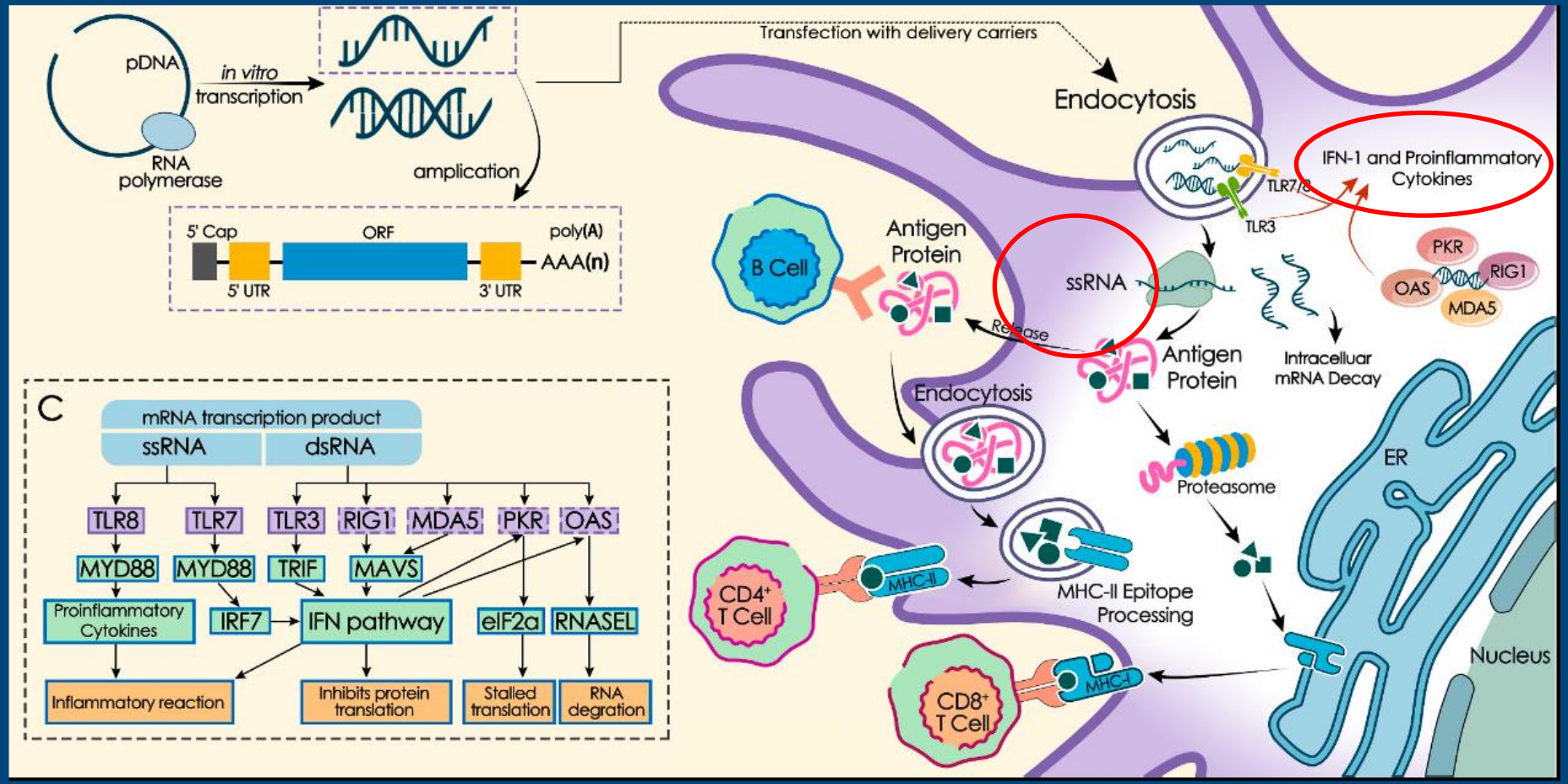
DNA synthese (schrijven)

https://youtu.be/Dwrte-CBomw

=> synthetische biologie

https://youtu.be/DxoLoOtyllU

mRNA in Vaccin
Direct naar ribosoom, en meer

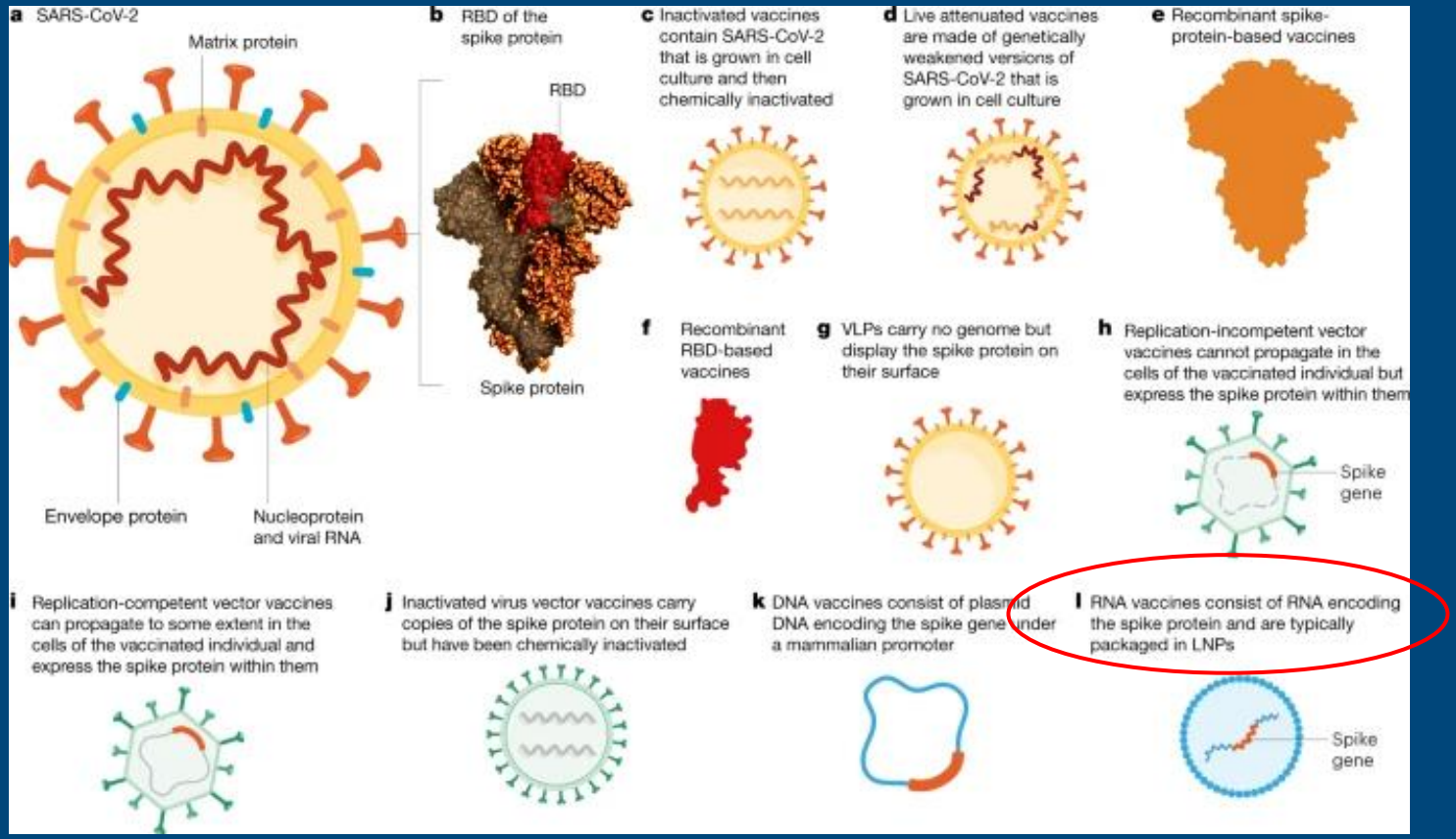


Werkingsmechanisme is niet helemaal duidelijk!
Intellectual Property (IP)

mRNA tegen kanker

- https://youtu.be/R83JCXSjvJo?t=2121

(SARS-CoV-2) vaccines



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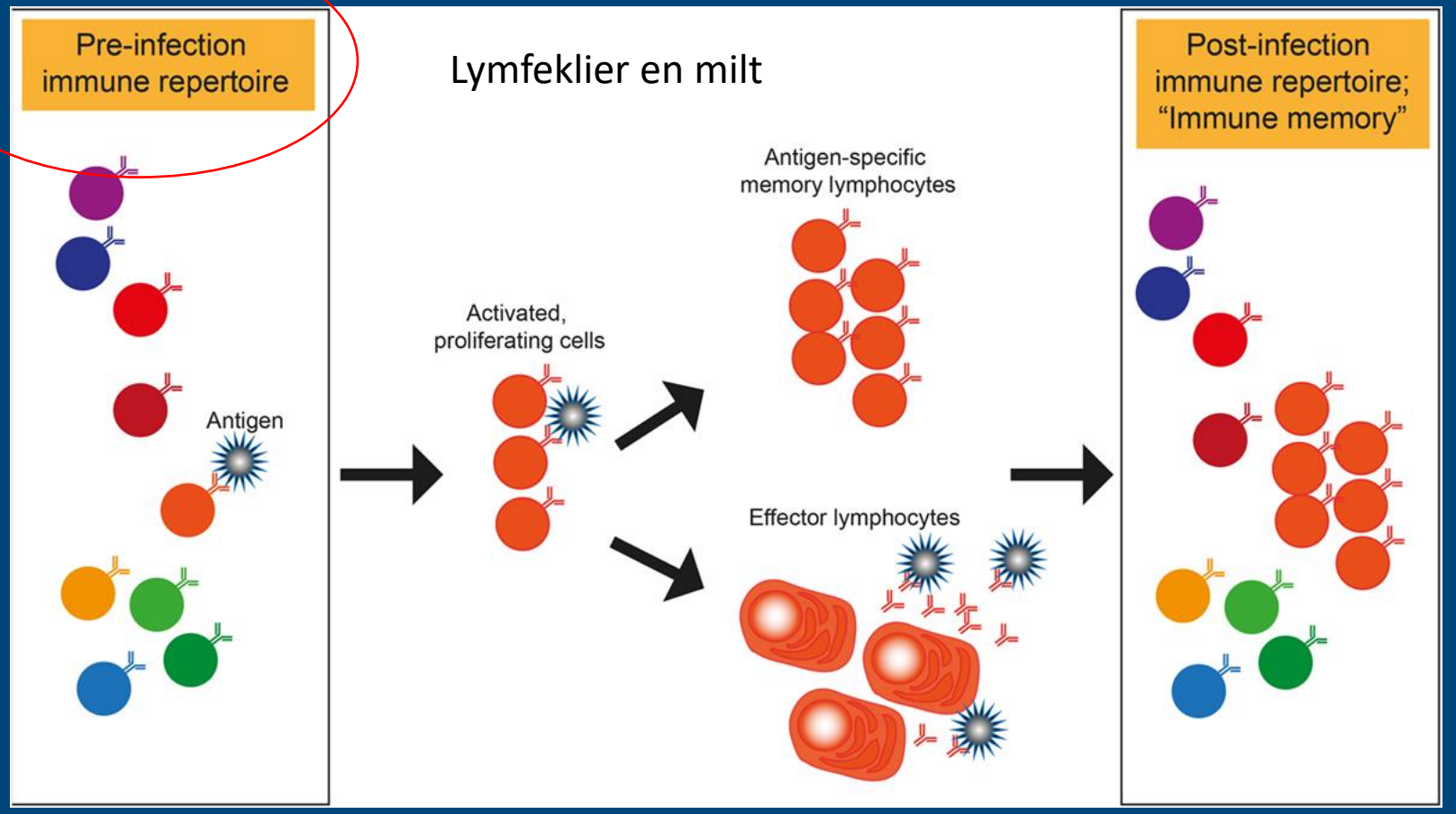
Het leerproces van de specifieke afweer: Repertoire en memory



An immune system that produces a wide variety, will likely have one or two subtypes that recognise any germ we are exposed to
https://en.wikipedia.org/wiki/Immune_repertoire

Waar het afweersysteem niet op moet reageren

- Lichaams eigen cellen (self)
- Voedingsstoffen
- Niet gevaarlijke stoffen in de omgeving (pollen)
- Bacterien op de huid/ in de darm
- Schimmels op de huid/ in de darm
- Virussen (bacteriofagen) in de darm
- Virusresten (transposons) in het genoom

- NB Dezelfde bacterie in het bloed wel op reageren => gevaar

MHC-I en CTL

- CD8 positieve T-cell, herkent MHC-I
- MHC-I zit op elke cel

⇒ In de gaten houden van wat er in de cel gebeurt

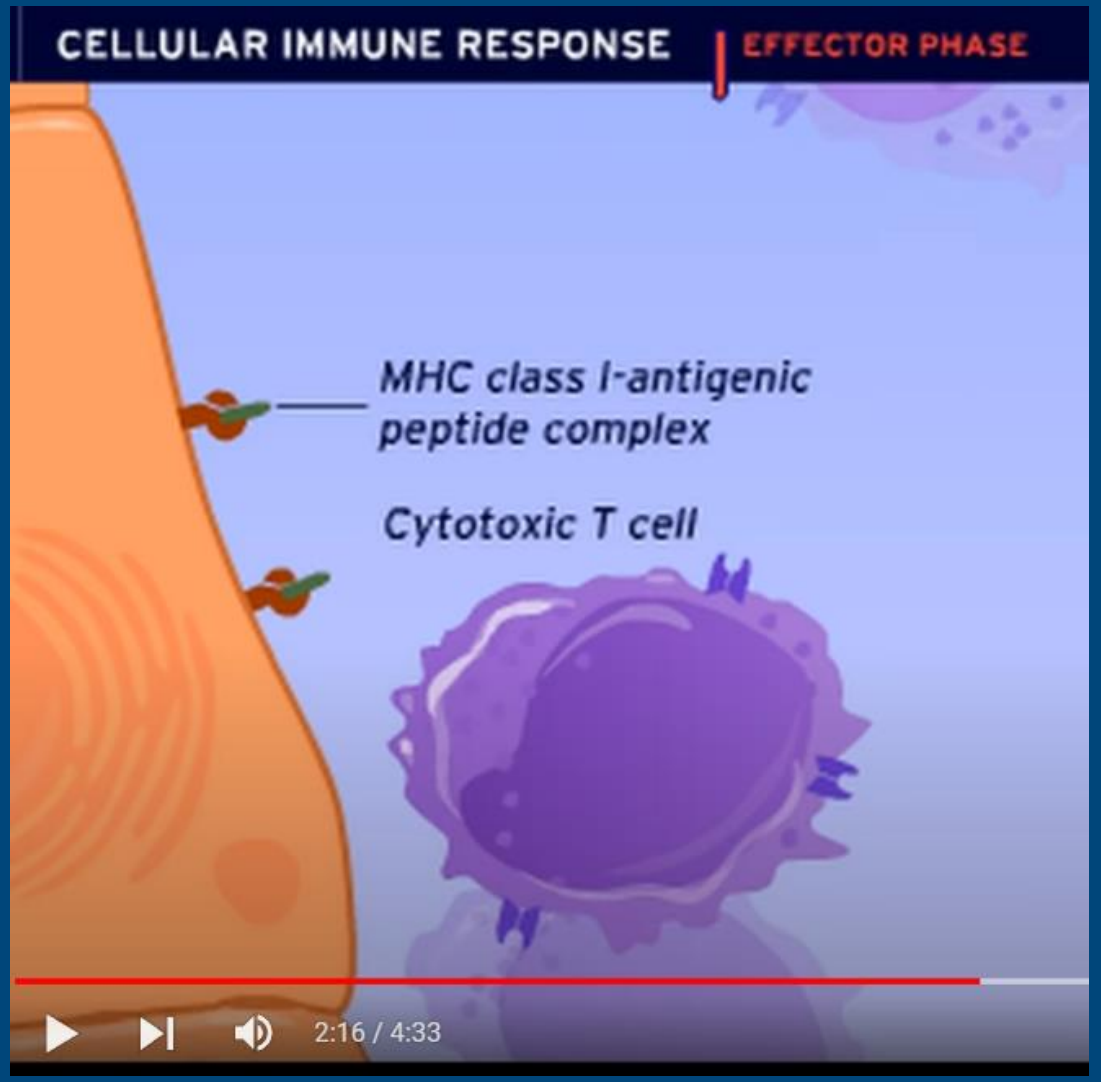
=> Tolerant voor self

Herkenning => Iets niet goed => doding

Kan virus zijn, of transformatie (kanker)

Maar er is vaak ook nog een gevaar signaal nodig, vanwege perifere controle

https://youtu.be/oUpcRfpEh3c



Reageren op lichaamsvreemd en gevaar
Voor de rest moet het tolerant zijn.

- Alleen lichaamsvreemd moet worden aangevallen

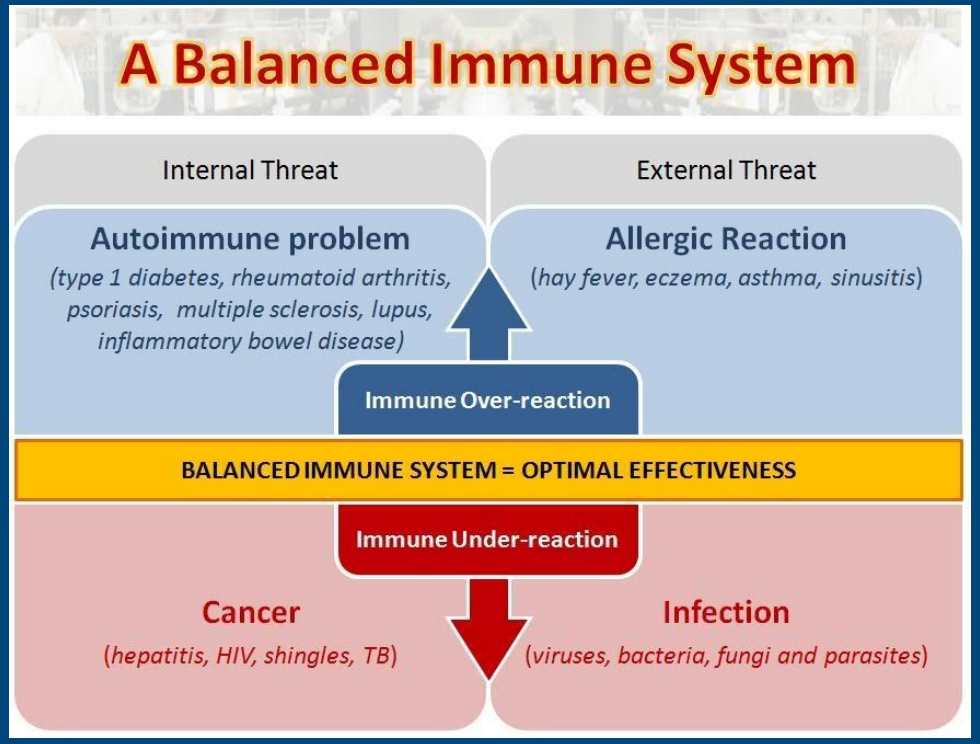
⇒ Centrale Tolerantie (Opleiding)

⇒ “Self non-self discrimination”

- Maar niet alles wat lichaamsvreemd is (pollen), is gevaarlijk.

=> Perifere Tolerantie (Controle)

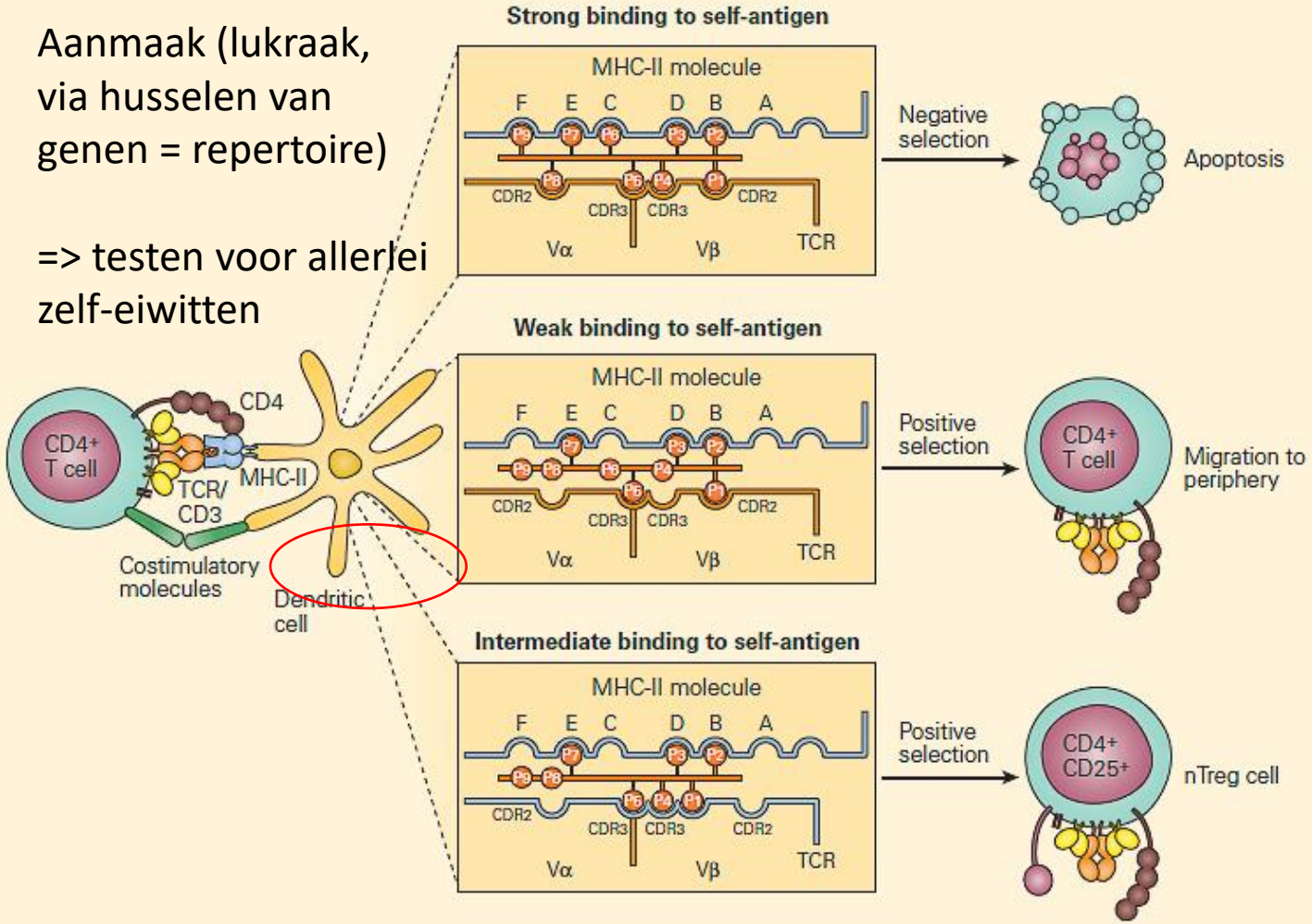
=> “Danger hypothesis



Central T-cell tolerance (thymus)
It's complicated

Aanmaak (lukraak, via husselen van genen = repertoire)

=> testen voor allerlei zelf-eiwitten



DC in Thymus/beenmerg

Instead of Yes/no
=> Weak/strong

Peptides are <u>self</u> =>
Strong is not good
=> autoimmunity

Weak means good MHC recognition

Treg help prevent autoimmunity

https://www.immunopaedia.org.za/immunology/advanced/2-central-peripheral-tolerance/

Centrale tolerantie, in Thymus / Beenmerg
T en B cel repertoire => self/non-self discrimiation

- Miljarden varianten,
- 5% overleeft selectie

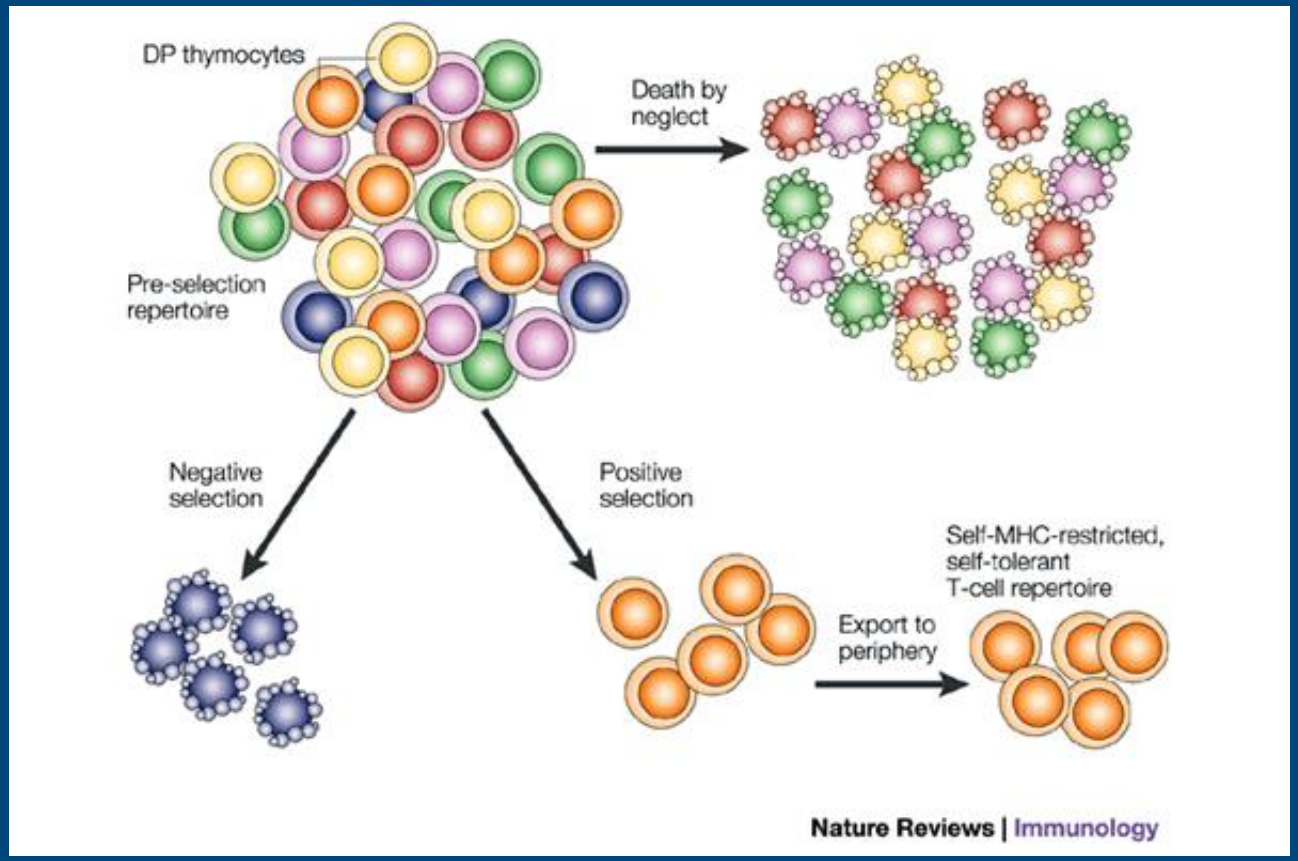
no MHC recognition

=> death by neglect

- Self-peptide recognition
  => negative selection

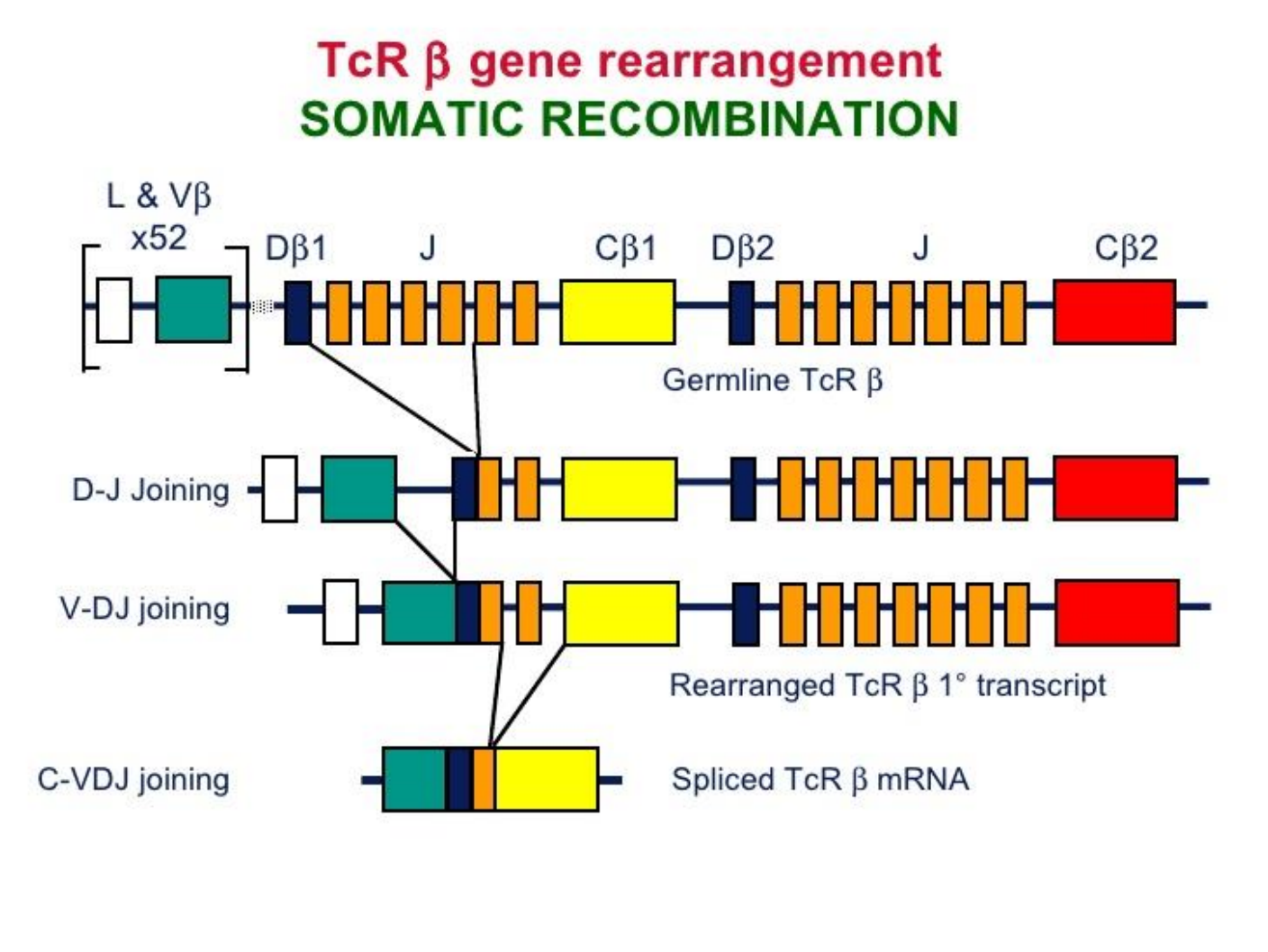
- Repertoire is (non-self) antigeen dat kan worden herkent

NB Thymus / BM omgeving
=> onvolledige weergave van het lichaam



https://www.youtube.com/watch?v=rHx30H3dUKQ
https://www.youtube.com/watch?v=2jEBTeAgtFY

Hoe maak je miljarden varianten:
T-cell receptor gene-rearrangement



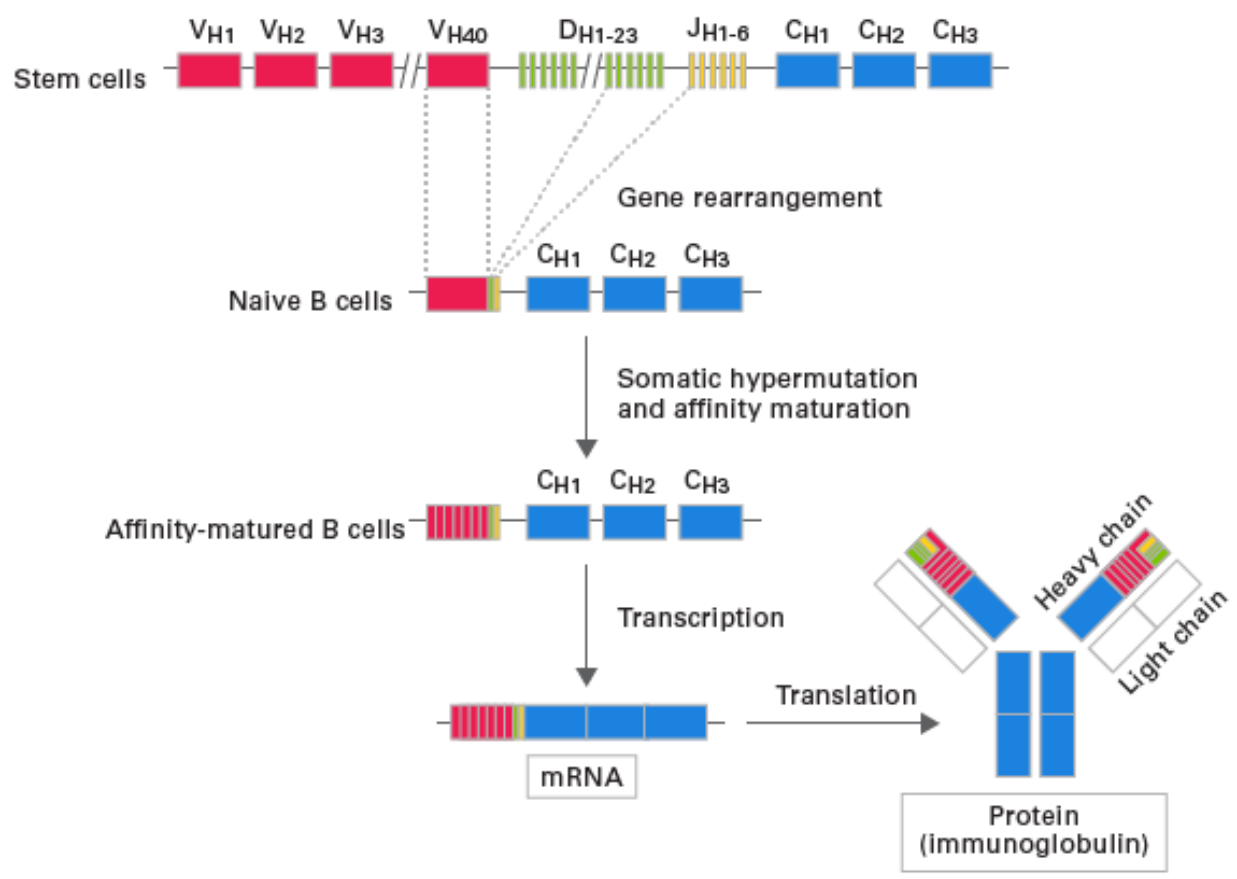
- Uniek voor afweer
- Verder alleen bij Meiose
- https://youtu.be/LmpuerlbJu0

- Genetische destabilisatie staat aan de basis van kanker!

⇒Gevaarlijke strategie

⇒Afweercel gaat gemakkelijk ten gronde

B-cell receptor gene-rearrangement
=> affinity maturation



- Affinity maturation also induces Isotype switch from IgM to IgG
- After activation antibody is released into the ciculation!

=> Humoral immunity

- NB Other classes are IgE, IgA
- Snelle evolutie, die de verandering van ziekmakers kan bijbenen!

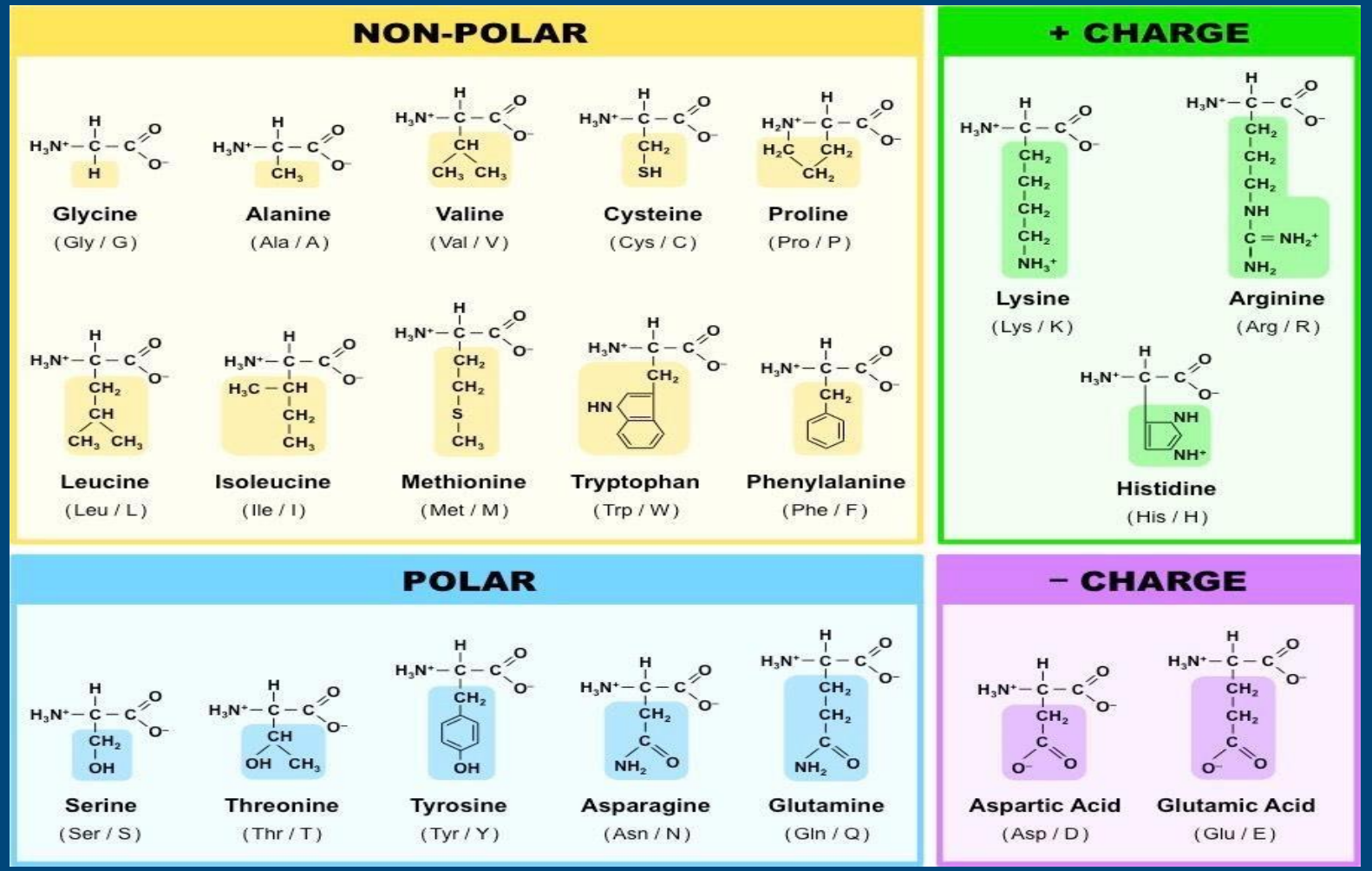
vragen

- Aminozuren
- Beeldvorming
- NSP corona
- Dex
- Agency

- Excursie

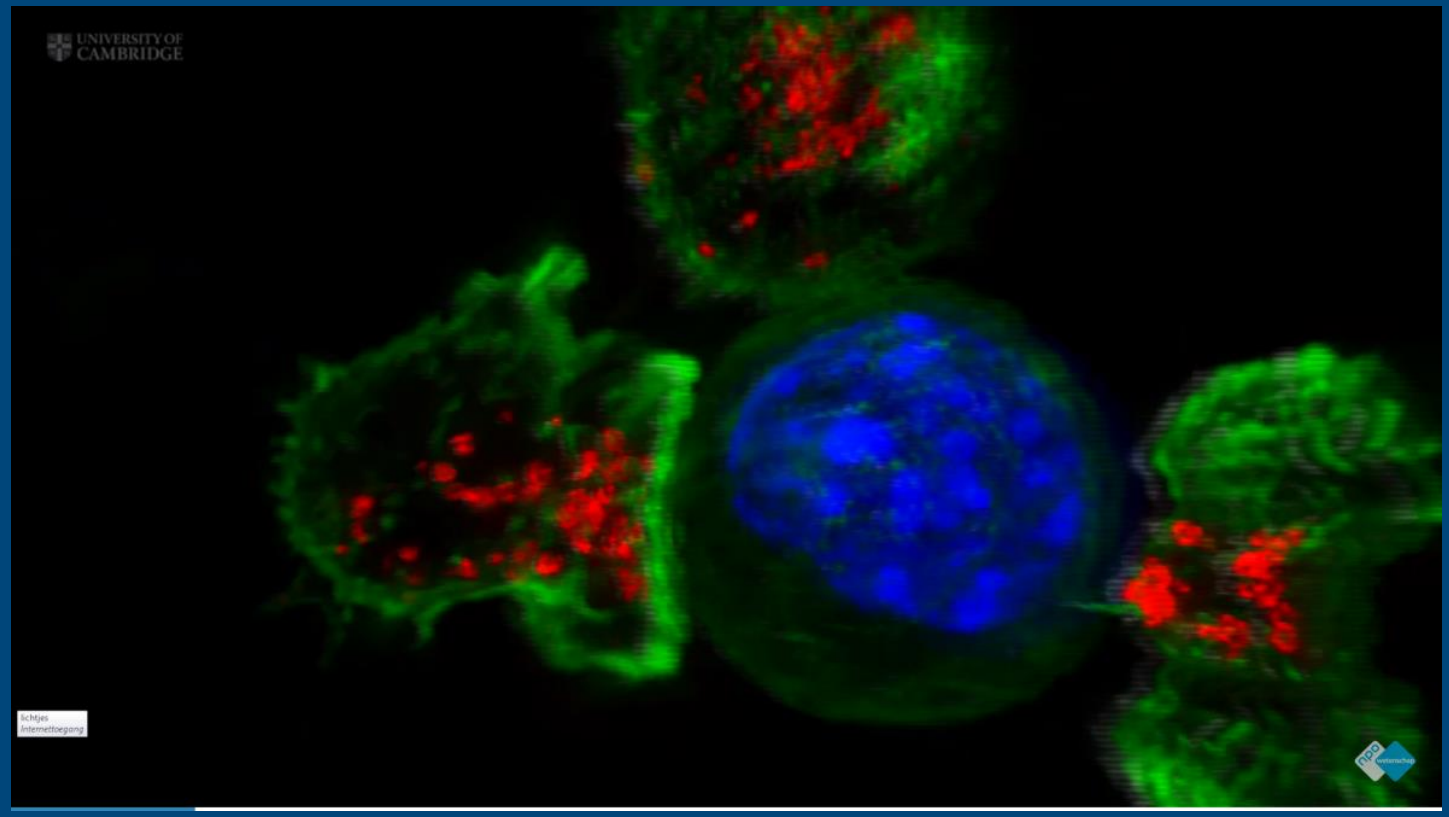
=> ga ik over nadenken (kan evt in combinatie met cursus biotech tilburg voorjaar 2025)

Cursus celbiologie: Aminozuren (=> eiwitten)
20 lego-blokjes waarmee je kunt maken wat je wilt



Polar (polair): elektronen zijn ongelijk verdeeld.

T-cel valt een kankercel aan



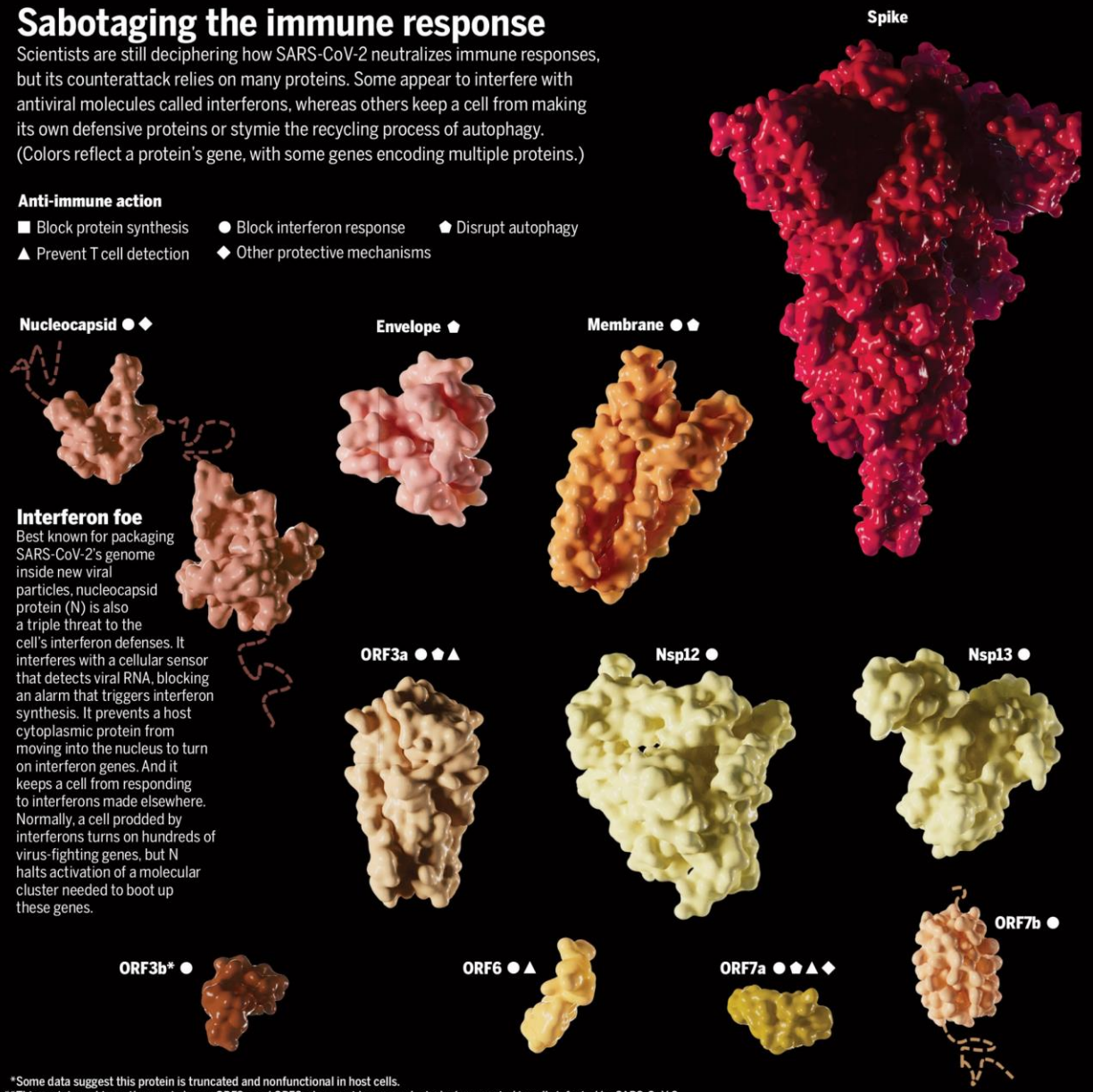
- https://youtu.be/fXOsltJn6Zo
- Voor het eerst is in 3D in beeld gebracht hoe cytotoxische T-cellen kankercellen aanvallen door giftige eiwitten (rood) in de kankercel te "spuiten". De T-cel is in het groen weergegeven en de kankercel in het blauw. -http://www.npowetenschap.nl

Sabotaging the immune response

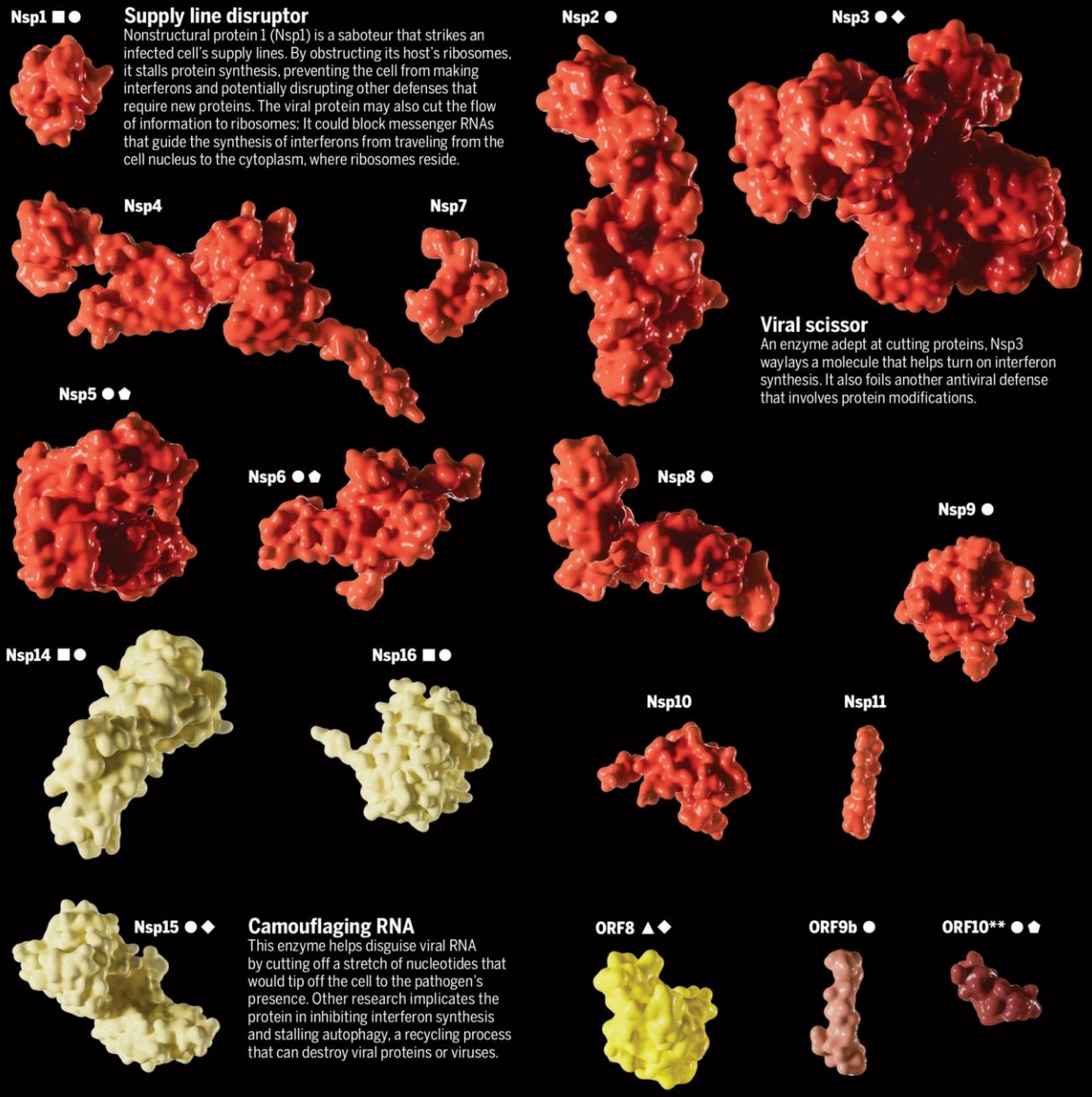
Scientists are still deciphering how SARS-CoV-2 neutralizes immune responses, but its counterattack relies on many proteins. Some appear to interfere with antiviral molecules called interferons, whereas others keep a cell from making its own defensive proteins or stymie the recycling process of autophagy. (Colors reflect a protein's gene, with some genes encoding multiple proteins.)

Anti-immune action

■ Block protein synthesis ● Block interferon response ⬟ Disrupt autophagy
▲ Prevent T cell detection ◆ Other protective mechanisms



Interferon foe
Best known for packaging SARS-CoV-2's genome inside new viral particles, nucleocapsid protein (N) is also a triple threat to the cell's interferon defenses. It interferes with a cellular sensor that detects viral RNA, blocking an alarm that triggers interferon synthesis. It prevents a host cytoplasmic protein from moving into the nucleus to turn on interferon genes. And it keeps a cell from responding to interferons made elsewhere. Normally, a cell prodded by interferons turns on hundreds of virus-fighting genes, but N halts activation of a molecular cluster needed to boot up these genes.



Supply line disruptor
Nonstructural protein 1 (Nsp1) is a saboteur that strikes an infected cell's supply lines. By obstructing its host's ribosomes, it stalls protein synthesis, preventing the cell from making interferons and potentially disrupting other defenses that require new proteins. The viral protein may also cut the flow of information to ribosomes: It could block messenger RNAs that guide the synthesis of interferons from traveling from the cell nucleus to the cytoplasm, where ribosomes reside.

Viral scissor
An enzyme adept at cutting proteins, Nsp3 waylays a molecule that helps turn on interferon synthesis. It also foils another antiviral defense that involves protein modifications.

Camouflaging RNA
This enzyme helps disguise viral RNA by cutting off a stretch of nucleotides that would tip off the cell to the pathogen's presence. Other research implicates the protein in inhibiting interferon synthesis and stalling autophagy, a recycling process that can destroy viral proteins or viruses.

*Some data suggest this protein is truncated and nonfunctional in host cells.
**This protein and two others not shown, ORF9c and ORF3c, have not been conclusively documented in cells infected by SARS-CoV-2.

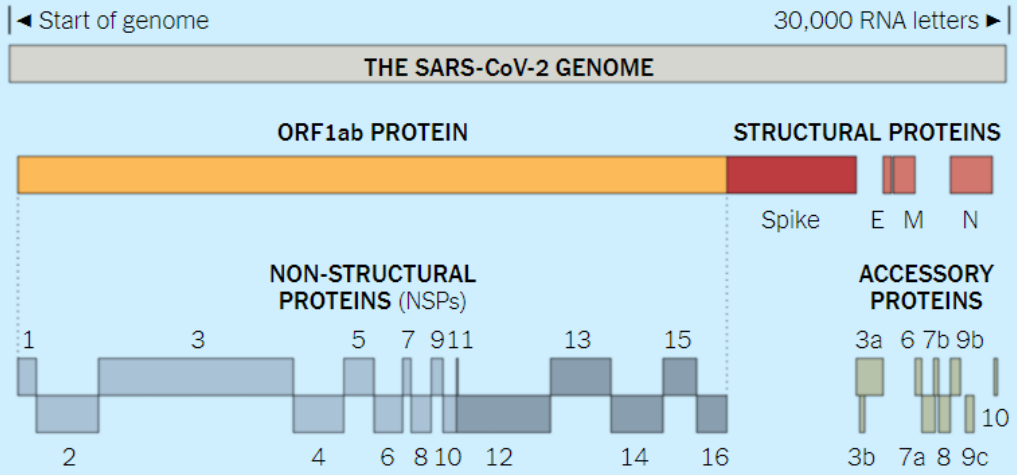
CREDITS: (GRAPHIC) V. ALTOUNIAN AND C. SMITH/*SCIENCE*; (PROTEINS) HTTPS://SCIM.AG/VIRALARSENAL

https://www.science.org/doi/10.1126/science.adf2350

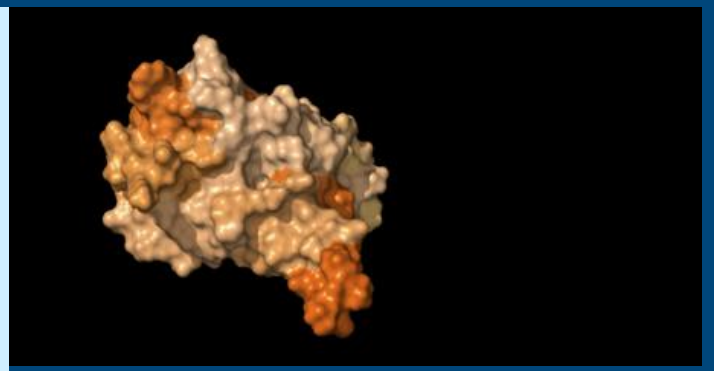
Cellular Saboteur · NSP1

Non-structural protein-1 slows down the infected cell's production of its own proteins. This sabotage forces the cell to make more virus proteins and prevents it from assembling antiviral proteins that could stop the virus.

=> wat maakt Corona bijzonder



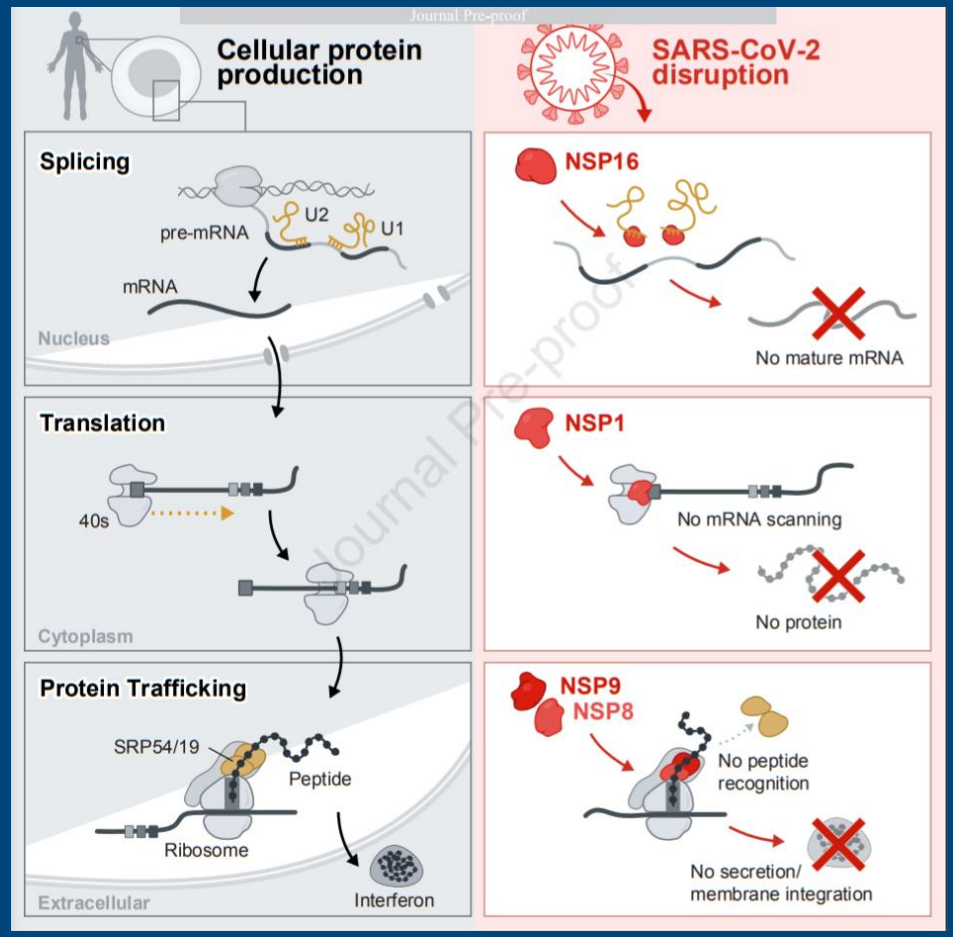
Research on other coronaviruses has given scientists a good understanding of what some of the SARS-CoV-2 proteins do. But other proteins are far more mysterious, and some might do nothing at all.



https://www.nytimes.com/interactive/2020/04/03/science/coronavirus-genome-bad-news-wrapped-in-protein.html

SARS-CoV-2 disrupts splicing, translation, and protein trafficking to suppress host defenses

SARS-CoV-2 is a recently identified coronavirus that causes the respiratory disease known as COVID-19. Despite the urgent need, we still do not fully understand the molecular basis of SARS-CoV-2 pathogenesis. Here, we comprehensively define the interactions between SARS-CoV-2 proteins and human RNAs. NSP16 binds to the mRNA recognition domains of the U1 and U2 splicing RNAs and acts to suppress global mRNA splicing upon SARS-CoV-2 infection. NSP1 binds to 18S ribosomal RNA in the mRNA entry channel of the ribosome and leads to global inhibition of mRNA translation upon infection. Finally, NSP8 and NSP9 bind to the 7SL RNA in the Signal Recognition Particle and interfere with protein trafficking to the cell membrane upon infection. Disruption of each of these essential cellular functions acts to suppress the interferon response to viral infection.
Our results uncover a multipronged strategy utilized by SARS-CoV-2 to antagonize essential cellular processes to suppress host defenses



Dexamethason:
onderdrukt algemene afweer, dus ook veel bijwerkingen

Adverse effects

- Acne
- Amnesia
- Birth defect
- Cataract (in cases of long-term treatment, it occurs in about 10% of patients)
- Confusion
- Depression
- Dyspepsia
- Euphoria
- Headaches
- Impaired skin healing and wound repair
- Etc.

https://en.wikipedia.org/wiki/Glucocorticoid

⇒ruimte voor verbetering (personalized medicine)

=> immunotherapie (college 4)

Cursus Celbiologie

- Lex Fridman podcast
- https://youtu.be/TiFKLK-ycBk

=> bioelectricity

=> biological computation

=> cells have agency

(reageren op hun omgeving)

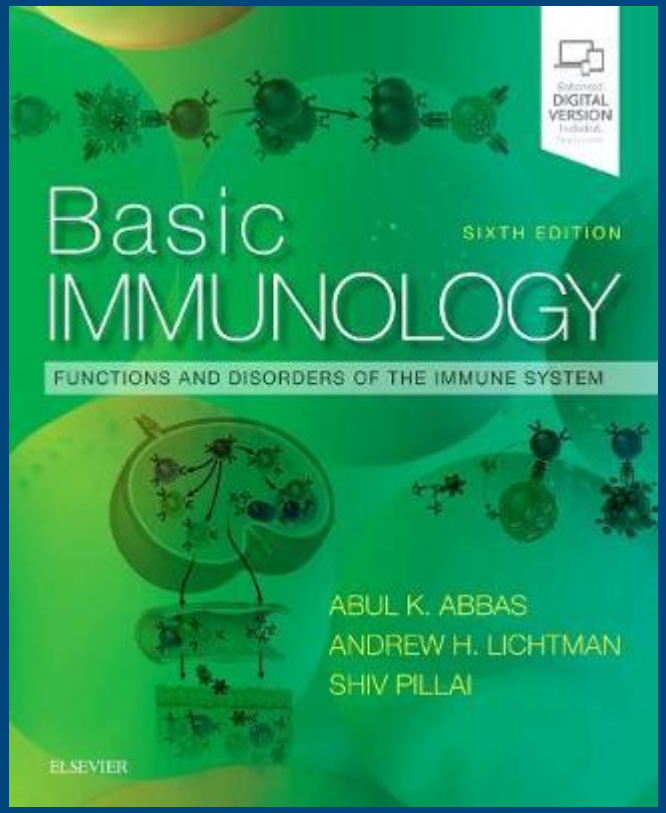
=> cel is een (levende) basis bouwsteen

=> degrees of freedom (controle!?)

Informatie in het netwerk

https://www.youtube.com/watch?v=p3lsYlod5OU&pp=ygUhbGV4IGZyaWRtYW4gcG9kY2FzdCBtaWNoYWVsIGxldmlu

Volgende week



Boek: Abbas, Basic Immunology.
Aanrader, maar niet noodzakelijk

1. **Onderdelen van het afweersysteem**
   Cellen, signaalstoffen

2. **Hoe leert het afweersysteem**
   Tolerantie, memory

3. **Huidige kennis**
   (RNA-)vaccins, antilichamen

4. **Intracellulaire afweer**
   RNA detectie, PCR (mol.biol.)

5. **Afweer en veroudering**
   Symbiose, ethiek

https://www.youtube.com/watch?v=zQGOcOUBi6s