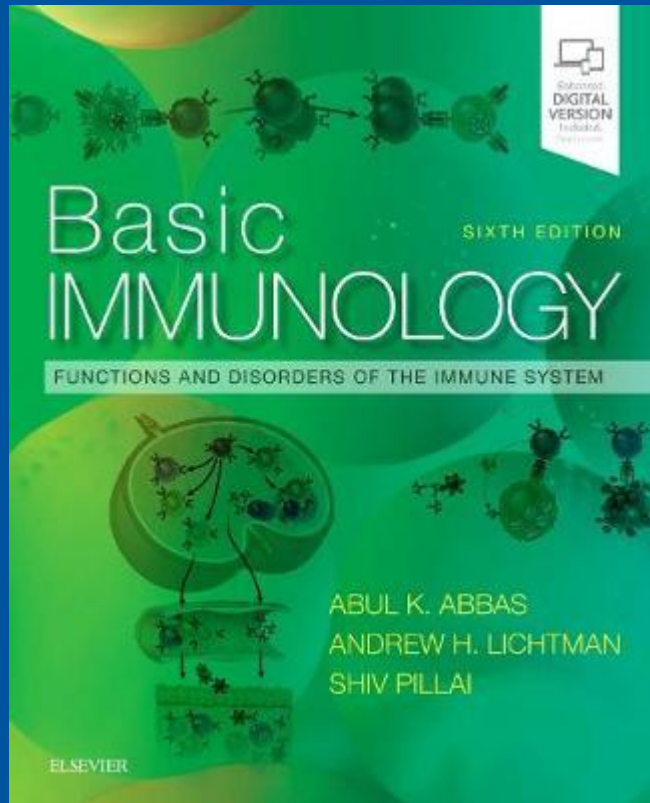


Immunologie / afweer college 4



1. Onderdelen van het afweersysteem
cellen, signaalstoffen, antilichamen
2. Hoe leert het afweersysteem
memory, (RNA-)vaccins
3. Intracellulaire afweer
RNA detectie, PCR (tests)
4. Ziekte en veroudering
virussen bacterien en leven => wat maakt corona bijzonder
5. Vragen en ethiek
ingrijpen in het leven

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

<https://youtu.be/7g0fkC3CywM>

(COVID) vaccines are difficult to compare

=> Methode RL

Versie 1.0

Jenner (volledig virus,
maar koe ipv mens)

Versie 2.0

Geinactiveerd (c) mazelen

Versie 3.0

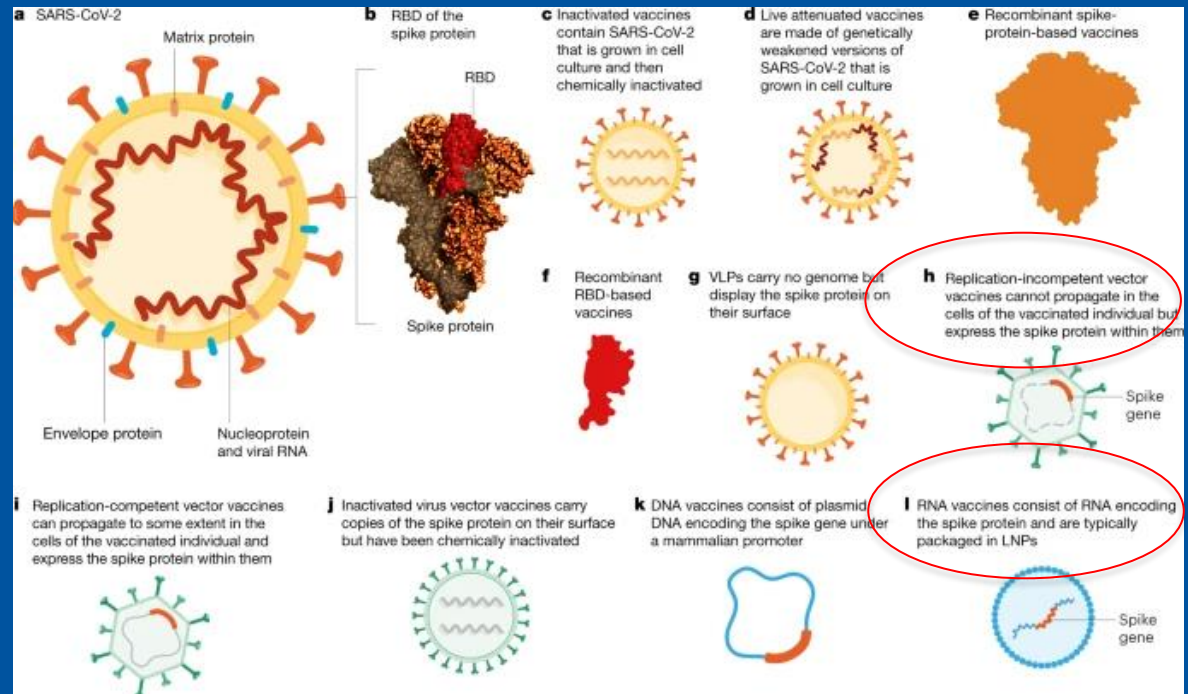
Uitgekleed (h)

Versie 4.0

Geen virus meer (i)

=> Alleen **informatie**

=> Plug and play

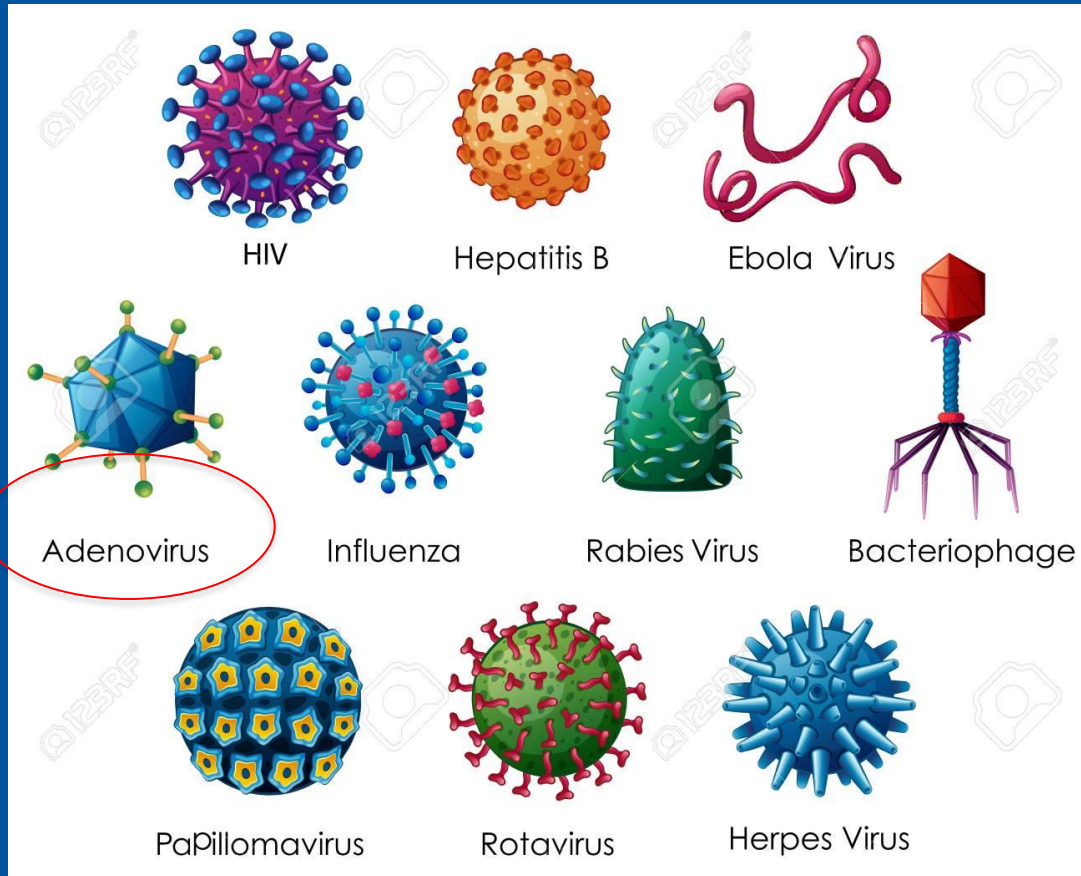


Vgl met elektrische auto. Is ook nog veel onzeker over, maar is waarschijnlijk beter dan vorige versies. Maar moderne benzine auto's zijn ook heel efficient.

NB Elk vaccin infecteerd ook andere typen cellen dan alleen DC

Biotech:

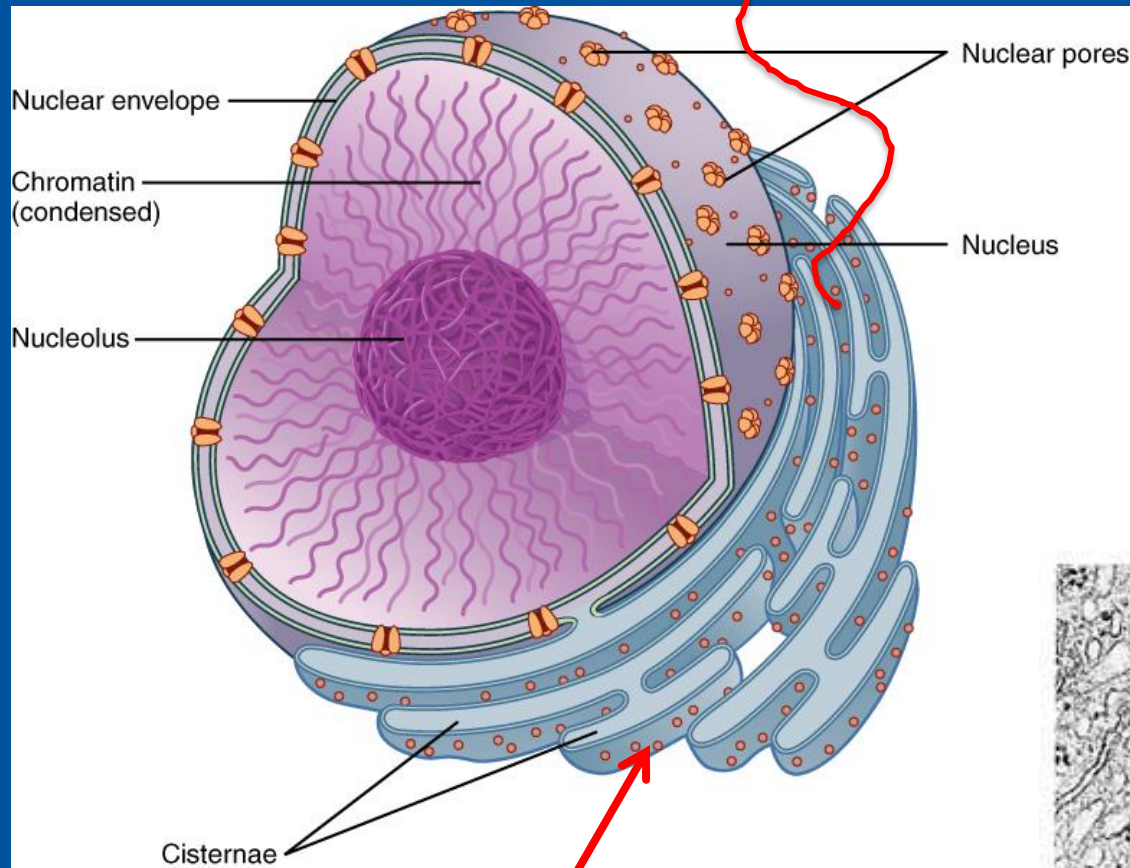
Virus als vector



- Zijn bij uitstek geschikt om genetisch materiaal in cellen te krijgen (doen ze van nature).
- 10% van ons genoom is oud virus materiaal
- **We gebruiken getemde virussen om virussen te bestrijden**
- Maar is ingewikkeld om te maken en te testen (=> recombinatie, waarbij het virus weer helemaal actief wordt uitsluiten)
- Er is vaak al bestaande afweer tegen deze virussen
=> goede afweerreactie

De celkern: Organel met DNA

RNA



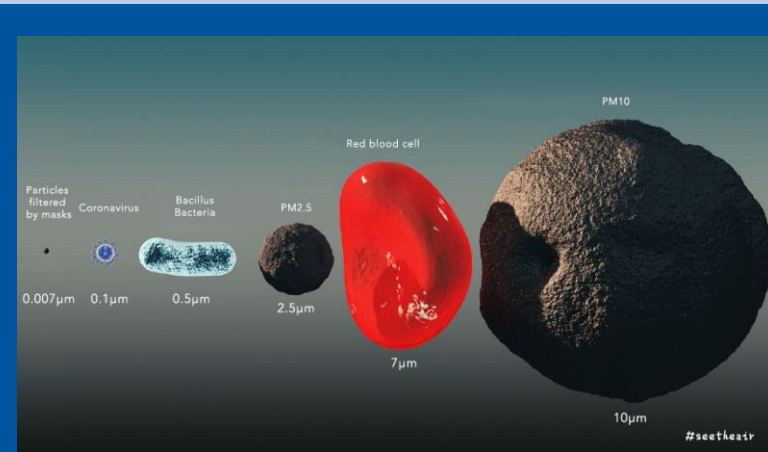
RNA (van virus of vaccin)
wordt direct vertaald bij de
ribosomen.

**NB Zelfde truc die het
corona virus gebruikt wordt
nu ingezet voor vaccin**

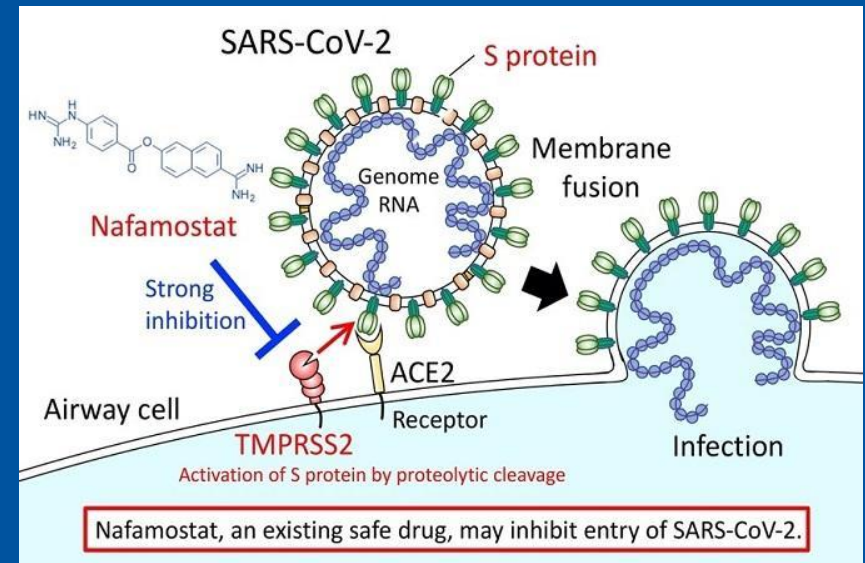
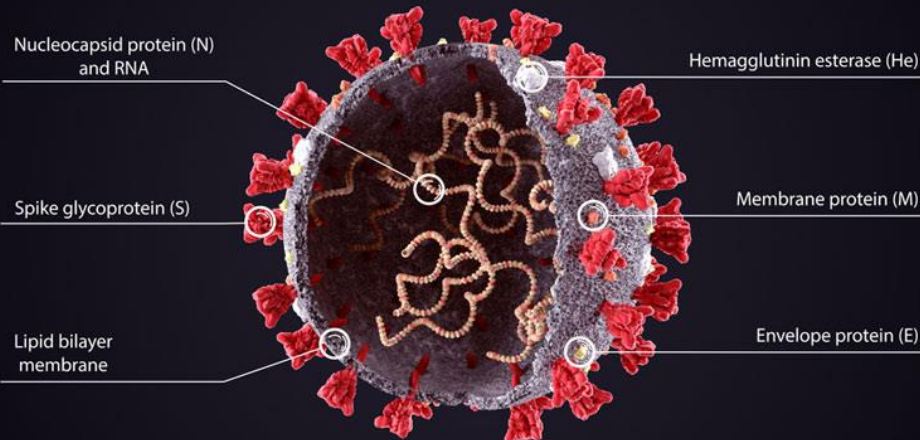
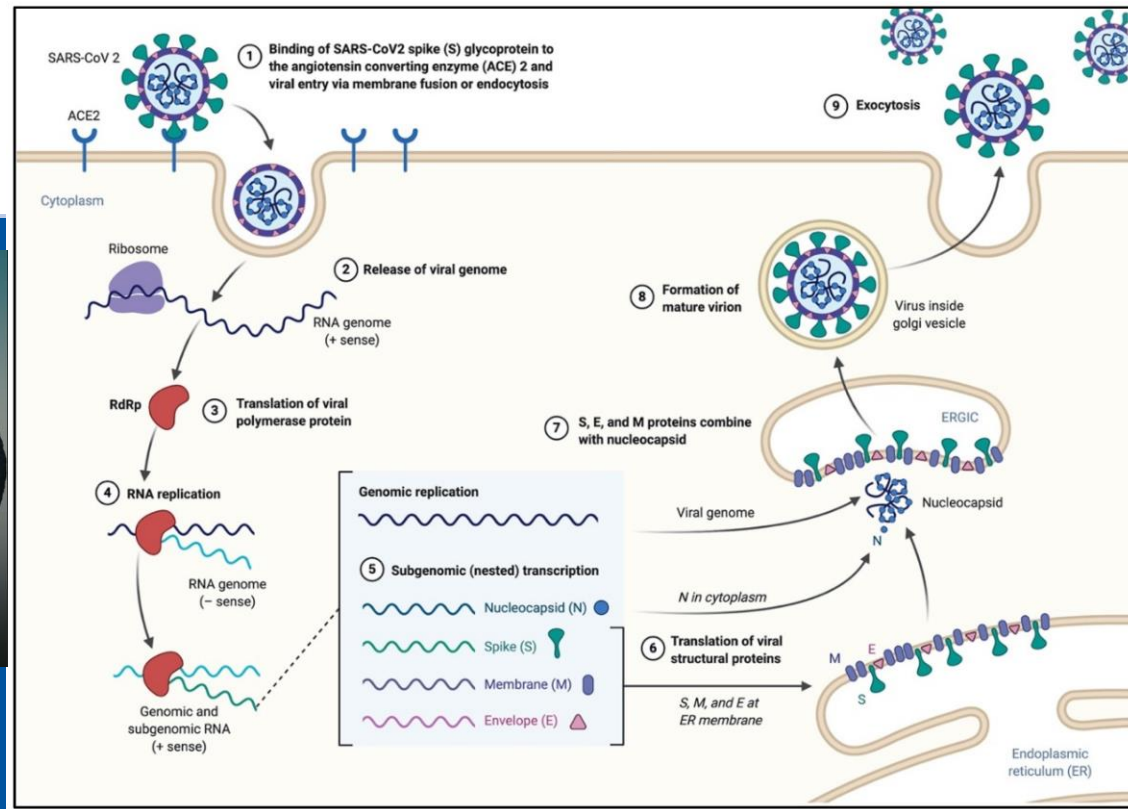
Rond de celkern zit het endoplasmatisch reticulum.
Hier bevinden zich de ribosomen (de bolletjes),
waar van mRNA eiwit wordt gemaakt (translatie)



Een virus is vooral informatie In een beschermend laagje



mRNA vaccins zijn volledig
synthetische virussen



Janssen: 3.0 maar net even anders

Astrazeneca AZD1222, ook bekend als het vaccin van Oxford–AstraZeneca, Covishield, of ChAdOx1 nCoV-19 gebruikt als vector een gewijzigd **chimpansee-adenovirus** ChAdOx1 (replication-deficient)

Janssen Ad26.COV2.S of JNJ-78436735 is het vaccin van Janssen Pharmaceutica (Johnson & Johnson) en Beth Israel Deaconess Medical Center (BIDMC). Het is een **adenovirus-vaccin**

=> Maar 1 prik nodig (door manier waarop Spike wordt geproduceerd?)

Sputnik De eerste vaccinatie bevat een **adenovirus**, die zich niet kan reproduceren. Binnen 21 dagen volgt de tweede vaccinatie, gebaseerd op een **ander adenovirus** als vector dat het lichaam ook niet kent.

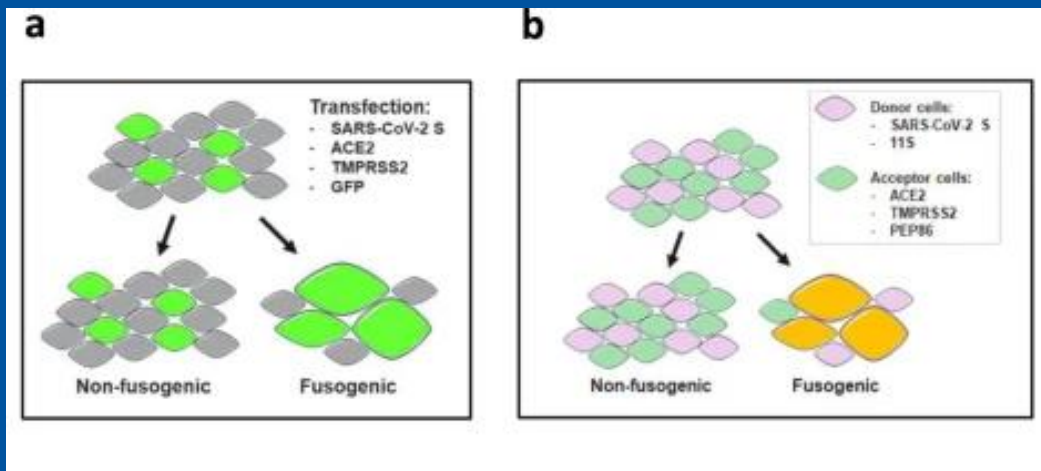
<https://nl.wikipedia.org/wiki/COVID-19-vaccin>

<https://en.wikipedia.org/wiki/Adenoviridae>

https://nl.wikipedia.org/wiki/Lijst_van_virussen

Ad26 vector-based COVID-19 vaccine encoding a prefusion-stabilized SARS-CoV-2 Spike immunogen

- the **design of the Spike protein** is critical for the characteristics of the immunogen and the resulting immune responses elicited by the vaccine.
 - Stabilizing substitutions enhance in vivo immunogenicity.
- => Langer aanwezig in milieu, => betere opname door DC ??



[https://en.wikipedia.org/wiki/Johnson %26 Johnson COVID-19 vaccine](https://en.wikipedia.org/wiki/Johnson_%26_Johnson_COVID-19_vaccine)
<https://www.nature.com/articles/s41541-020-00243-x>

Testing the benefits of mixing vaccines

Researchers in the United Kingdom have launched a study that will mix and match two COVID-19 vaccines in a bid to ease the daunting logistics of immunizing millions of people — and will potentially boost immune responses in the process. The clinical trial will test participants' immune responses to one shot of the Oxford–AstraZeneca vaccine — which uses a harmless virus to carry a key coronavirus gene into cells — and one shot of the Pfizer–BioNTech vaccine, which uses RNA instructions to trigger an immune response. Vaccine developers often combine two vaccines to combat the same pathogen — a strategy known as a heterologous prime-boost. It could make vaccination programmes more flexible by speeding up the process and reducing the impact of supply-chain disruptions

<https://www.nature.com/articles/d41586-021-00315-5>

Het wordt er niet makkelijker op met die globalisering..



Leiden maakt nu twee coronavaccins
9 december 2020

De Leidse medicijnenproducent Halix krijgt een belangrijke rol in de aanmaak van het Oxford-vaccin tegen corona. In opdracht van multinational AstraZeneca gaat Halix de productie opschalen. Halix opende een jaar geleden in het Leide Bioscience Park de nieuwe 'productiefaciliteit' waar op bestelling medicijnen gemaakt kunnen worden voor andere biotech- en farmabedrijven. => **nog geen akkoord EMA**

In January, AstraZeneca said it would have to cut the number of doses it could deliver to the EU. It blamed production delays **in Belgium and the Netherlands**.

BBC: Where is the AstraZeneca vaccine made?

The Oxford-AstraZeneca vaccine is made in the UK at two sites: in Oxford and Keele. A third plant in Wrexham puts the vaccine into vials and packages it up for distribution.

The UK has ordered 100 million doses. Almost all will come from within the **UK**, but 10 million doses are being made by the Serum Institute in **India**.

Het Nederlands Vaccin Instituut is door de Nederlandse overheid verkocht aan het **Serum Institute of India** (SII).

=> **Had dat nu gehouden.. => industriebeleid (vaccin Janssen in flesjes in VS => amerikaans!)**

Politicians must dial down the rhetoric over COVID vaccines

Vaccine confidence will be the casualty of Europe's war of words over the AstraZeneca–Oxford vaccine.

Ethiek:

AstraZeneca on hold

“Preventieve geneeskunde heeft ook nadelen”

Ingreep bij gezonde mensen is ethisch lastig (als er nog slechts een kans op ziekte is. (maar veiligheidsgordels zijn er uiteindelijk ook gekomen, ondanks inboeten van het gevoel van vrijheid en geen gevoel eigen keuze)

“Stelling: We maken ons druk om bijwerkingen van een vaccin, maar we stoppen ons lichaam vol met suiker, vet en alcohol. En bewegen te weinig wat veel ernstigere consequenties heeft.

En vinden gebruik van medicijnen met veel meer bijwerkingen wel normaal als er eenmaal ziekte is (slaapmiddelen, statines, bloeddrukverlagers zoals ACE-remmers => Prikkelhoest, Smaakstoornissen = wat Corona ook doet)

=> Niet meer geven aan zorgpersoneel, maar wel aan patienten?

(mensen die anders ernstig ziek worden => **direct belang**)

⇒ Nee, middel is minder ernstig dan de kwaal (1^e keer dat dit zo is gezegd door de overheid!)

⇒ **Toch alweer twijfel gezaaid**

Coronavaccin op de weegschaal van pijn en nut

De afweging wordt gemaakt door de Pharmacovigilance Risk Assessment Committee (PRAC), de veiligheids-commissie van de EMA. In de PRAC zitten afgevaardigden van alle Europese lidstaten, en zij vragen als dat nodig is externe experts erbij. Samen wegen ze of de balans tussen werkzaamheid en schadelijkheid positief is. Dat gebeurt voor de markttoelating, en ook daarna, als er een nieuw signaal is van een mogelijke bijwerking, zoals afgelopen week. „Dan komt de PRAC weer bij elkaar om alle ziektegevallen goed te bestuderen”, zegt Miriam Sturkenboom, farmaco-epidemioloog van het UMC Utrecht. „Hoe ernstig is het, wat zijn mogelijke andere oorzaken van die ziekte, hoe vaak komt het voor na vaccinatie? En als het verband zou hebben, wat is dan de balans tussen de werkzaamheid en de schadelijkheid?”

Onder Sturkenbooms leiding is dit jaar in kaart gebracht hoe vaak tientallen verschillende ziektebeelden normaal gesproken voorkomen in Europa. Zo is snel te zien of een ernstige bijwerking opvallend veel vaker voorkomt na vaccinatie.

„Met dit systeem kunnen we snel uitrekenen hoe vaak we een ziekte verwachten. En we kunnen ook ander onderzoek doen, bijvoorbeeld vaccins vergelijken. Zien we die vorm van hersentrombose vaker bij AstraZeneca dan bij Pfizer? Het systeem staat klaar, daar hebben we de afgelopen maanden hard aan gewerkt.”

Er zijn ook andere, maatschappelijke aspecten denkbaar die zouden kunnen meewegen in de beslissing. Zoals de ernst van de pandemie. Of het niet-medische coronaleed. Het vertrouwen in de vaccinatie. Maar die weegt de PRAC niet mee. „We zijn ons natuurlijk heel bewust van wat er gebeurt”, zegt Straus, „maar we houden ons bij de feiten en bij het middel. We kijken naar de kwaliteit van het vaccin, naar de effectiviteit waarmee het ziekte kan voorkomen, en naar de bijwerkingen.”

What scientists do and don't know about the Oxford–AstraZeneca COVID vaccine

NATURE, 24 MARCH 2021



How effective is the vaccine?

On 22 March, the company said in a press release that a preliminary analysis had found two doses to be 79% effective at preventing COVID-19 in a trial of 32,449 adults across the United States, Peru and Chile. **No participants who received the vaccine were hospitalized or died**, even though 60% had pre-existing conditions associated with increased risk of severe disease, such as diabetes or obesity. Only 141 cases of COVID-19 were reported overall, **although the breakdown of those who received the vaccine, and those who did not, has not yet been revealed.**

What is the vaccine's role in the pandemic?

Unlike many of the vaccines, which are expensive and must be stored at very low temperatures, the Oxford–AstraZeneca vaccine **can be kept in an ordinary fridge and costs a few dollars per dose.** And, because it is expected to be produced on a huge scale, it could play a vital part in quelling the pandemic.

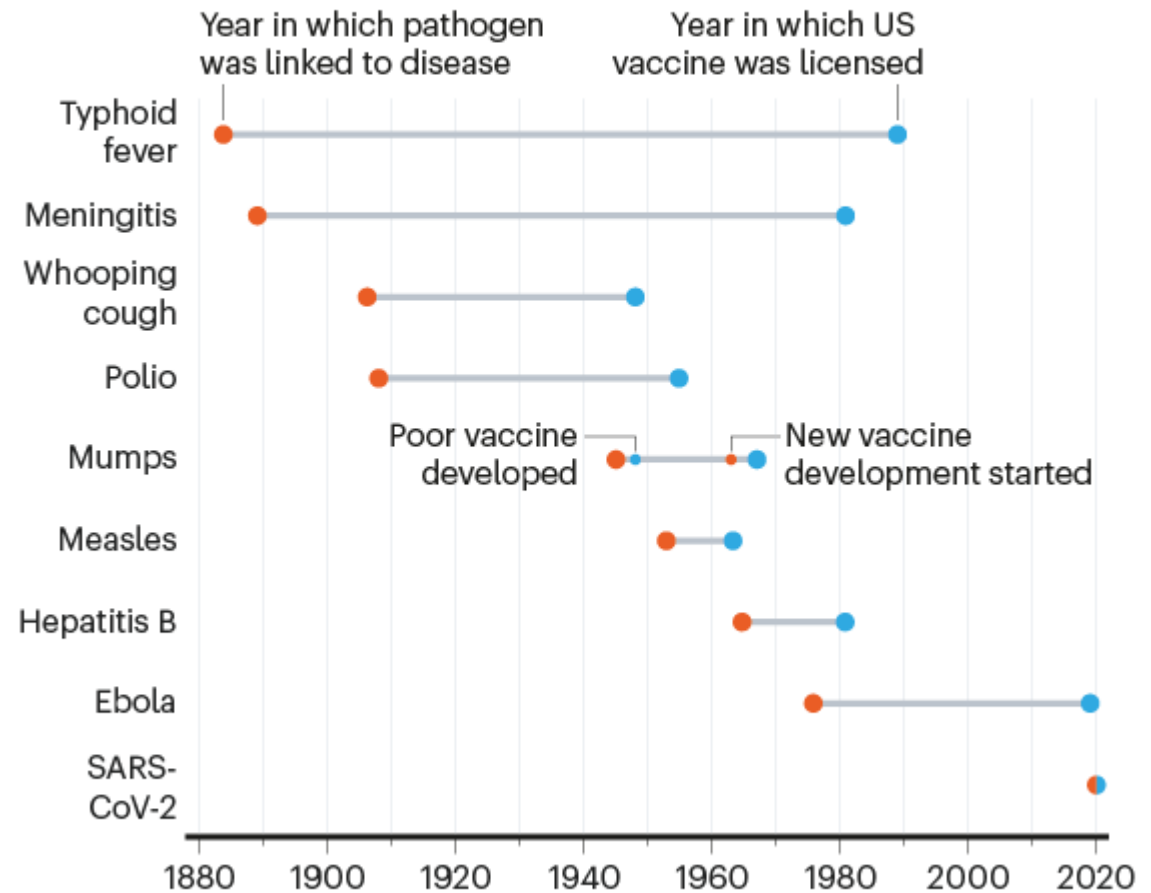
For the moment, “in many countries, especially on the **African continent**, the AstraZeneca vaccine is the only one that will be available in substantial quantities,”

<https://www.nature.com/articles/d41586-021-00785-7>

The world was able to develop COVID-19 vaccines so quickly because of years of previous research on related viruses and faster ways to manufacture vaccines, enormous funding that allowed firms to run multiple trials in parallel, and regulators moving more quickly than normal. It's tempting to hope that **other vaccines might now be made on a comparable timescale**. These are sorely needed: diseases such as malaria, tuberculosis and pneumonia together kill millions of people a year, and researchers anticipate further lethal pandemics, too.

VACCINE INNOVATION

Most vaccines take years to develop, but scientists created multiple vaccines for SARS-CoV-2 within a year.

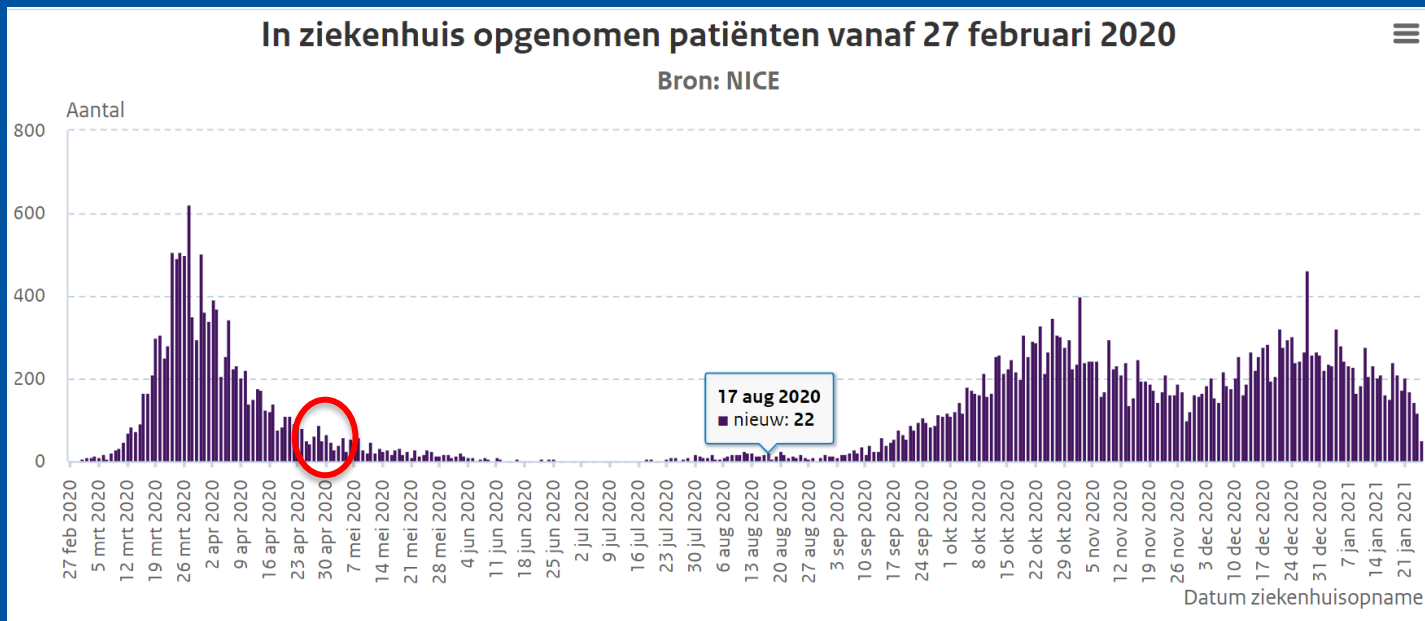


Vaccin alleen is niet het antwoord

Bijna iedereen heeft het virus al gezien in het 1^e jaar (zweedse model)
Het zal beter gaan door beter weer, behandeling en vaccinatie

Belangrijkste impact vaccins is op de zorg
=> Zorgmedewerker kunnen blijven werken
=> En **behandelingen** zijn verbeterd

=> Combinatie van preventie (quarantaine, vaccin), klimaat en steeds
beter behandeling gaat ons redden. **In Mei is alles beter** door



<https://www.rivm.nl/coronavirus-covid-19/grafieken>

Corona

Voorkomen en Behandelen

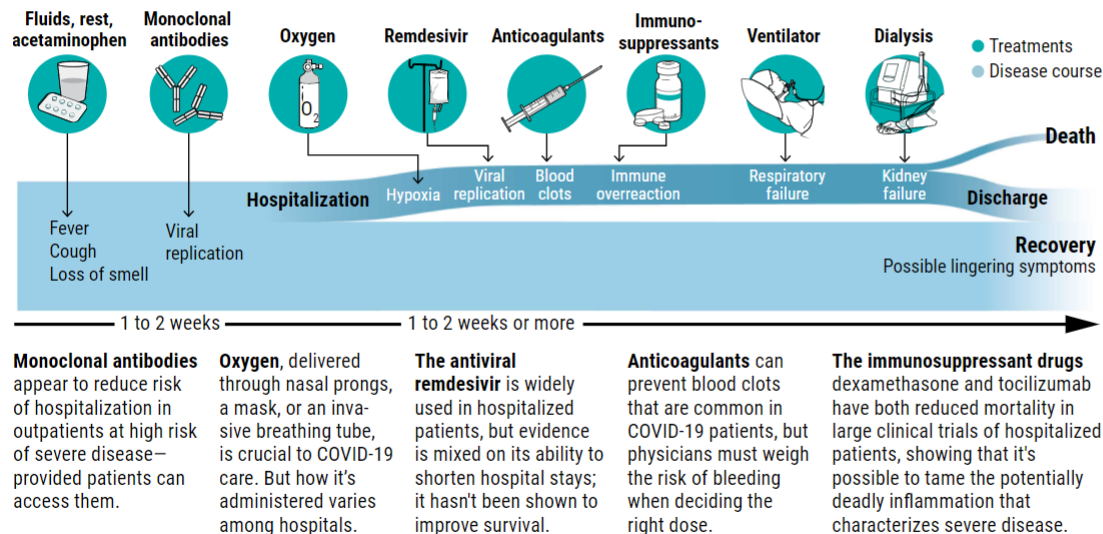
- Gezond blijven (bewegen, gevarieerd eten)
 - Afstand houden, ventilatie, buiten
 - (hand)hygiene, mondkapjes
 - Testen
 - Vaccin
 - Afweer stimuleren (bcg)
 - Antilichamen
 - Antivirale middelen
 - Afweer onderdrukken (dexamethason)
 - Anti-stolling
 - En wetenschappers beter ondersteunen => meer behandelingen
 - Zorg beter ondersteunen (salaris!)
- ⇒ Er is best veel aan te doen!

Corona behandelning

<https://www.sciencemag.org/news/2021/03/how-do-you-treat-coronavirus-here-are-physicians-best-strategies>

Cornerstones of care

Doctors have few treatments for the early stages of COVID-19, but have developed a small arsenal of therapies to employ as symptoms become more severe. Research continues on how and when to administer drugs, oxygen, and other treatments.



N. DESAI/SCIENCE

Antibodies have to be infused at a hospital or specialized site within days of the first symptoms—a logistical challenge.

What's more, official guidance is equivocal on antibodies. With clinical trials ongoing, NIH treatment guidelines say there are “currently insufficient data to recommend either for or against” most monoclonal antibodies,

Virus remmer via neus:

Intranasal fusion inhibitory lipopeptide prevents direct-contact SARS-CoV-2 transmission in ferrets

Containment of the COVID-19 pandemic requires reducing viral transmission. SARS-CoV-2 infection is initiated by membrane fusion between the viral and host cell membranes, mediated by the viral spike protein. We have designed **lipopeptide fusion inhibitors** that block this critical first step of infection, and based on in vitro efficacy and in vivo biodistribution selected a dimeric form for evaluation in an animal model. Daily intranasal administration to ferrets completely prevented SARS-CoV-2 direct-contact transmission during 24-hour co-housing with infected animals, under stringent conditions that resulted in infection of 100% of untreated animals. These lipopeptides are highly stable and thus may readily translate into safe and effective intranasal prophylaxis to reduce transmission of SARS-CoV-2.

<https://nos.nl/artikel/2369119-neusspray-bescherm-t-fretten-tegen-corona-onderzoek-bij-mensen-volgende-stap.html>

<https://science.sciencemag.org/content/early/2021/02/16/science.abf4896>

virus remmers

Een virus volgt een ingewikkeld pad
=> Meerdere interventie mogelijkheden:

Maar alleen Antilichamen en Remdesivir
zijn op dit moment bewezen effectief.

<https://www.who.int/news-room/commentaries/detail/covid-19-and-the-use-of-angiotensin-converting-enzyme-inhibitors-and-receptor-blockers>

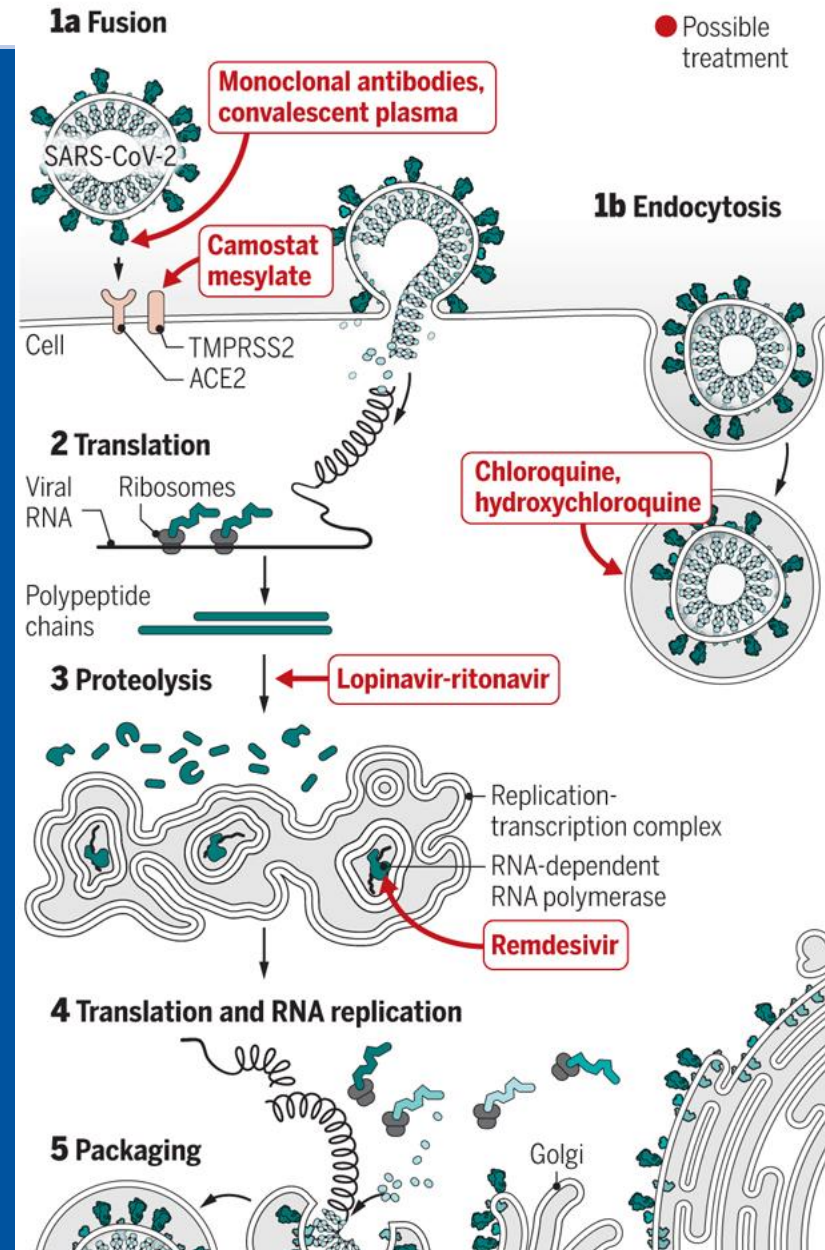
[Published: 16 March 2021](#)

Clofazimine broadly inhibits coronaviruses including SARS-CoV-2

<https://www.nature.com/articles/s41586-021-03431-4>

Lines of attack

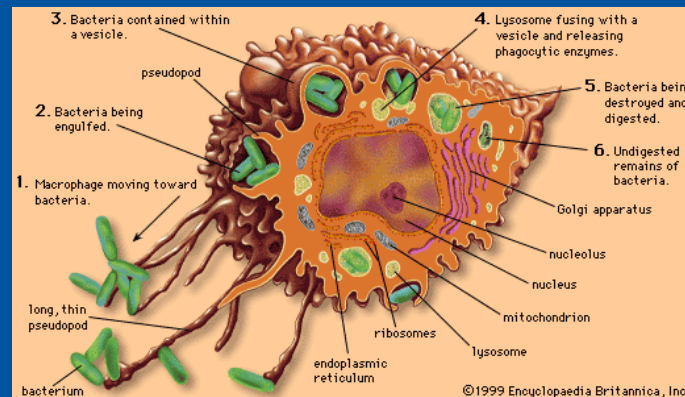
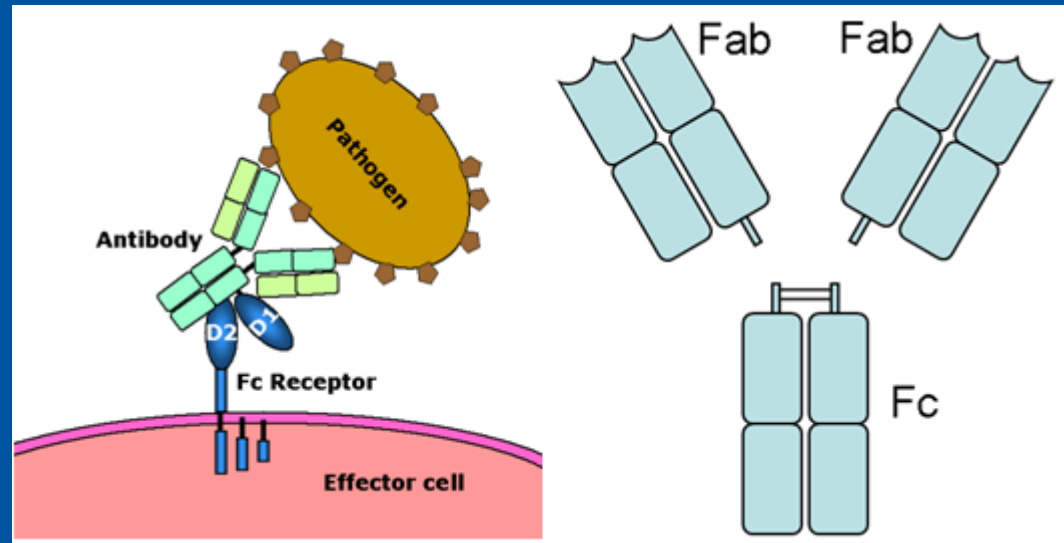
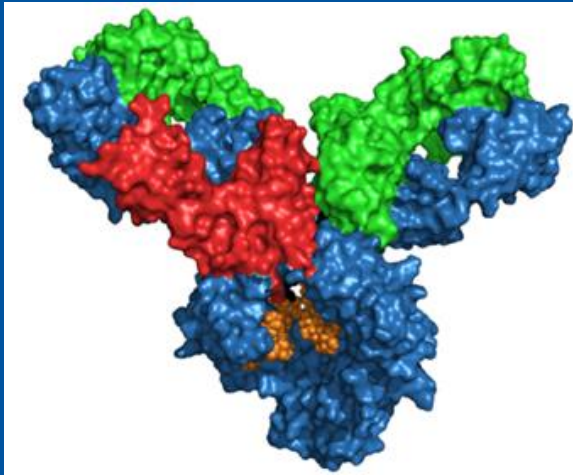
Experimental treatment strategies attempt to interfere with different steps (numbered) in the coronavirus replication cycle.



Antilichamen

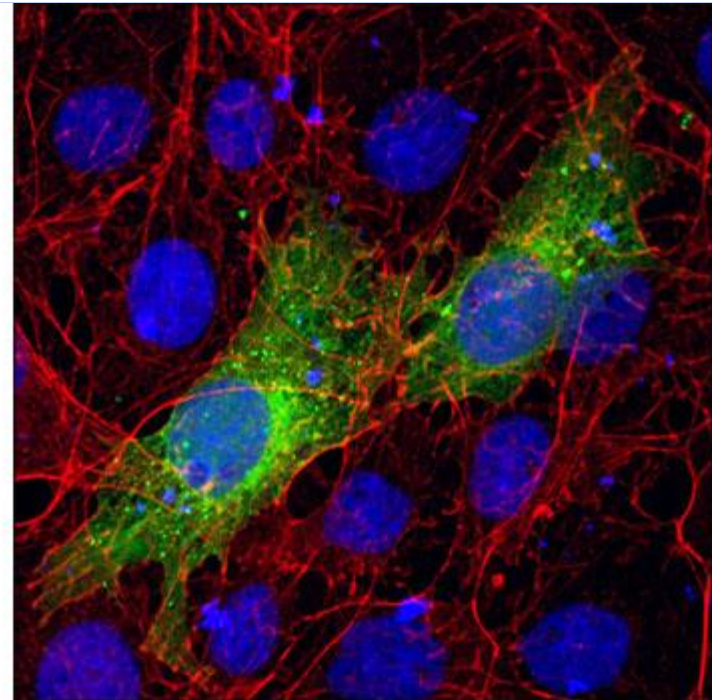
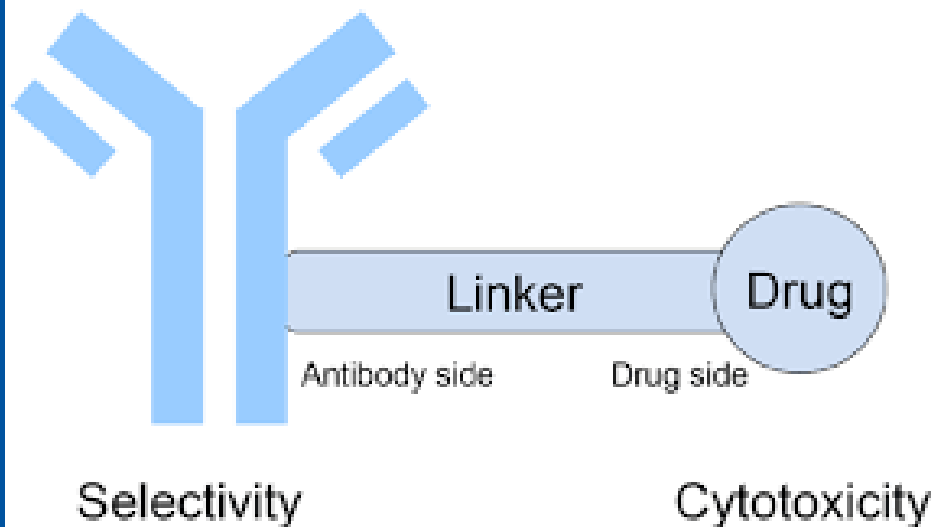
Heeft Fc-gedeelte en antigeen herkennend (Fab) deel
Fc-receptoren op Fagocyten binden antilichamen en zorgen voor extra efficiënt opruimen van ziekmakers

⇒ Versterken ontsteking
(pro-inflammatoir),



Antilichamen: Onderzoek en geneesmiddel

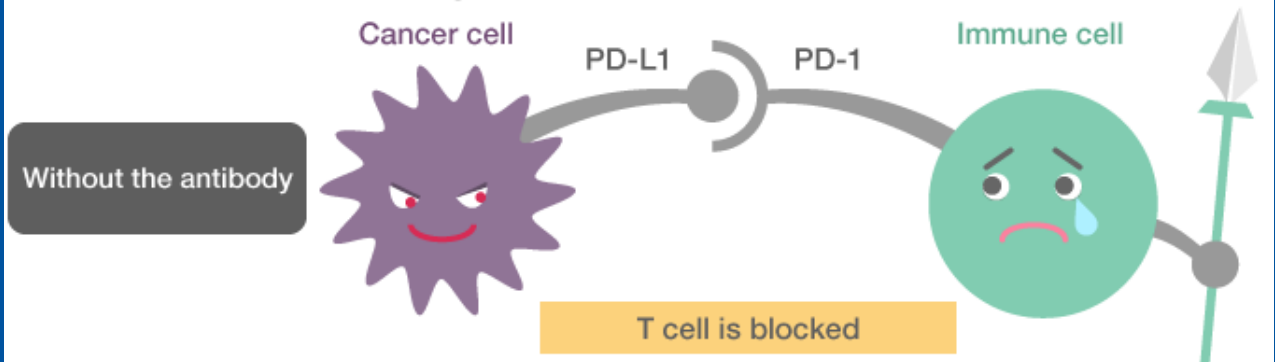
- Kennis
- Geneesmiddel
(kanker)



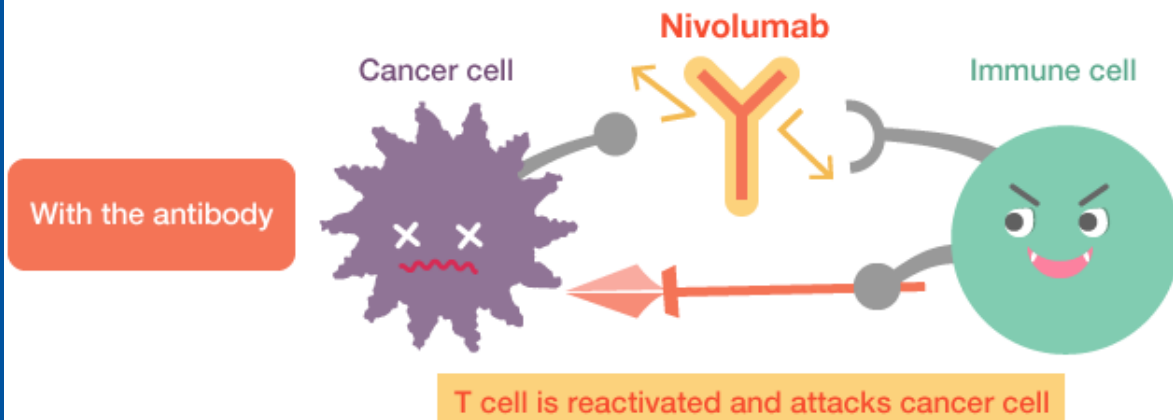
Blokkade van interactie

perifere tolerantie: PD-1 blockade => misbruikt door tumor

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.

Programmed cell death in immune cells 1, or PD-1 is widely expressed on activated immune cells, such as T cells and B cells, and functions as brakes on the immune system, effectively inhibiting the body's immune response. Molecules that behave like this are known as immune checkpoints.

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

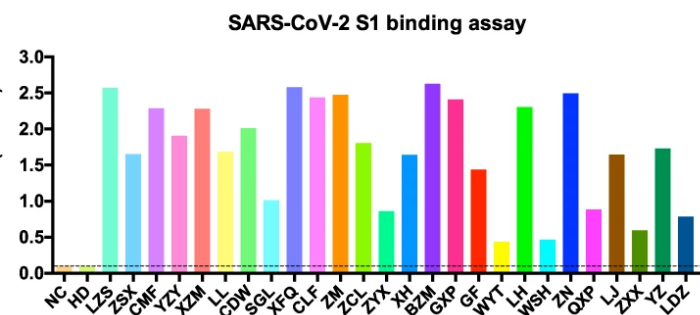
Vaccin v. virus remmer

- Vaccin beschermt nog niet zieke mensen
⇒ hoge veiligheidseisen => duurt lang om te ontwikkelen
- Virus remmer voor al zieke mensen
⇒ Laatste redmiddel (ander ethiek)
- ⇒ wel zo vroeg mogelijk => voorspellen wie heel ziek gaat worden

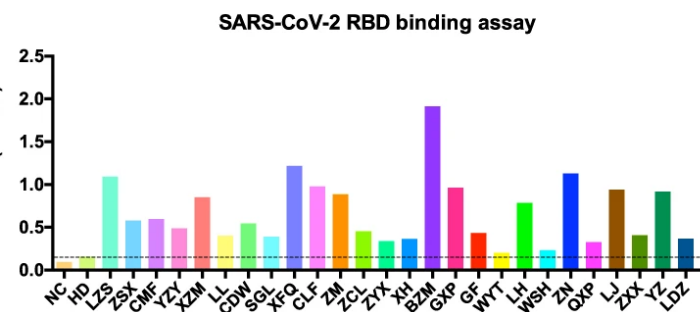
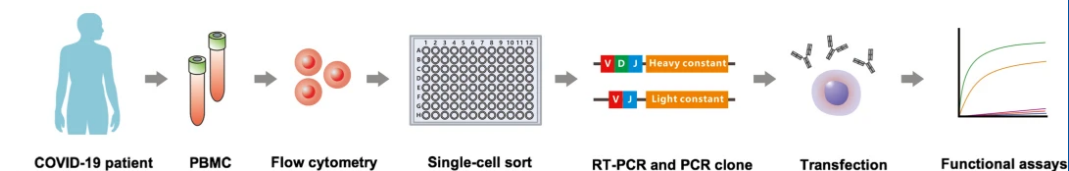
How blood from coronavirus survivors might save lives => virus remmer

- Passieve immunisatie
- The FDA's classification today of convalescent plasma as an 'investigational new drug' against coronavirus allows scientists to submit proposals to test it in clinical trials, and lets doctors use it compassionately to treat patients with serious or life-threatening COVID-19 infections, even though it is not yet approved.
- <https://www.nature.com/articles/d41586-020-00895-8>
- Genes for effective antibodies
 - ⇒ In yeast (mol.biol.)
 - ⇒ Large amounts for treatment

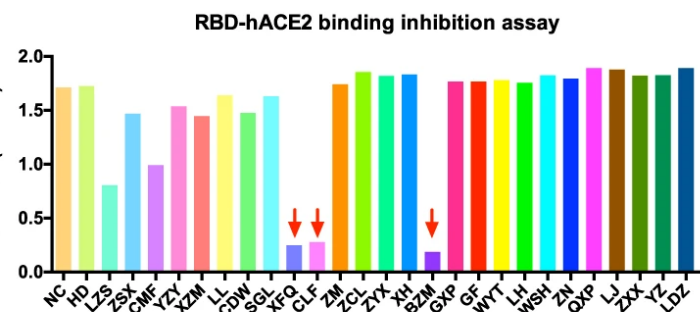
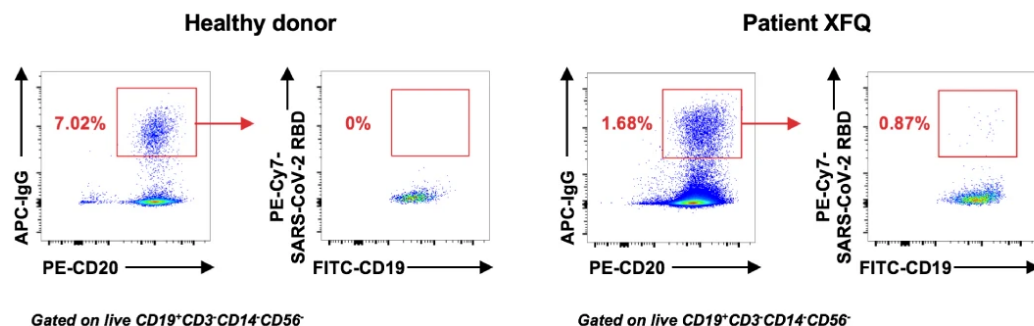
Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor



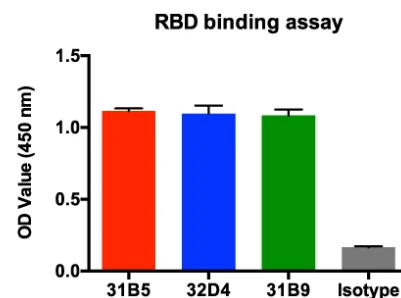
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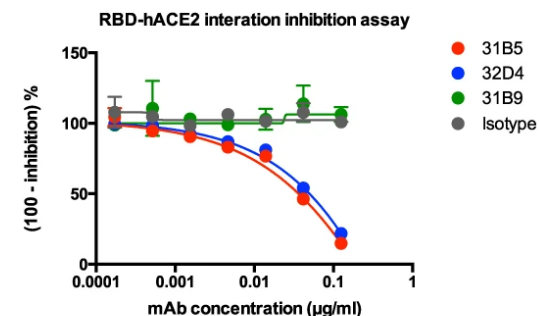
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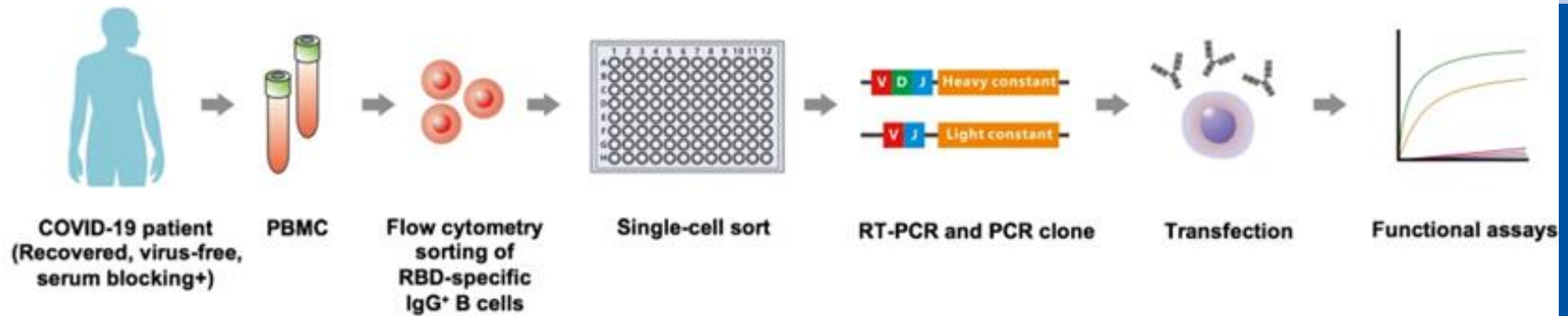
f



g



May I borrow your immunity?



e

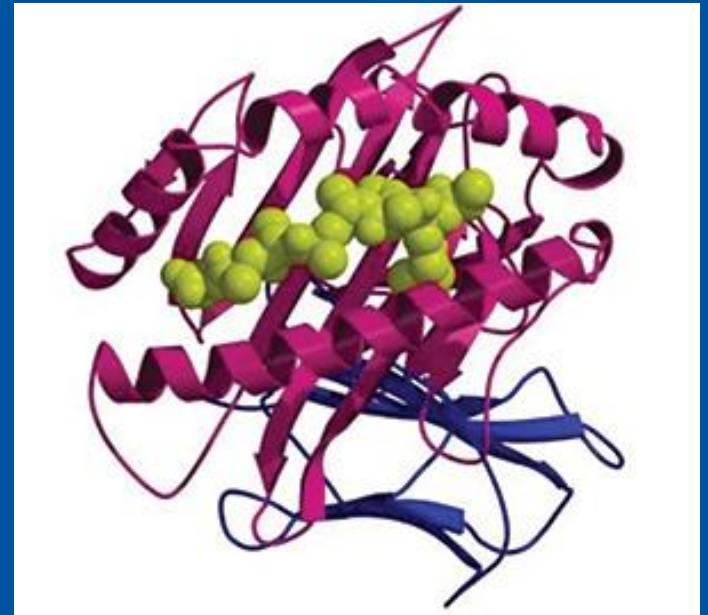
- Whenever a new virus emerges—be it HIV or SARS-CoV-2—a few lucky people put up a potent natural defense. Monoclonal antibody drugs let them share the health
- => bioreactor => opzuiveren
- Afweerreactie => idiotypisch.

=> MHC: 90% reageert OK, 1% uitstekend

<https://www.wired.com/story/covid-immunity-antibodies/>

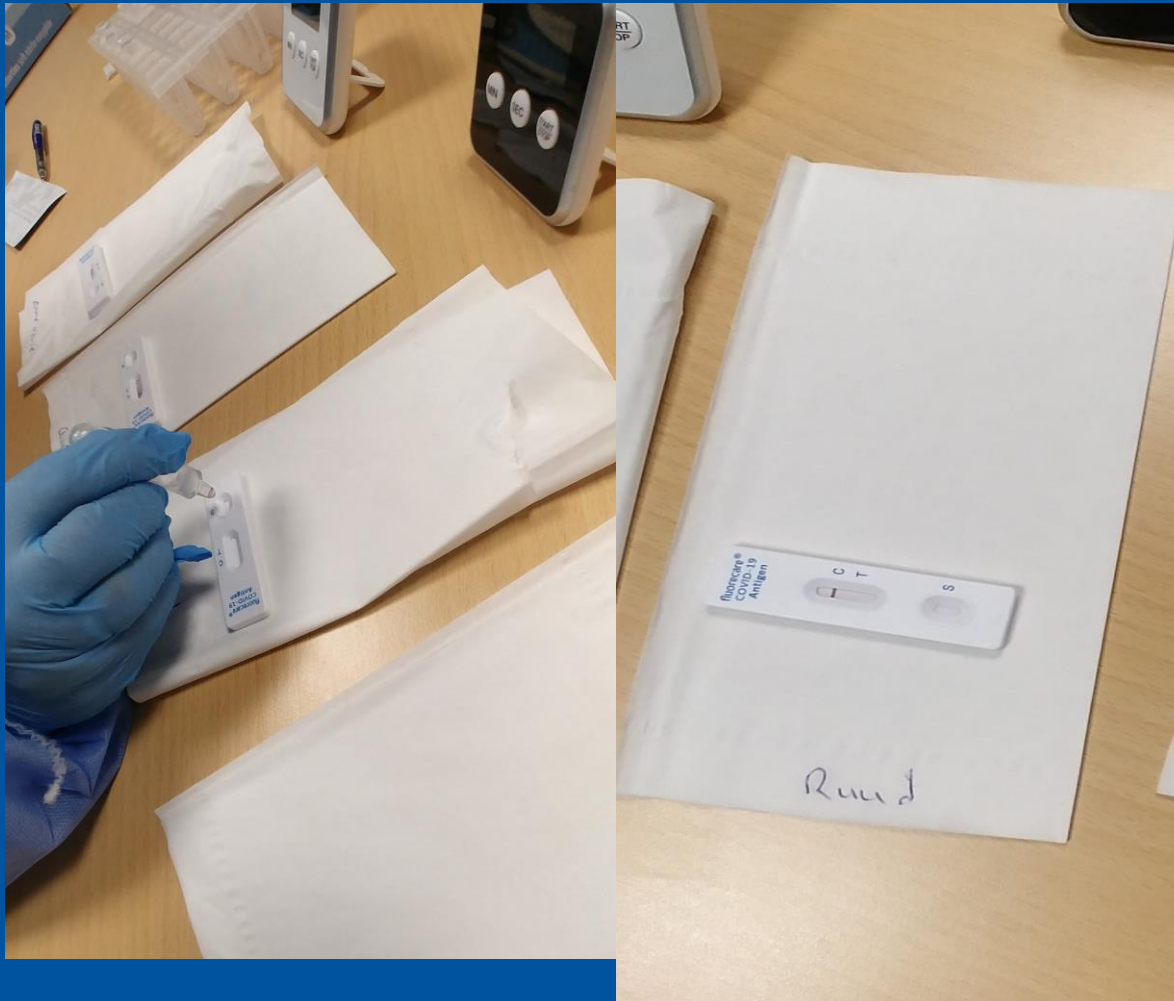
Haplotype and disease

- MHC in humans is called HLA
 - HLA variation is a crucial determinant of transplant rejection and susceptibility to a large number of infectious and autoimmune diseases.
 - Yet identification of causal variants is problematic owing to linkage disequilibrium that extends across multiple HLA and non-HLA genes in the MHC
 - Indianen ziek door kolonisten
- ⇒ boek: *Zwaarden, paarden en ziektekiemen*;
- A/B/C (HLA-I), DP/DQ/DR (HLA-II)
- ⇒ Iedereen heeft een combinatie van verschillende MHC's
- ⇒ altijd wel wat reactie (minder ernstig ziektebeeld?).



Corona sneltest

Ministerie keurt zelftests goed



- Neus/keel swab in vloeistof
- Mengen
- Druppel op plaatje
- 15min wachten

Vloeistof, evt met virus loopt langs plek met antilichamen specifiek voor Corona (T) . Zodra die iets binden komt er een kleurverandering.

NB net als zwangerschapstest

NB Op C zitten antilichamen tegen eiwitten die iedereen heeft in de slijmvliezen

Ruud is negatief!

Serologie

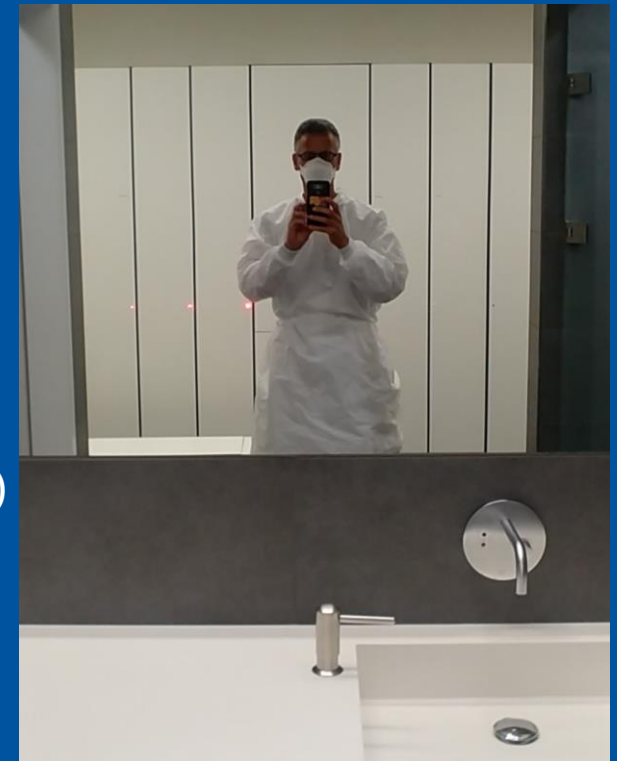


Antilichamen in bloed (titer)
⇒ Retrospectief (achteraf)

⇒ Nu niet mogelijk voor individu
⇒ Maakt het lastig voor Corona slachtoffer
die geen test heeft gedaan (vgl met Q-koorts)

=> Outfit serologie
(nog haarnet en 2x handschoenen erbij)

Nu wel mogelijk in Luxemburg!
⇒ Betere beslissingen over vaccinatie strategie
Voor samenleving: Hoe zit het met verspreiding
Voor individu: **Geen vaccin nodig, bij titer.**



Evolution of antibody immunity to SARS-CoV-2

Immunofluorescence and PCR analyses of intestinal biopsies obtained from asymptomatic individuals at 4 months after the onset of coronavirus disease 2019 (COVID-19) revealed the persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel of 7 out of 14 individuals. We conclude that the memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection in a manner that is consistent with **antigen persistence**.

Virus blijft langere tijd actief!

⇒ Langer antilichamen (net als bij mazelen)

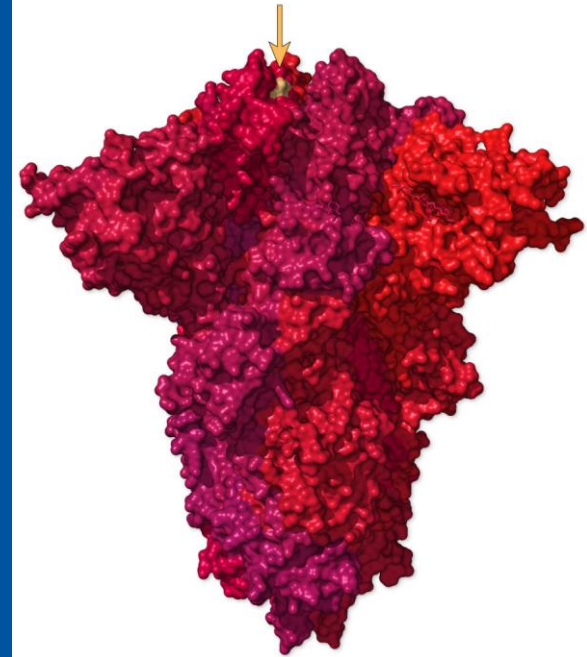
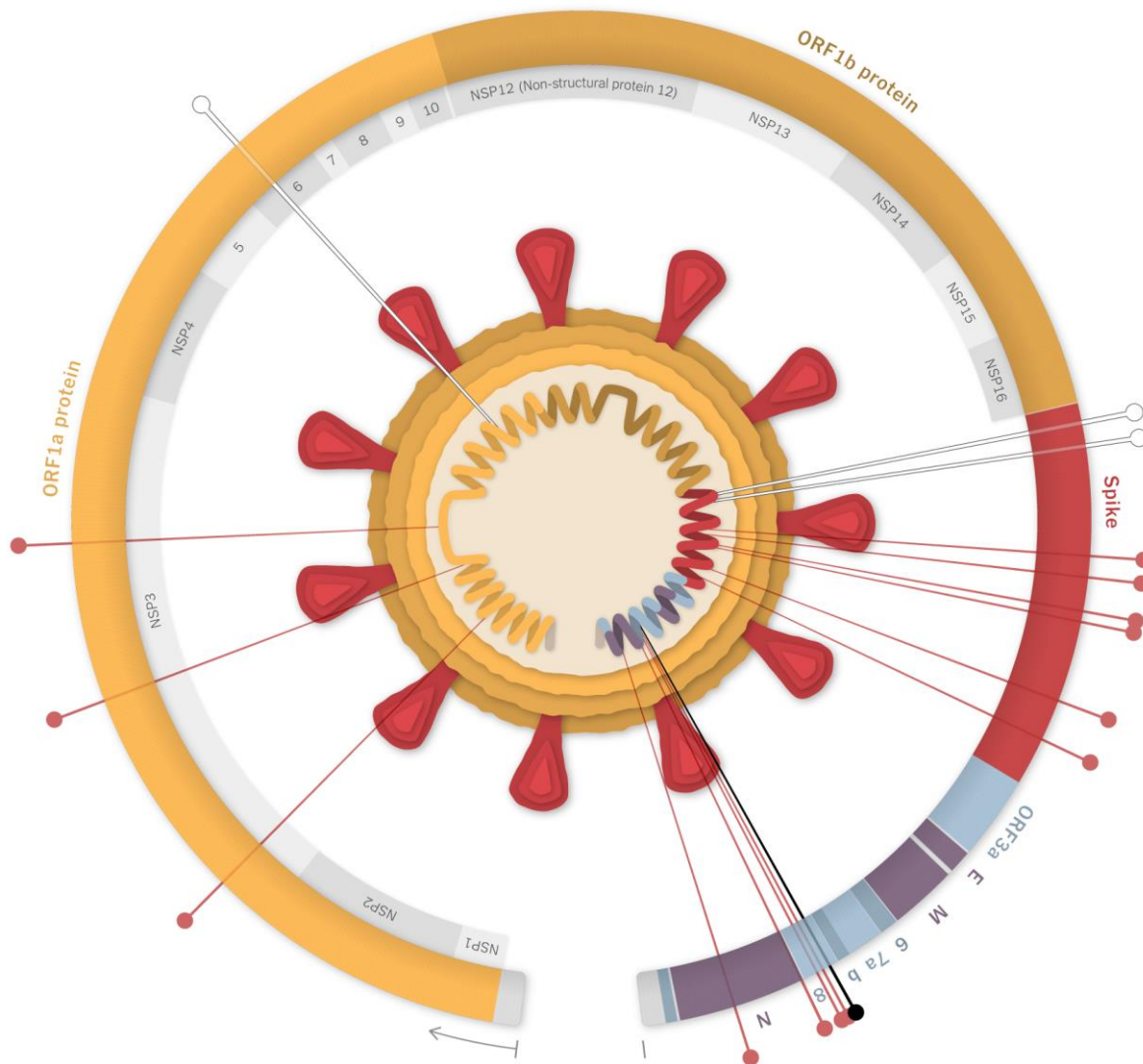
⇒ besmettelijk?

⇒ Endemisch

⇒ Mee leren leven

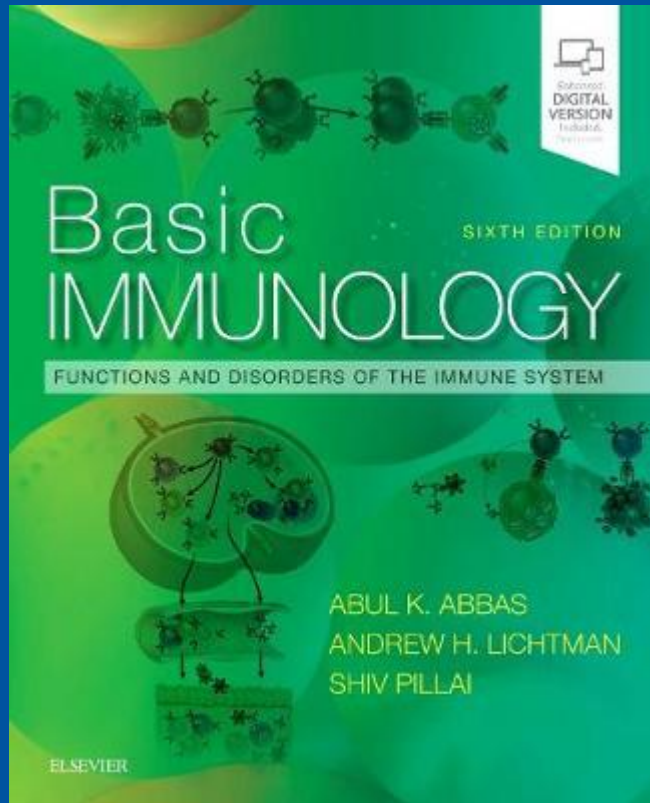
⇒ Belang van serologisch onderzoek

<https://www.nytimes.com/interactive/2021/health/coronavirus-mutations-B117-variant.html>



A number of researchers suspect that B.1.1.7 gained many of its mutations within a single person. People with weakened immune systems can remain infected with replicating coronaviruses for several months, allowing the virus to accumulate many extra mutations.

Immunologie / afweer college 4

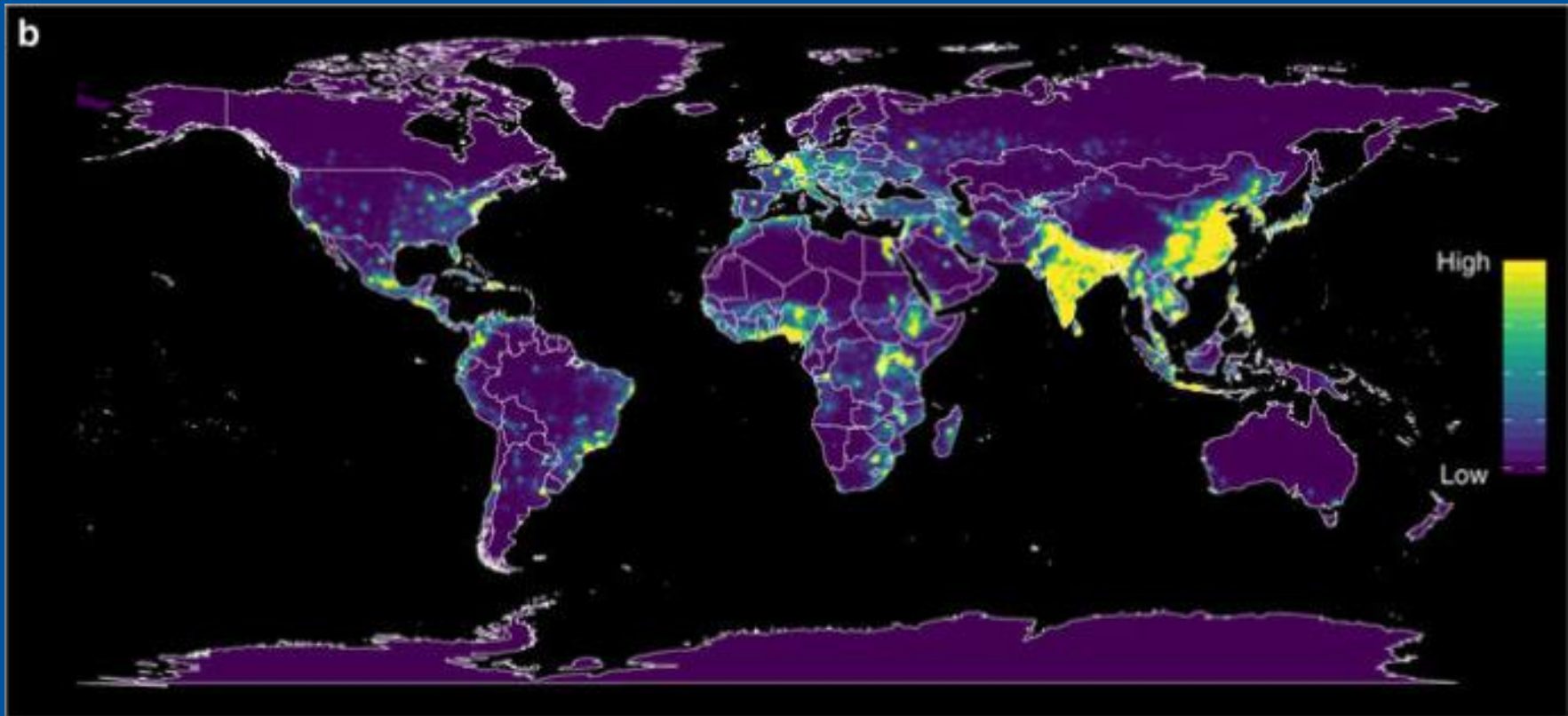


1. Onderdelen van het afweersysteem
cellen, signaalstoffen, antilichamen
2. Hoe leert het afweersysteem
memory, (RNA-)vaccins
3. Intracellulaire afweer
RNA detectie, PCR (tests)
4. Ziekte en veroudering
virussen, en leven => wat maakt corona bijzonder
5. Vragen en ethiek
ingrijpen in het leven

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

<https://youtu.be/7g0fkC3CywM>

De volgende pandemie komt uit..



Global hotspots and correlates of emerging zoonotic diseases

Vraag: Het % van de bevolking dat direct met levende dieren in aanraking komt, daalt. Dus de kans dat er ziektes van dieren naar mensen overstappen, neemt af.

Maar tegenwoordig zeggen sommigen dat de kans dat er ziektes van dieren naar mensen overstappen toeneemt, en dat we dus contacten met dieren moeten verminderen. Hoe zit dit?

=> Juist nu meer mensen en meer dieren op een kluitje? In ieder geval veel meer kans op mutaties

Newly emerging (and re-emerging) infectious diseases have been threatening humans since the neolithic revolution, 12,000 years ago, when human hunter-gatherers settled into villages to domesticate animals and cultivate crops. These beginnings of domestication were the earliest steps in man's systematic, widespread manipulation of nature. Ancient emerging zoonotic diseases with deadly consequences include smallpox, falciparum malaria, measles, and bubonic/pneumonic plague. Some, e.g., the Justinian plague (541 AD) and the Black Death (1348 AD), killed substantial proportions of humans in the "known" world, i.e., the world known to those whose recordings of it survive, predominantly in Asia, the Middle East, and Europe. Only a century ago, the 1918 influenza pandemic killed 50 million or more people, apparently the deadliest event in recorded human history. The HIV/AIDS pandemic, recognized in 1981, has so far killed at least 37 million. And the past decade has witnessed unprecedented pandemic explosions: H1N1 "swine" influenza (2009), chikungunya (2014), and Zika (2015), as well as pandemic-like emergences of Ebola fever over large parts of Africa (2014 to the present). COVID-19, is but the latest example of an unexpected, novel, and devastating pandemic disease. One can conclude from this recent experience that **we have entered a pandemic era**. Disease emergence reflects dynamic balances and imbalances, within complex globally distributed ecosystems comprising humans, animals, pathogens, and the environment.

Nothing new

- SARS-CoV-2 is the **seventh coronavirus that is known to cause human disease**. The viruses can be classified into four genera: alpha, beta, gamma, and deltaCoVs. Previously identified human CoVs that cause human disease include the alphaCoVs **hCoV-NL63 and hCoV-229E** and the betaCoVs HCoV-OC43, HKU1, severe acute respiratory syndrome CoV (SARS-CoV), and Middle East respiratory syndrome CoV (MERS-CoV).
- Notably, new cases of MERS-CoV infecting humans are still being reported.
- Common human coronaviruses, including types 229E, NL63, OC43, and HKU1, usually cause mild to moderate upper-respiratory tract illnesses, like the common cold. **Most people get infected with one or more of these viruses at some point in their lives.**
- Viruses are part of our environment
⇒ Do more research

Human coronavirus OC43 and the 'Russian flu' pandemic

A pandemic of respiratory disease known as the 'Russian flu' occurred in 1889 and 1890 and caused approximately one million deaths globally. This pandemic has been speculated to be caused by an influenza A virus. However, a study from 2005 showed that OC43, which is a human betacoronavirus, diverged from the closely related bovine coronavirus during the time frame of the 'Russian flu'¹⁵⁹. This makes it plausible that OC43 — which is still circulating in humans, causing common colds — was the causative agent of this pandemic. Interestingly, it has been shown, at least in one case, that bovine coronaviruses can infect humans¹⁶⁰. The other three endemic coronaviruses in humans — NL63, 229E (both alphacoronaviruses) and HKU1 (betacoronavirus) — are speculated to also be of zoonotic origin¹⁶¹. NL63-like and 229E-like viruses have been found in bats^{162,163,164} and viruses related to HKU1 have been found in rats¹⁶⁵. This suggests that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is not the first coronavirus to cause a pandemic and, given the frequency of outbreaks (SARS-CoV in 2003 and MERS CoV since 2012), it is likely not the last one. Importantly, studying circulating human coronaviruses and their origin will likely inform us better about the future of SARS-CoV-2 in the human population as well as about future pandemics with other coronaviruses.

Huge trove of unknown viruses found in fish, frogs and reptiles

- *Analysis of more than 200 newly discovered RNA viruses confirms that they co-evolved with their vertebrate hosts over millions of years*

<https://www.nature.com/articles/d41586-018-04102-7>



A trove of bat coronaviruses

Bats in the province of Yunnan in southern China have yielded yet more coronaviruses closely related to the pandemic virus.

From the samples, the team sequenced 24 coronavirus genomes, of which 4 were new viruses closely related to SARS-CoV-2. One of the viruses isolated from a *Rhinolophus pusillus* bat shared 94.5% of its genome with the pandemic virus, making it the second-closest known relative to SARS-CoV-2. The closest known relative is a coronavirus called RATG13, which shares 96% of its genome with SARS-CoV-2 and was isolated from a *Rhinolophus affinis* bat in Yunnan in 2013.

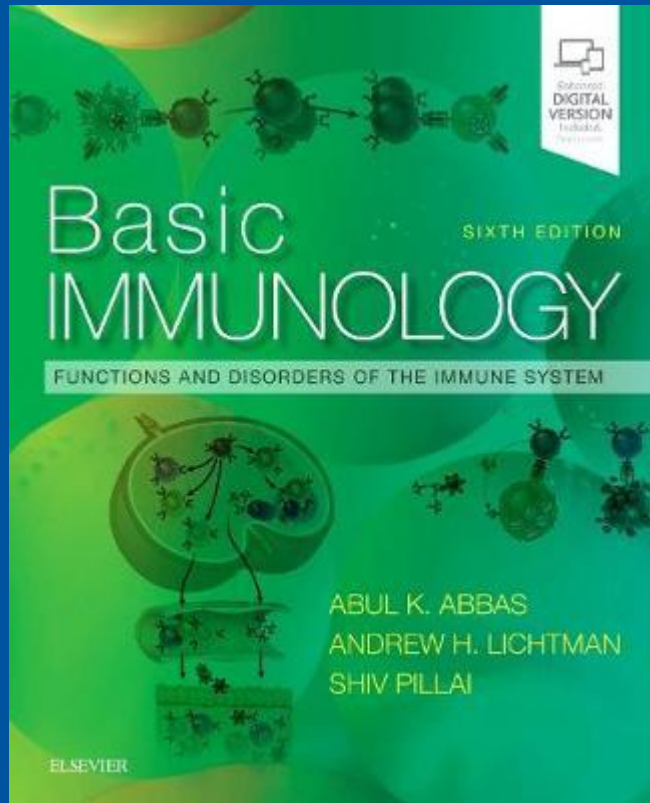
The results suggest that viruses closely related to SARS-CoV-2 continue to circulate in bats and are highly prevalent in some regions.

Nature **591**, 351 (17-03-2021)



H. Zhou *et al.* Preprint at bioRxiv
<https://doi.org/gh73mk>; 2021).

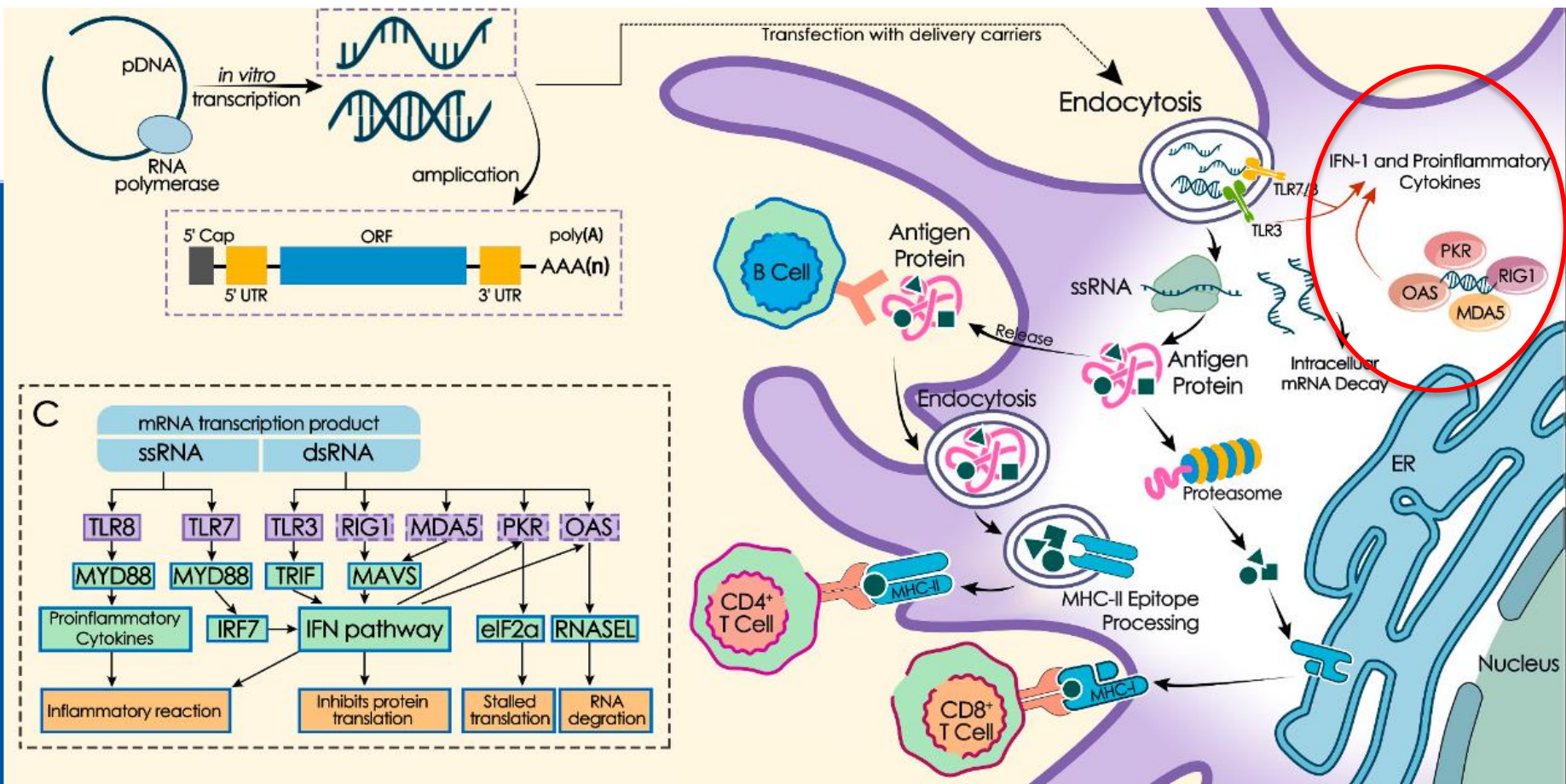
Immunologie / afweer college 4



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RNA geeft boost aan intracellulaire afweer (Interferon respons)

Self-adjuvant effect. Various of pattern recognition receptors (PRRs) can recognize mRNA *in vitro*. ssRNA can be recognized by endosomal innate immune receptors which can stimulate the secretion of pro-inflammatory cytokines and type I interferon (IFN), which leads to antigen-presenting cells (APCs) activation and inflammatory reaction.

Gevaar als leidend principe

"Danger Hypothesis"

Locatie

Frequentie

Dosis

Soort

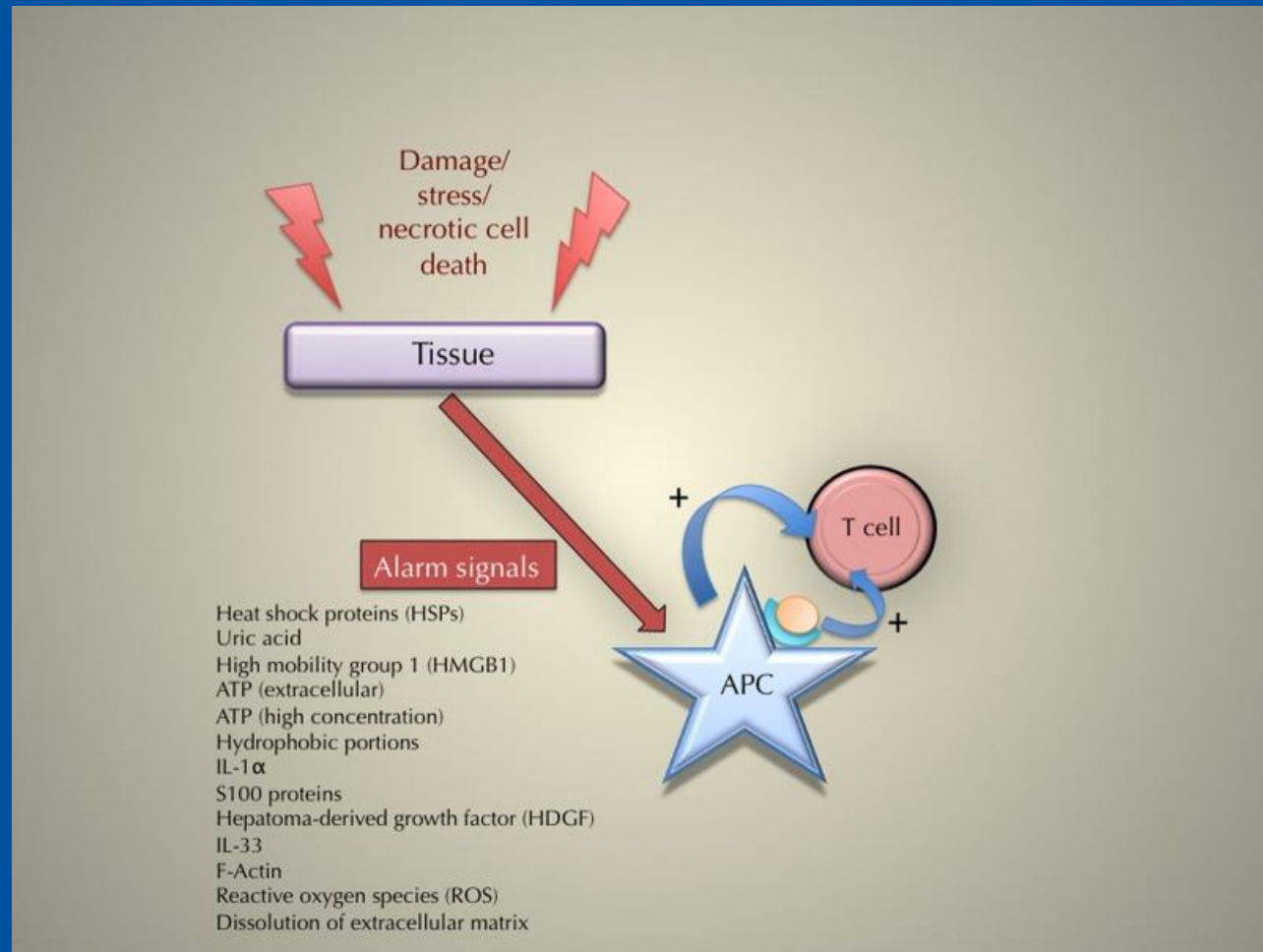
De reden waarom
vaccins via de huid
worden gegeven.

=> Is meteen een
duidelijk gevaar
signaal!

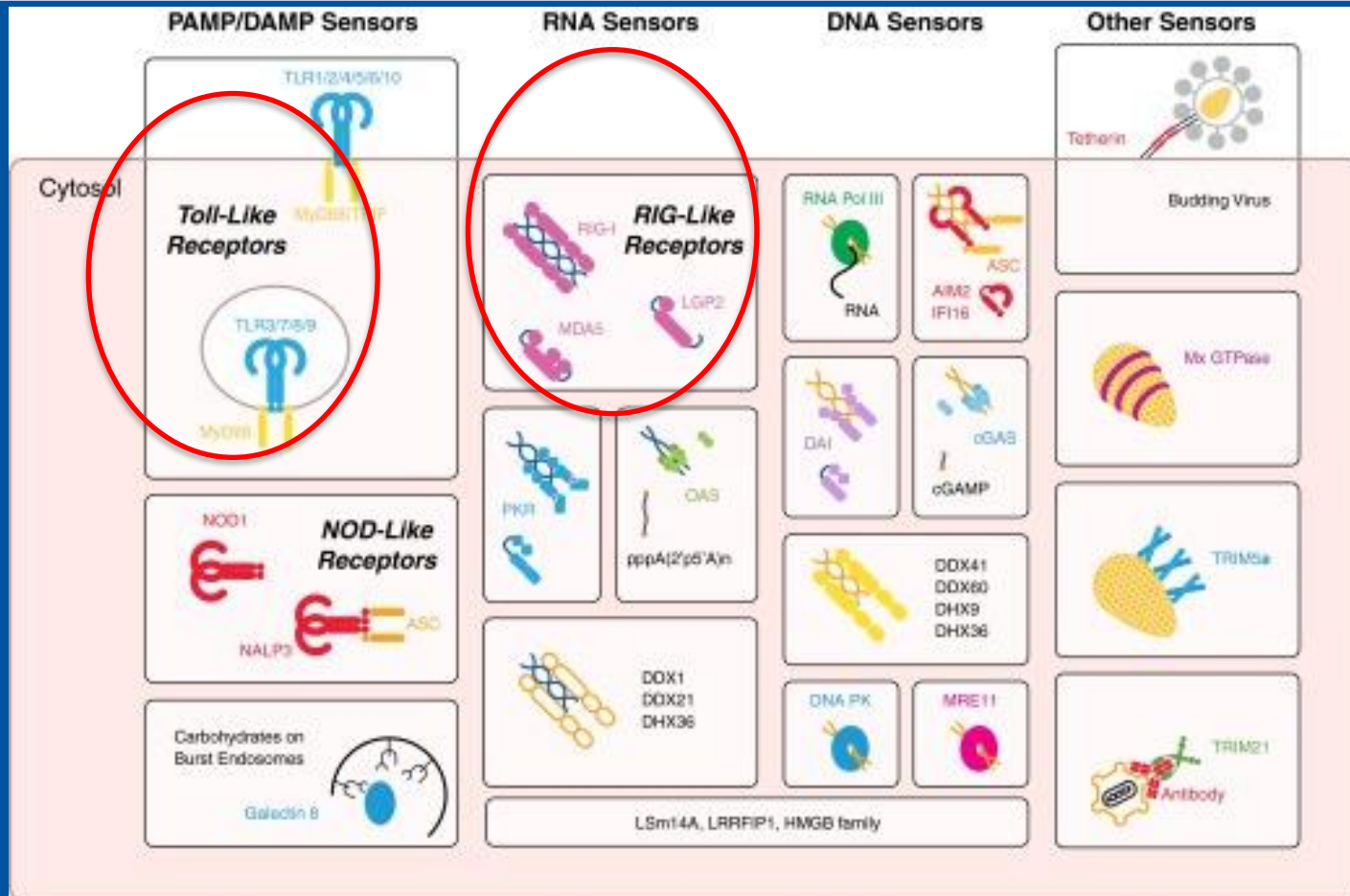
En een virus partikel
ook (versie 3.0)

=> adjuvans

En RNA blijktbaar ook
(versie 4.0)



Intracellulaire afweer => interferon aspecifiek!

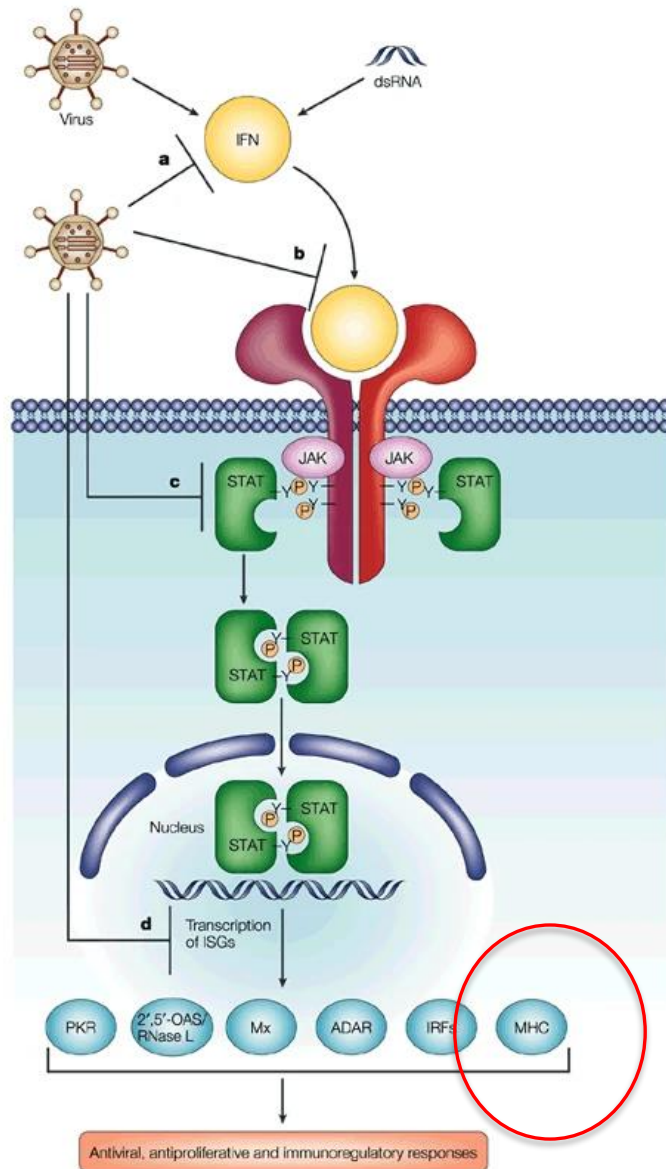


pathogen sensors are soluble, cytoplasmic proteins. **TLR**, **NLR**, and galectin-8 sensing of burst endosomes detect danger associated with infection.

https://www.sciencemag.org/topic/crispr?r3f_986=http://science.sciencemag.org/content/327/5962/167.full

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4192899/>

Viruses and interferon: a fight for supremacy



Type I interferons (IFNs) are a group of antiviral cytokines that are induced during viral infection by viral-replication products, such as double-stranded (ds)RNA. IFNs exert their biological functions by binding to specific cell-surface receptors. In turn, this triggers the intracellular IFN signalling pathway — mainly the JAK–STAT pathway — which eventually induces the expression of a large number of IFN-stimulated genes (ISGs). The ISGs, the workhorses of the IFN response, set up an antiviral, antiproliferative and immunoregulatory state in the host cells. However, most, if not all, viruses have evolved a broad spectrum of strategies to block and interfere with the IFN pathway.

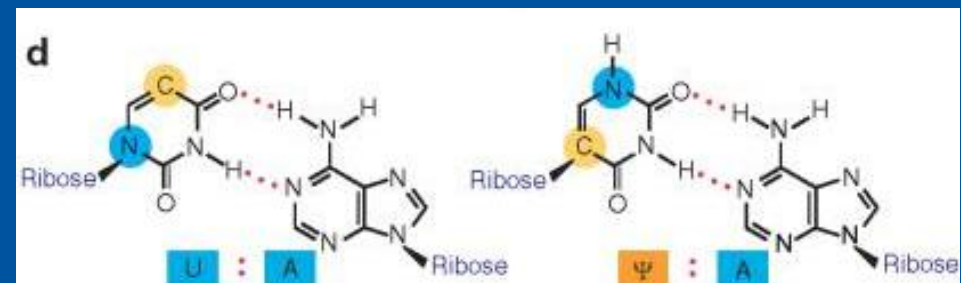
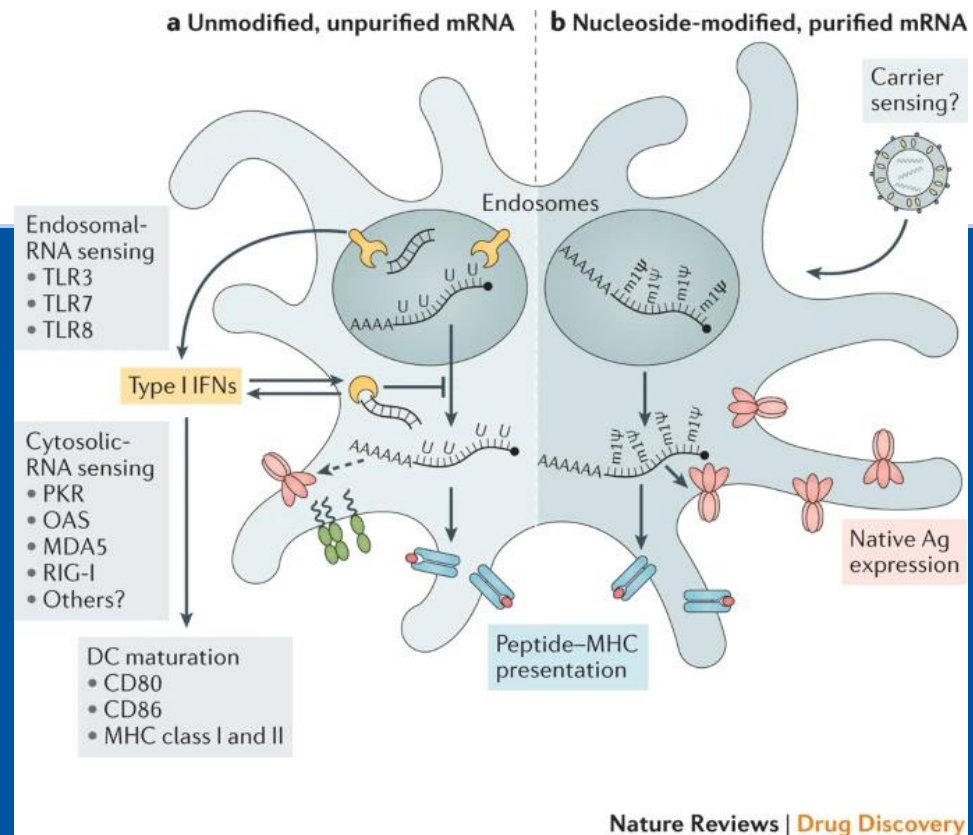
NB De geïnfecteerde cel produceert deze voor zichzelf (autophagy), en de omgeving.

<https://www.nature.com/articles/nri888>

mRNA vaccines

a new era in vaccinology

- 2018, nature review
- ⇒ Was al jaren in ontwikkeling
- ⇒ Corona was gat in de markt
- NB Veel virussen veroorzaken kanker
- mRNA cancer vaccines, including dendritic cell vaccines, have been employed in numerous cancer clinical trials, with some promising results showing antigen-specific T cell responses and prolonged disease-free survival in some cases.
- Engineering of the RNA sequence has rendered synthetic mRNA more translatable than ever before and
- **modified nucleosides decrease innate immune activation and increase translation => BioNtech/Moderna**



<https://www.nature.com/articles/nrd.2017.243>

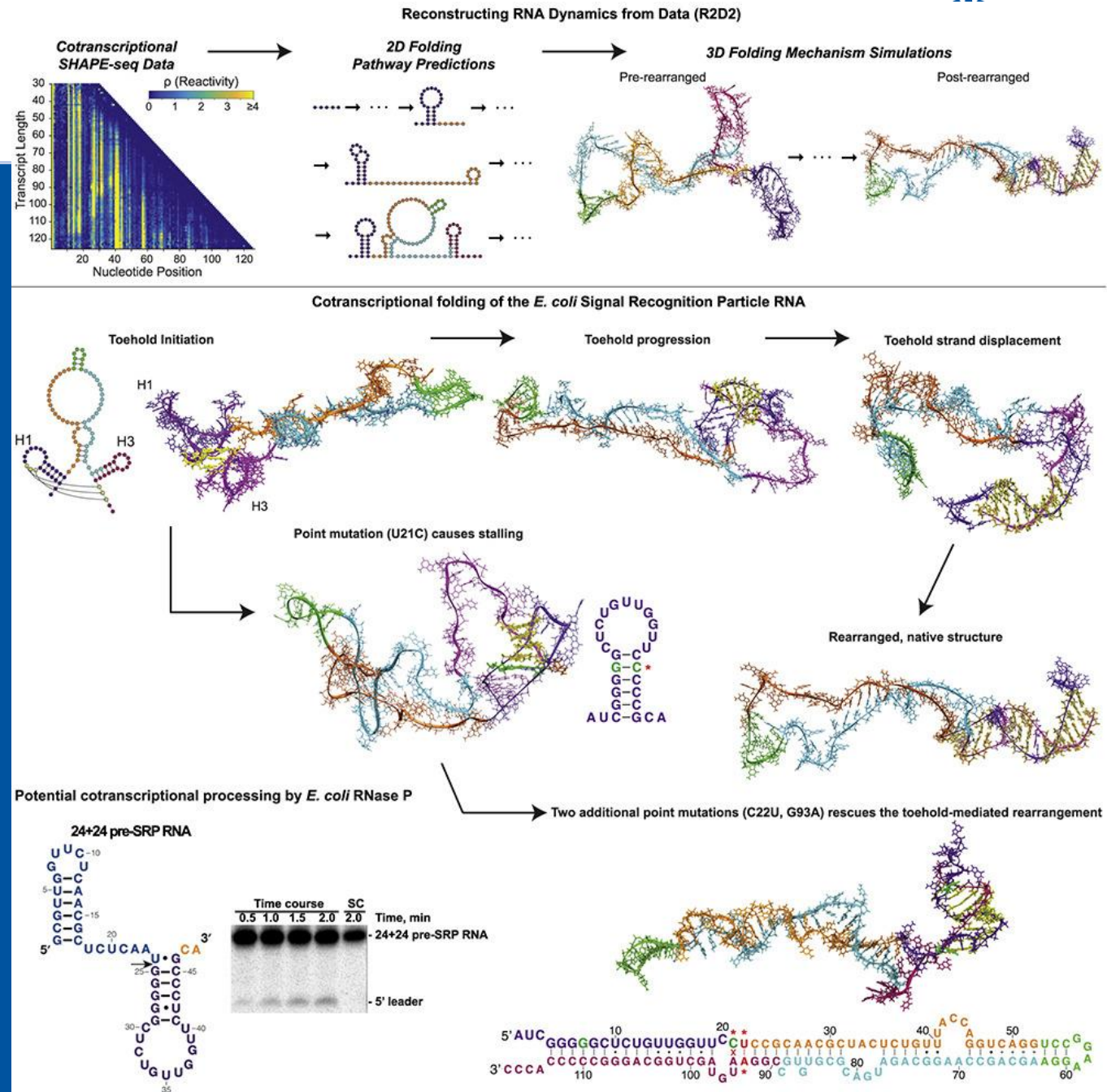
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2775451/>

Eigenlijk
ingewikkelder
dan DNA

3D als eiwit !

Modificaties bij
vaccins

<https://www.sciencedirect.com/science/article/abs/pii/S1097276520309369?via%3Dihub>



Modulation of immunogenicity of RNA

Exogenous mRNA is inherently immunostimulatory, as it is recognized by a variety of cell surface, endosomal and cytosolic innate immune receptors.

Depending on the therapeutic application, this feature of mRNA could be beneficial or detrimental. It is potentially advantageous for vaccination because in some cases it may provide **adjuvant activity** to drive dendritic cell maturation and thus elicit robust T and B cell immune responses. However, innate immune sensing of mRNA has also been associated with the inhibition of antigen expression and may negatively affect the immune response. Although the **paradoxical effects** of innate immune sensing on different formats of mRNA vaccines are incompletely understood, some progress has been made in recent years in elucidating these phenomena.

NB Curevac gebruikt juist ongemodificeerd RNA

Vaccin, nadelen

Afweersysteem reageert niet zomaar.

- ⇒ Gevaarsignaal
- ⇒ Veiligheid
- ⇒ Brede werking onder de bevolking nodig
- ⇒ Kost veel tijd
- ⇒ Allergien?
- ⇒ Maatschappelijke weerstand, vooral tegen gebruik adjuvants.

- NB Geen adjuvants in huidige vaccins
- Wel nog bij sanofi

COMMON COMPONENTS OF VACCINES

As well as the active components, vaccines contain a number of other substances. This graphic examines these and the reasons for their inclusion.

ACTIVE COMPONENTS



A form of the virus, bacteria or toxin that causes the disease is used as the antigen. This antigen is modified from the original form so it no longer causes disease, but still elicits an immune response from the body. To modify the disease-causing agent, it can be treated with specific chemicals, so it cannot replicate. It can also be treated so it does not cause serious disease, or only parts of the disease-causing agent that do not cause serious symptoms can be used.

ADJUVANTS



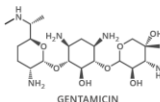
ALUMINIUM HYDROXIDE



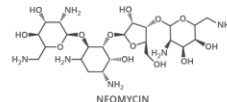
ALUMINIUM PHOSPHATE

Added to enhance the body's immune response to the vaccine. How they work isn't entirely understood, but it's thought they help keep antigens near the site of injection. This means they can be easily accessed by the immune system cells. There is no evidence of any serious adverse effects from adjuvants, though they can cause some minor reaction near the injection site.

ANTIBIOTICS



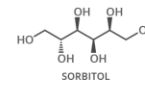
GENTAMICIN



NEOMYCIN

Antibiotics are used in the manufacturing process of the vaccine to prevent bacterial contamination. They are later removed, and only residual quantities remain in the vaccine after the production process.

STABILISERS



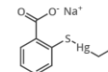
SORBITOL



MAGNESIUM SULFATE

Vaccines need to be storable, so stabilisers are added to ensure the various components remain stable and effective. A variety of different stabilisers are used; either inorganic magnesium salts such as magnesium sulfate or magnesium chloride, or mixtures of lactose, sorbitol and gelatin. Monosodium glutamate and glycine are also used in some cases.

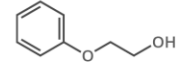
PRESERVATIVES



THIOMERSAL



PHENOL



PHENOXYETHANOL

Preservatives help prevent contamination of vaccines. They are used particularly in multi-dose vaccines. Thiomersal is a common preservative, though its use declined in the late 1990s when vaccines were falsely linked to child autism. This link was later shown to be an elaborate medical hoax, and there is no link between thiomersal and autism.

TRACE COMPONENTS



FORMALDEHYDE

These are left-over from the vaccine production process. Though they are purposefully removed, residual amounts remain. Formaldehyde is one such agent, used to deactivate viruses and detoxify bacteria, but amount remaining is several hundred times lower than the smallest amount known to cause harm in humans.

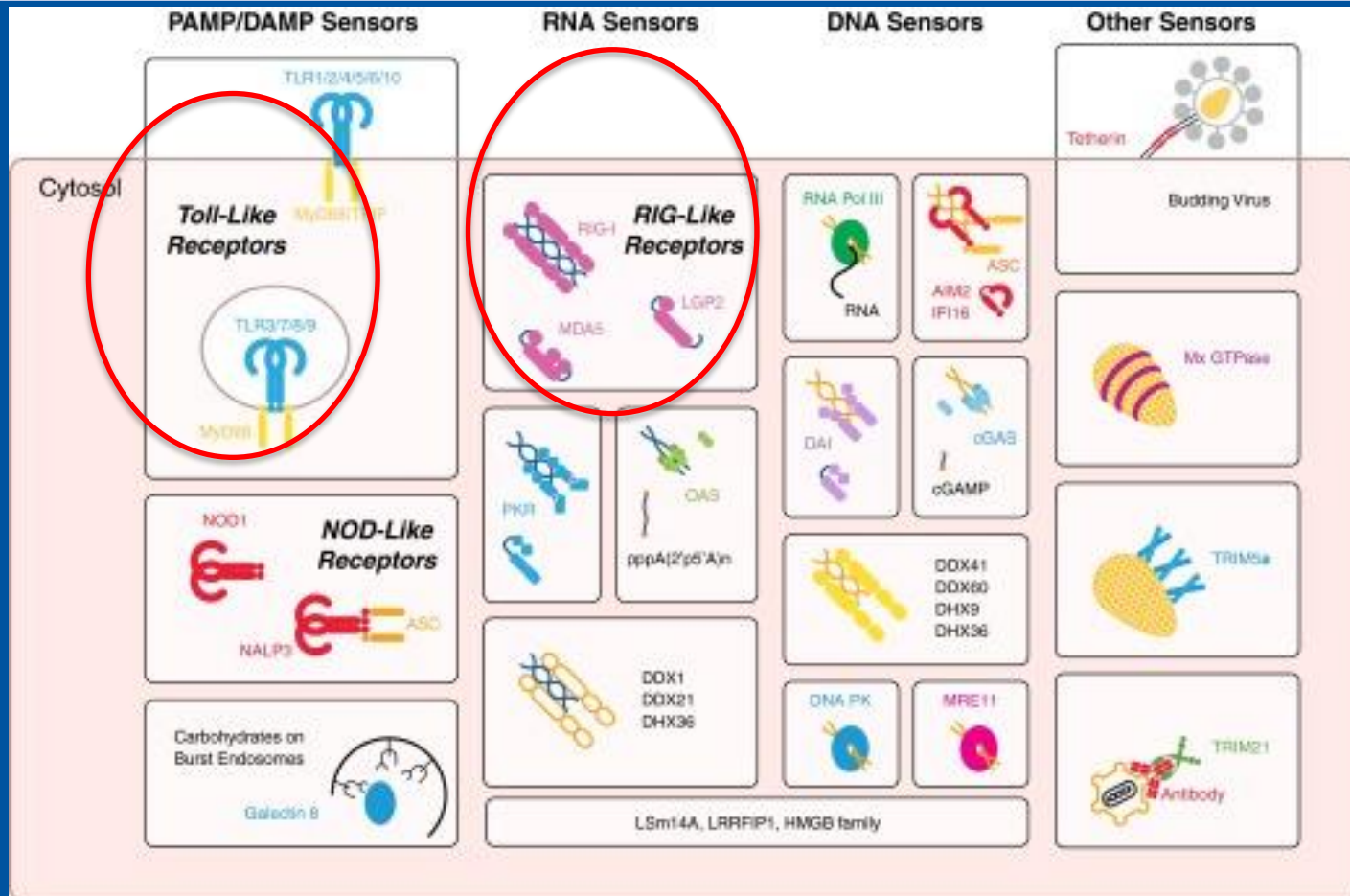


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https://en.wikipedia.org/wiki/Immunologic_adjuvant

Intracellulaire afweer => interferon aspecifiek!



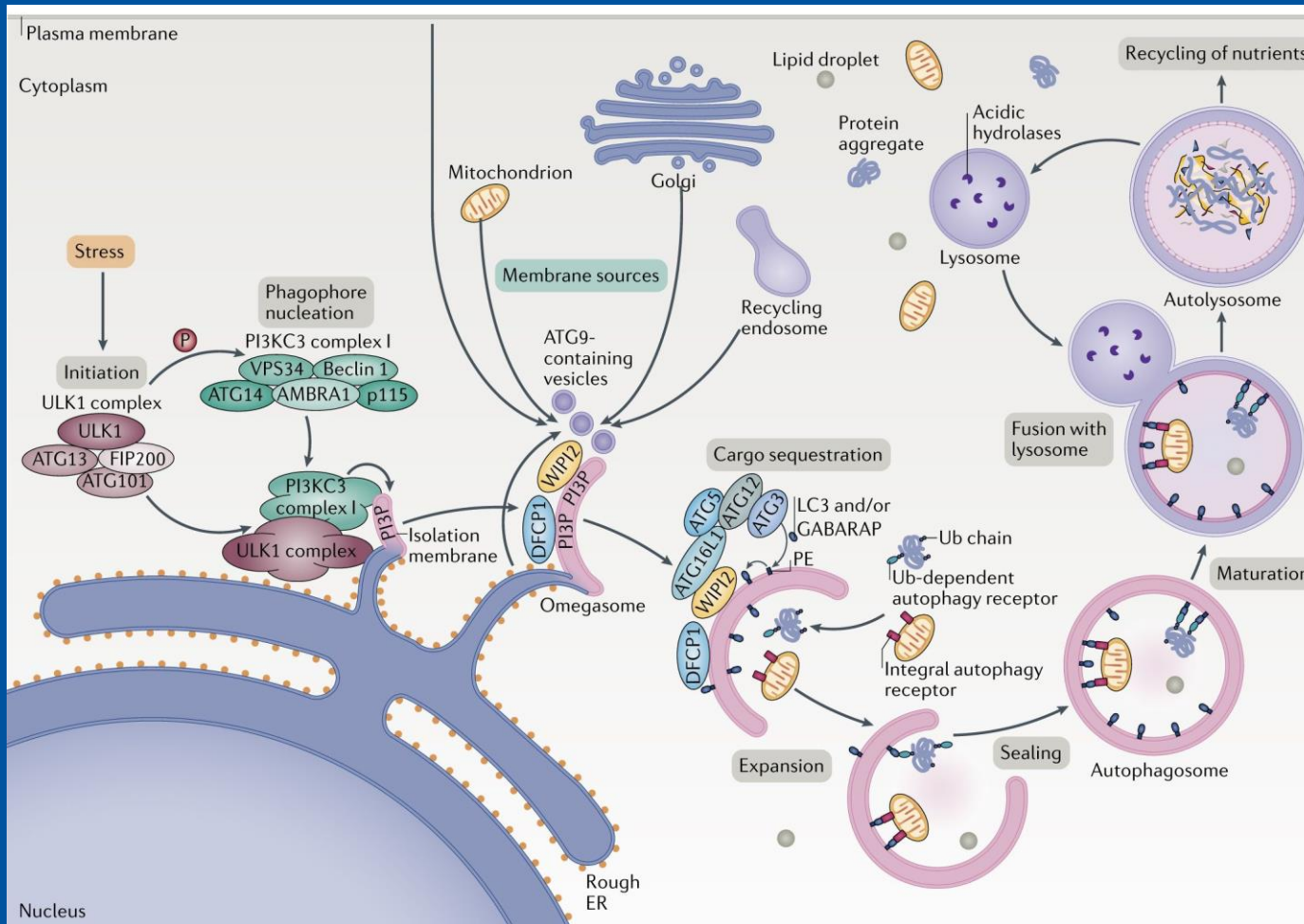
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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4192899/>

Autophagy

Overlap met de intracellulaire afweer



Autophagy (or *autophagocytosis*) is the natural, regulated mechanism of the cell that disassembles unnecessary or dysfunctional components.

It allows the orderly degradation and recycling of cellular components.

Ook na infectie

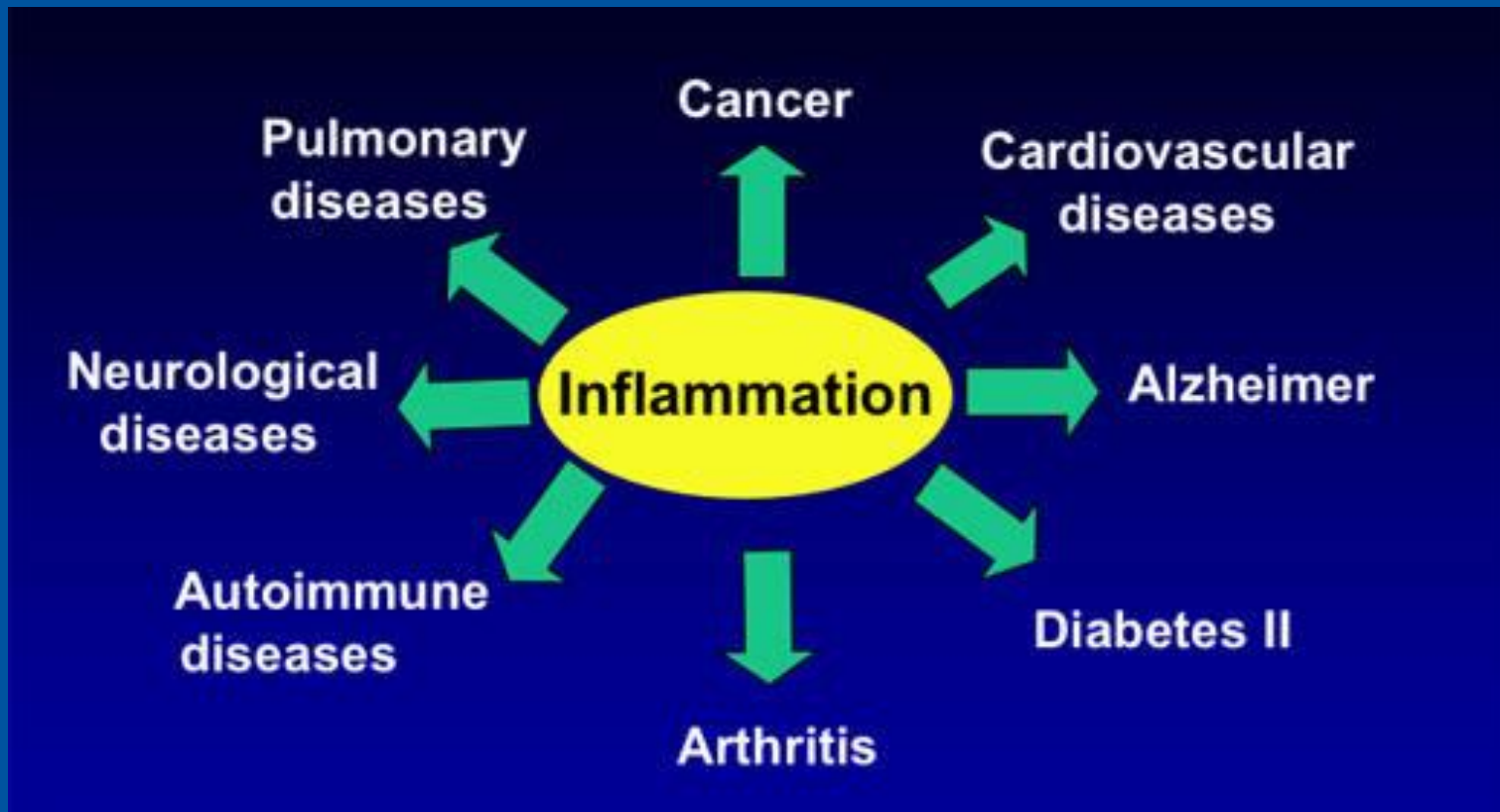
⇒ Opruimen virus

⇒ MHC-I

Foute autophagy

=> Alzheimers?

Chronische ontsteking en ziekte

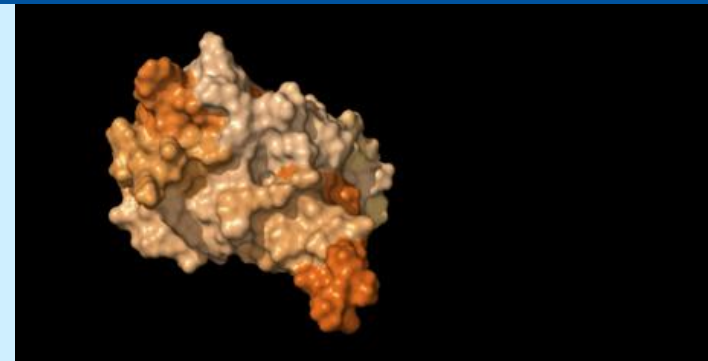
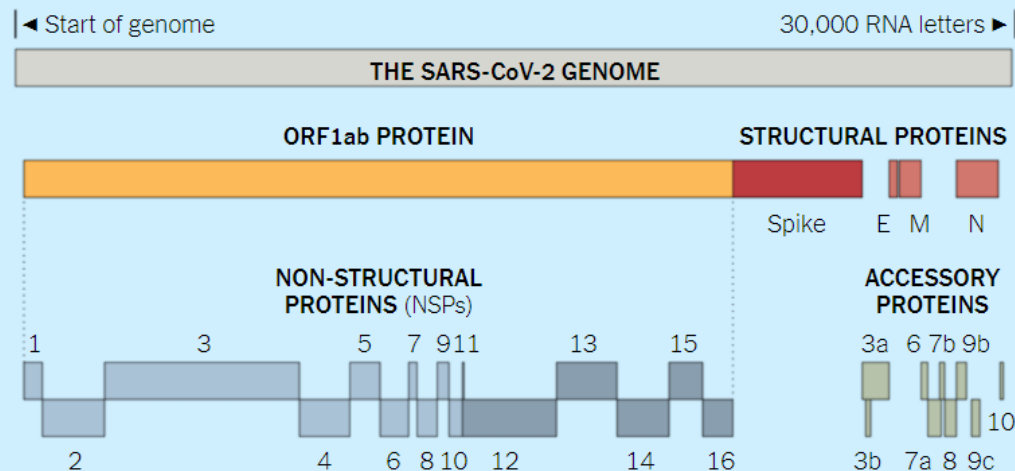


Ziekmakers spelen een belangrijke rol bij veroudering, via (chronische) ontsteking en verstoren van homeostase

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.

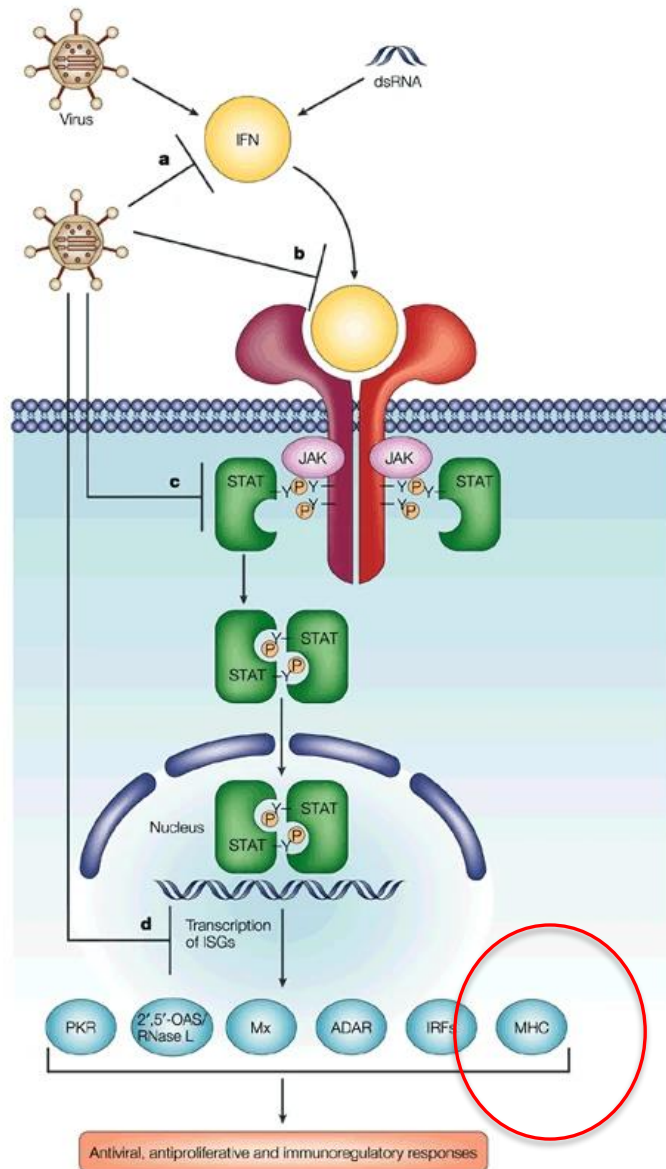
=> wat maakt Corona bijzonder



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>

Viruses and interferon: a fight for supremacy



Type I interferons (IFNs) are a group of antiviral cytokines that are induced during viral infection by viral-replication products, such as double-stranded (ds)RNA. IFNs exert their biological functions by binding to specific cell-surface receptors. In turn, this triggers the intracellular IFN signalling pathway — mainly the JAK–STAT pathway — which eventually induces the expression of a large number of IFN-stimulated genes (ISGs). The ISGs, the workhorses of the IFN response, set up an antiviral, antiproliferative and immunoregulatory state in the host cells. However, most, if not all, viruses have evolved a broad spectrum of strategies to block and interfere with the IFN pathway.

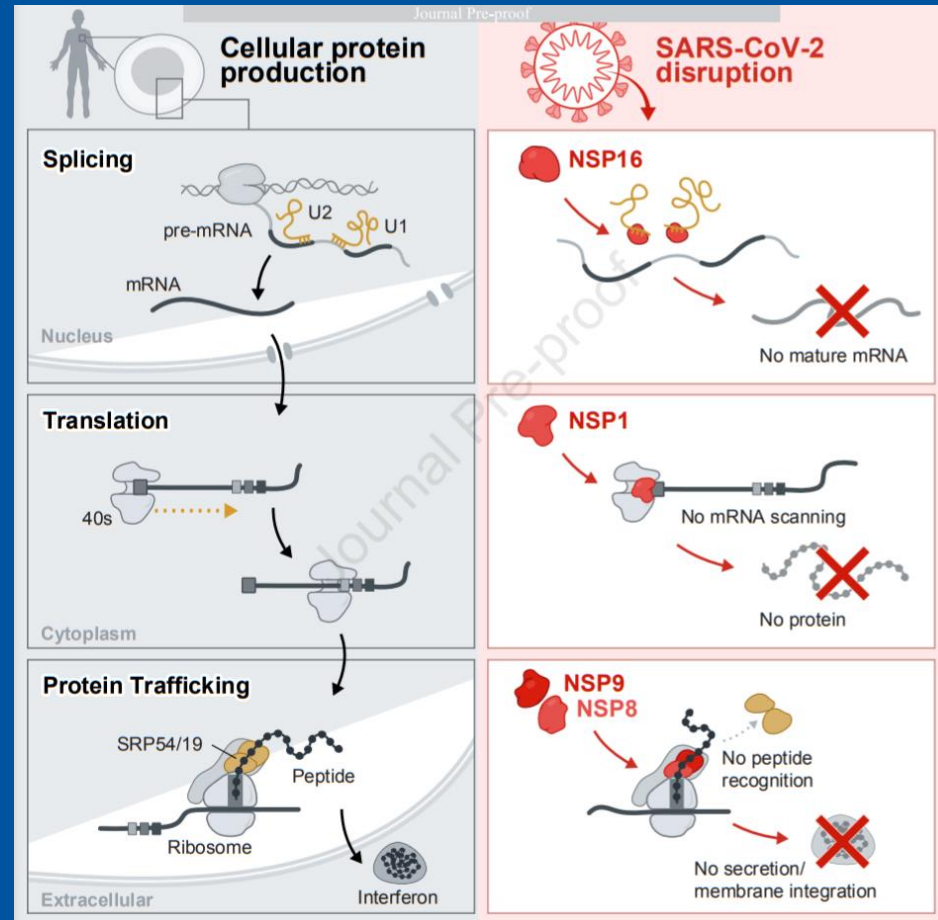
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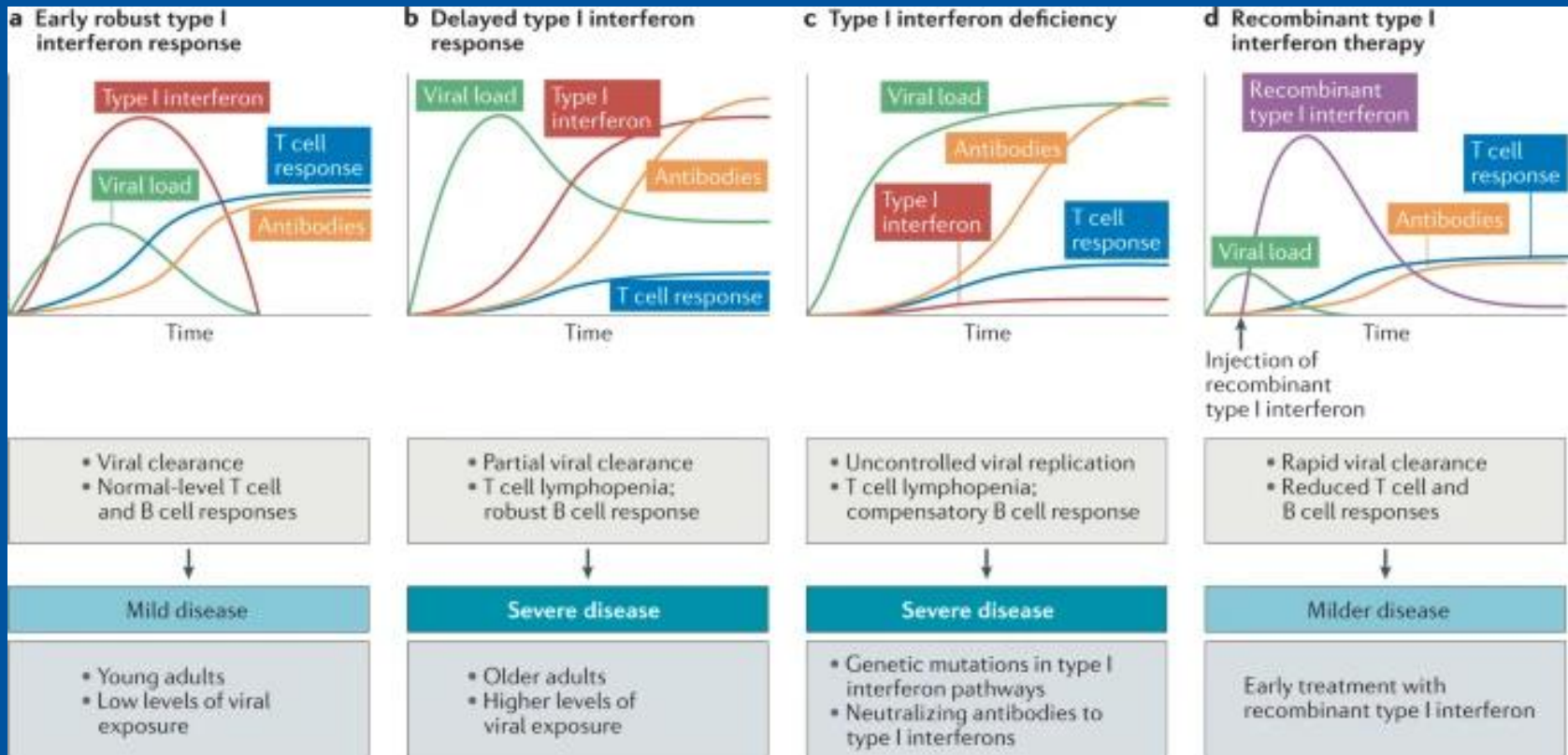
SARS-CoV-2 disrupts splicing, translation, and protein trafficking to suppress host defenses

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



How the timing of interferon responses might control innate and adaptive immunity to SARS-CoV-2.



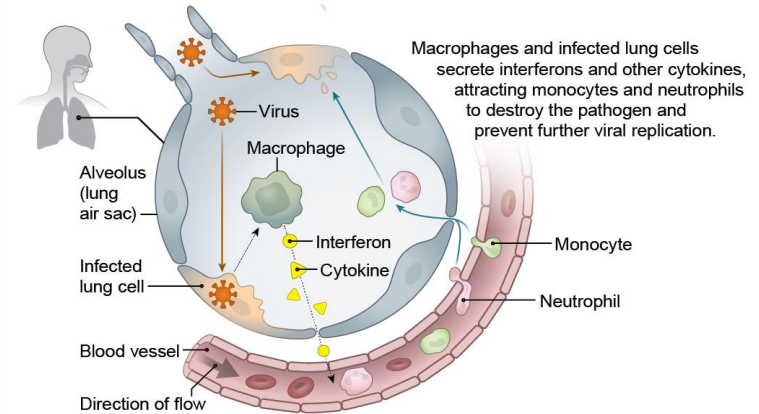
Crisis bij longontsteking

- Corona ontregelt de **Interferon** respons
- Doordat het virus te laat wordt opgemerkt komt de afweer in een soort overdrive om toch te proberen nog controle te krijgen over het virus.
 - ⇒ **overdrive door vet (IL-6)**
 - ⇒ **inflammaging**
- Daaraan overlijden dan veel mensen

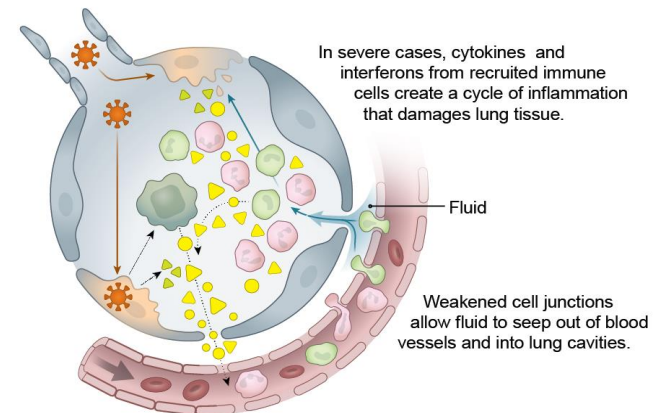
Innate Immunity and Inflammatory Storms

When the innate immune system works as it should, it disarms and destroys the SARS-CoV-2 virus. But the novel coronavirus is able to bypass this finely calibrated process, and chaos results in its wake. Too many of the signaling proteins, called cytokines, then descend on an infection site, exacerbating damage. Inflammation in infected lung cells damages tissues, and nearby blood vessels start to leak and fluid enters the lung cavity.

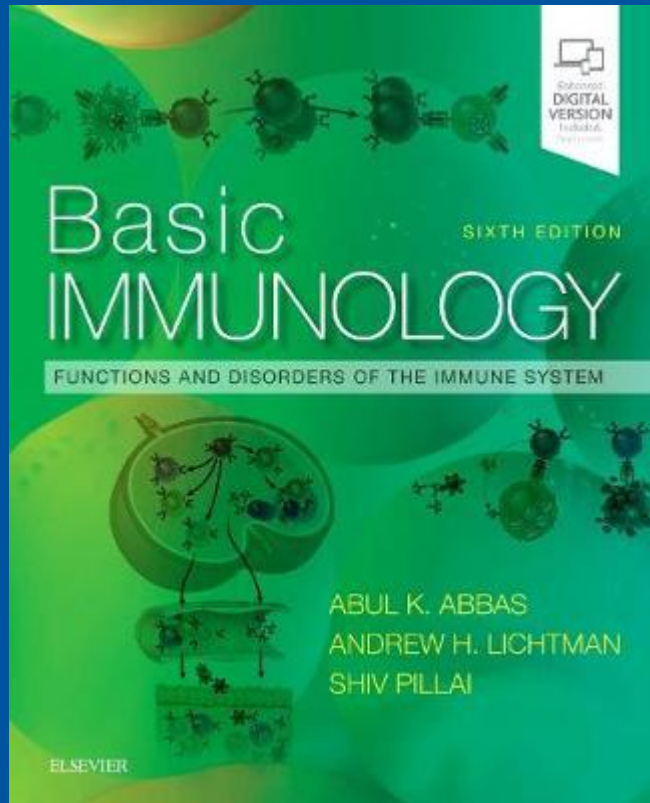
Beneficial Inflammatory Immune Response



Damaging Inflammatory Response



Immunologie / afweer college 4



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3. Intracellulaire afweer
RNA detectie, PCR (tests), CRISPR
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Boek: Abbas, Basic Immunology.
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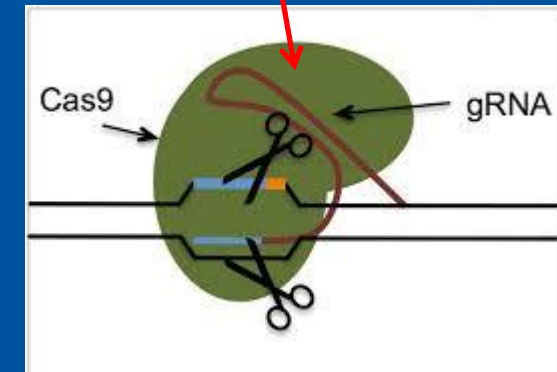
Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are pattern-recognition receptors similar to toll-like receptors (TLRs). While TLRs are transmembrane receptors, NLRs are cytoplasmic receptors that play a crucial role in the innate immune response by recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).

=> in ieder geval a-specifieke afweer in de cellen van mensen.
Maar nog veel onbekend.

Veel meer bekend uit onderzoek in bacterien

=> Bacterien hebben zelfs een specifieke afweer (CRISPR)

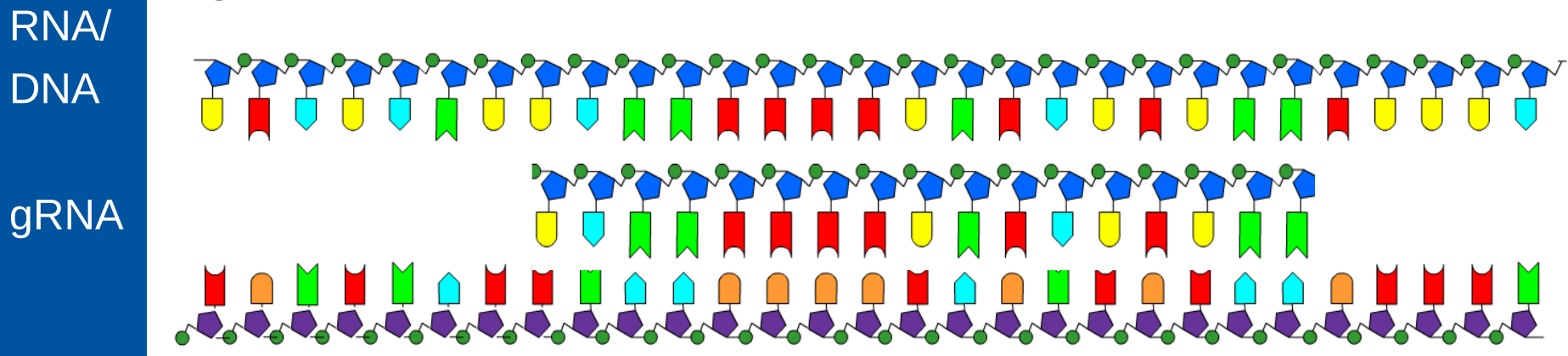
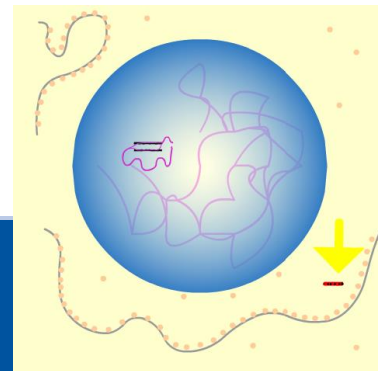
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4696971/>



<https://youtu.be/MnYppmstxls>
<https://youtu.be/4YKFw2KZA5o>

guideRNA/primer actie

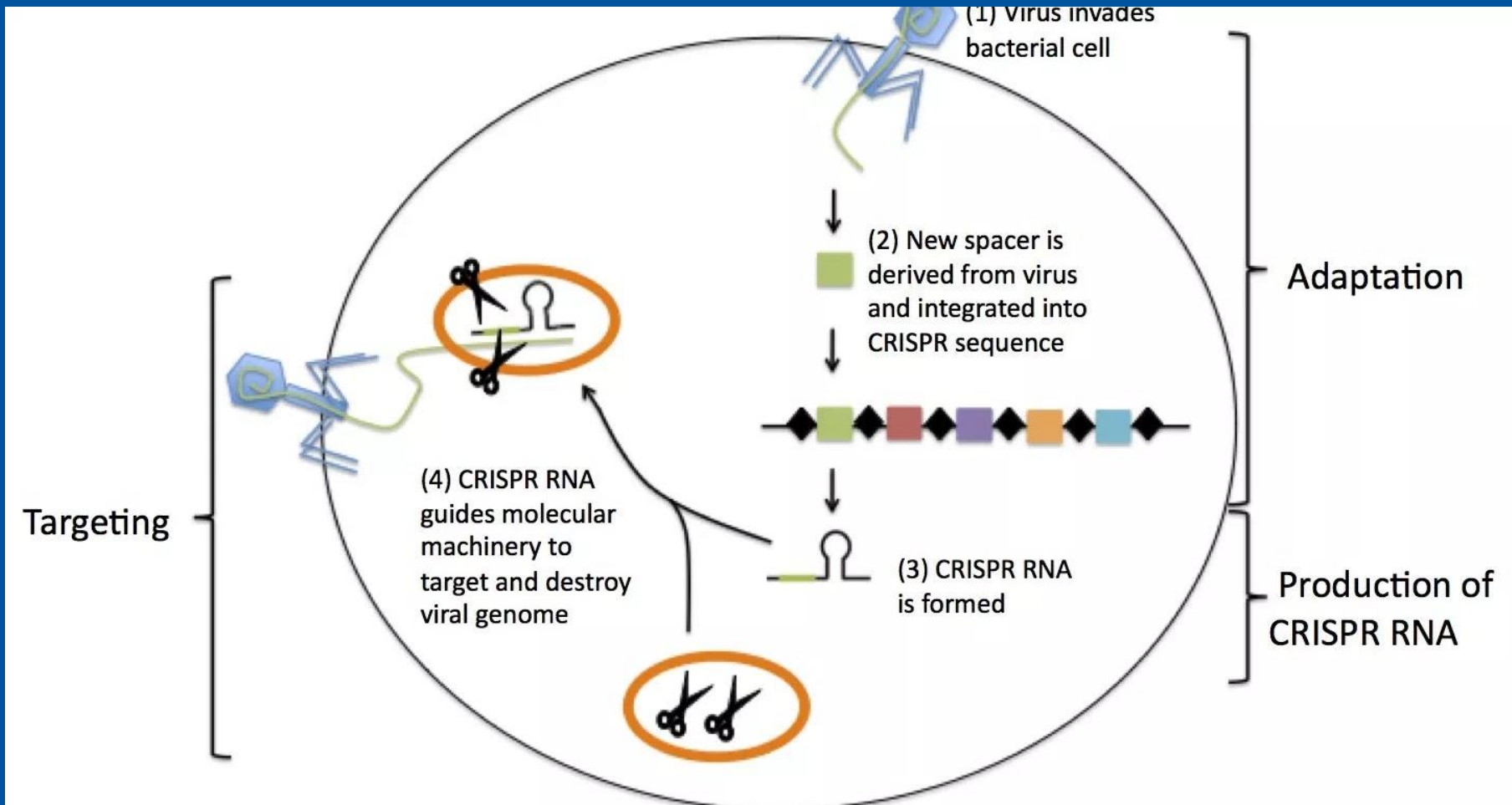
gRNA bindt aan RNA/DNA
Op 1 specifieke locatie



Kans = $\frac{1}{4}$ voor 1^e nucleotide, en $\frac{1}{4}$ voor 2^e nucleotide (er zijn 4 verschillende)
Kans = $\frac{1}{4} \times \frac{1}{4} = \frac{1}{4^2} = \frac{1}{16}$ voor 2 nucleotiden ($\frac{1}{4^n}$ voor n nucleotiden)
Kans = $\frac{1}{4^{20}}$ voor 20 nucleotiden = $\frac{1}{1000.000.000.000}$
Aantal nucleotiden in het genoom = 3.000.000.000

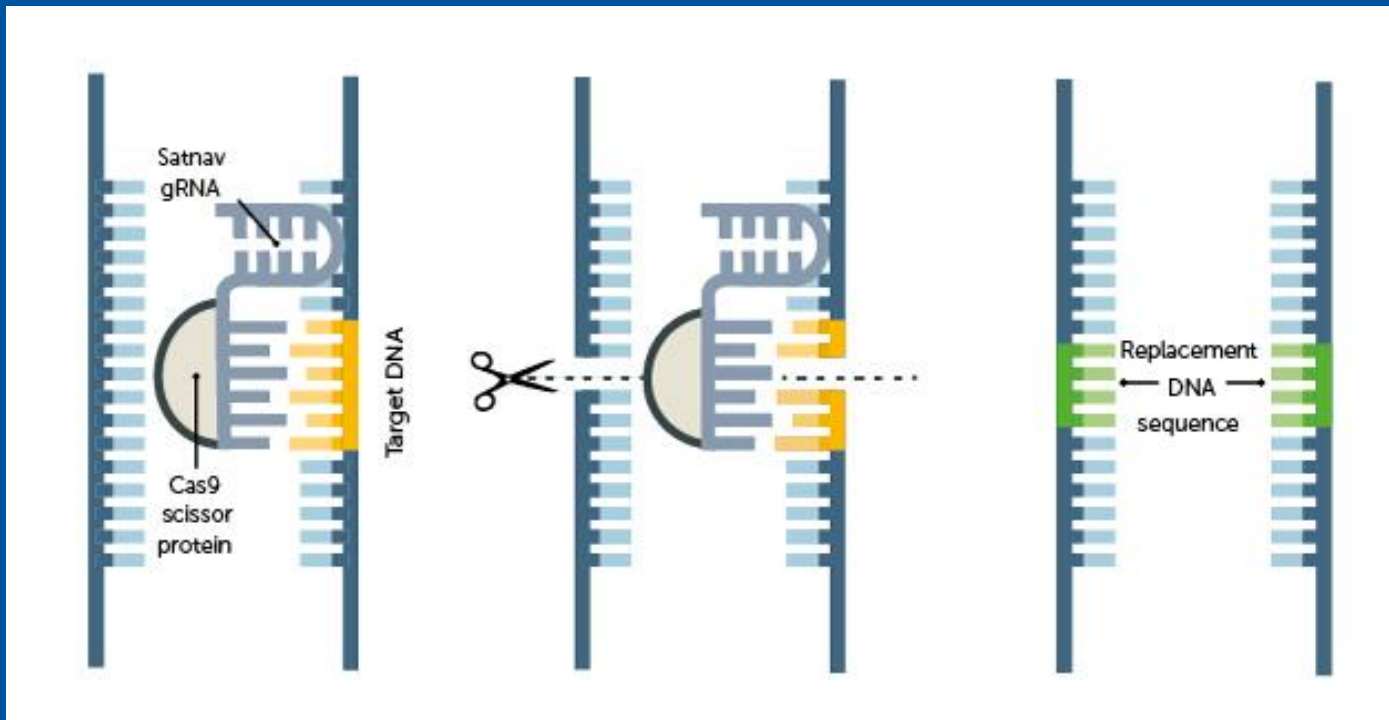
Klein stukje GuideRNA/primer zorgt al voor specifieke herkenning
=> in principe geen off-target effects

CRISPR, Intracellular bacterial defence against virus => specifiek, met memory !



Cas: an enzyme that cuts DNA

CRISPR targets ($\Rightarrow$ satnav), Cas cuts ($\Rightarrow$ scissor)



Modern biotechnology has modified Cas

- $\Rightarrow$ replace cut-out DNA with any desired sequence
- $\Rightarrow$ gene-therapy

Werken met de taal van het leven

Lezen =	Sequencing (human genome project)
Knippen =	Restrictie-enzymen (klonen van GFP gen) gRNA
Schrijven =	Synthese => primer /
Plakken =	Insertie => vaak nog virus (vector) voor nodig (=> CRISPR)

⇒Moleculaire Biologie Toolkit

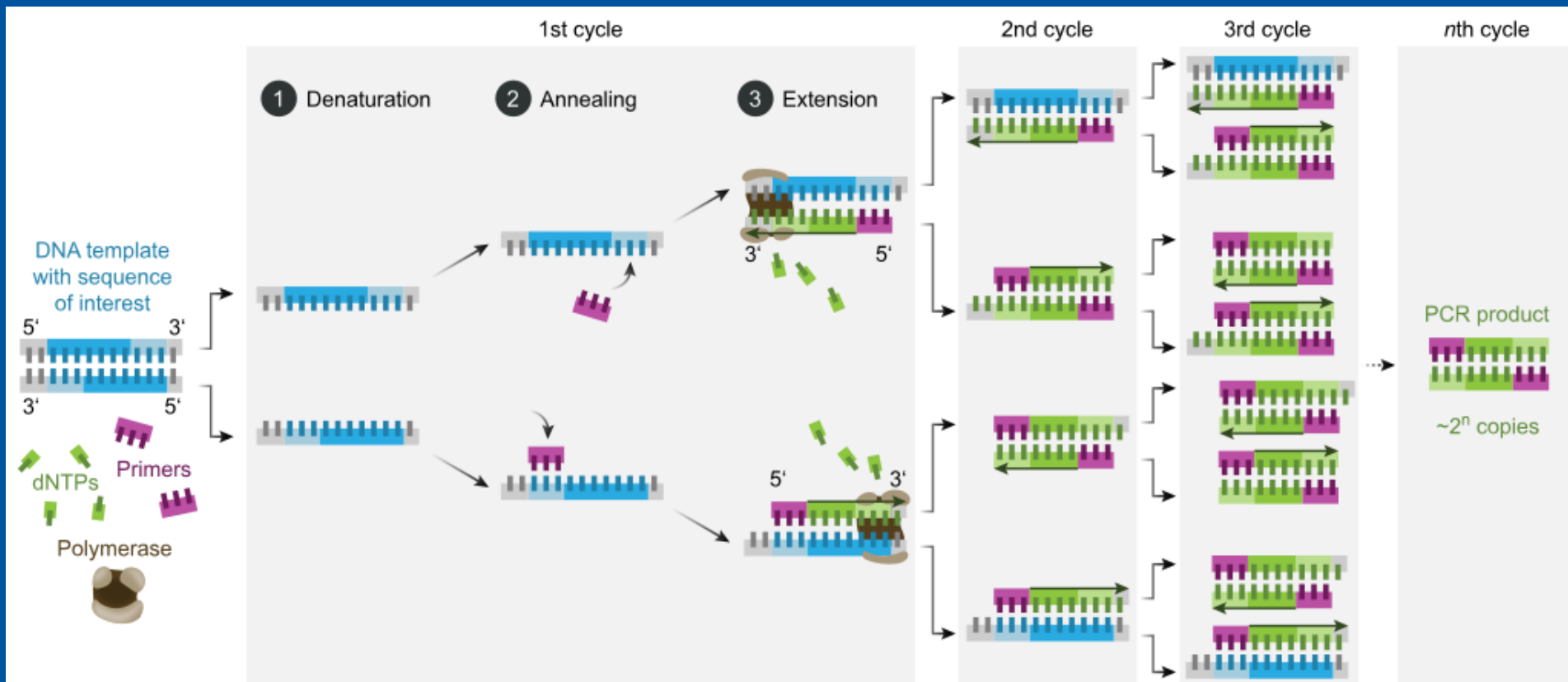
⇒DNA is een taal, en moleculaire biologie = taalkunde

Taalkunde en Grammatica; how do they do it.

Graig Venter => shotgun sequencing HUGO, flagship project.
3miljard => 1000 dollar genome,

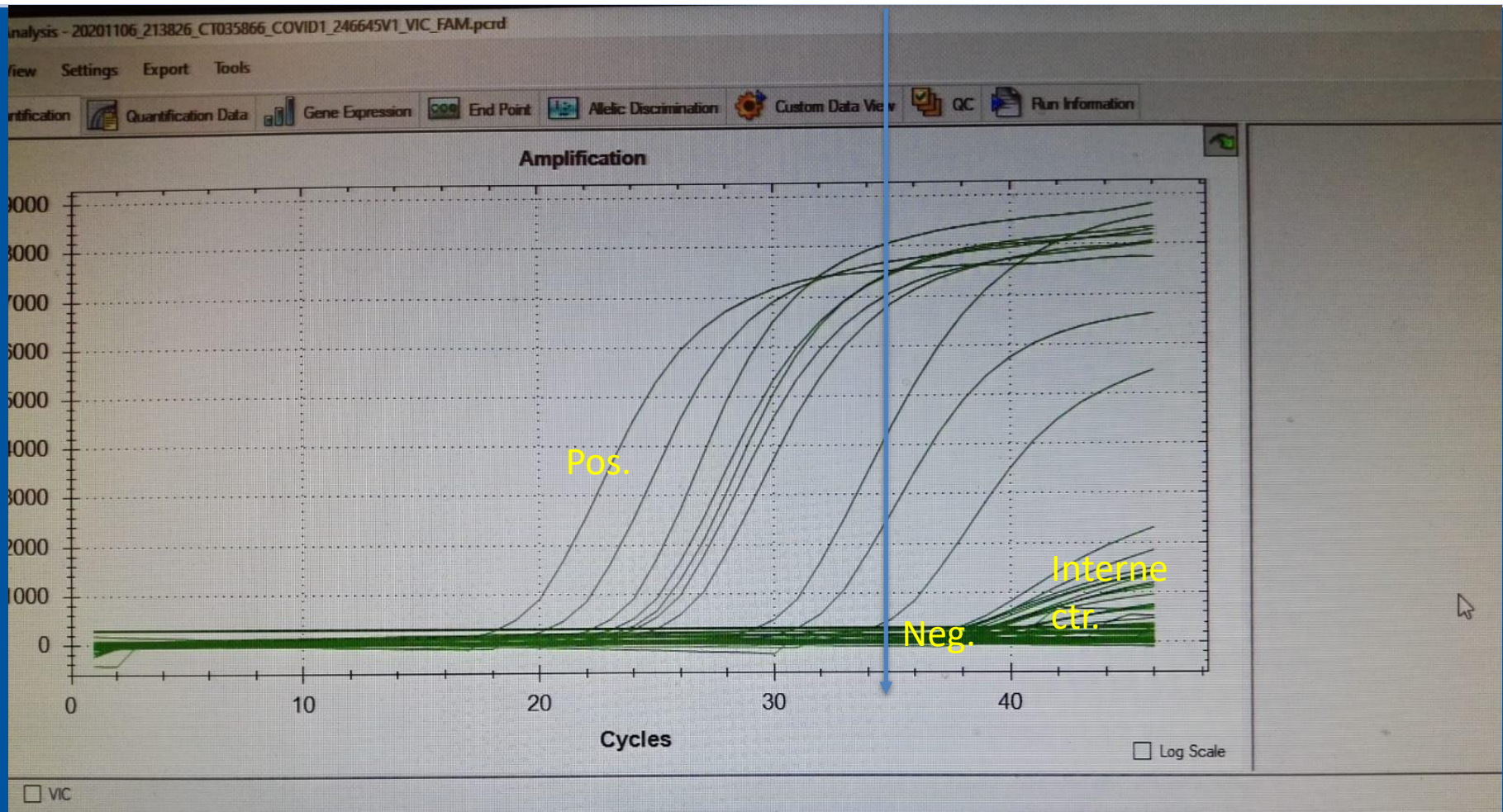
PCR => Amplification

Zelfs een kleine hoeveelheid materiaal kan zo worden gedetecteerd



- Meestal 45 cycli

PCR uitslag = semi-quantitatief: hoe later de curve hoe minder virus



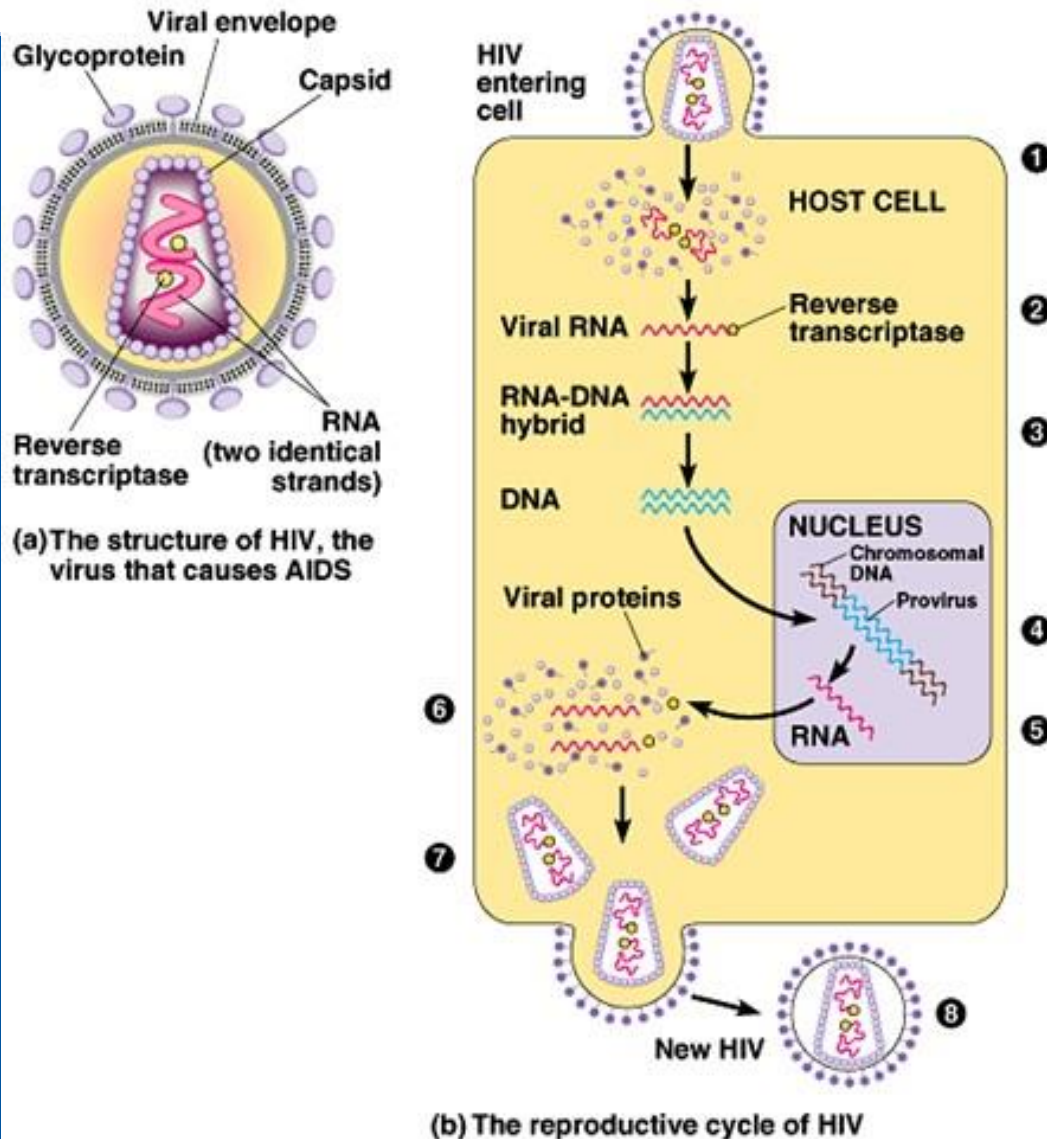
Na 35 cycli nog negatief => negatieve testuitslag.

Tot ~50 virus deeltjes geeft curve bij 35 cycli

⇒ 95% kans dat u niet meer besmettelijk bent voorbij 35

NB Kan nog gevoeliger en uitgebreider, maar dat kost ook meer tijd en geld

Retrovirus, reverse transcriptase: van RNA naar DNA



- Wordt gebruikt als stap voor daadwerkelijke PCR, om van RNA tot DNA te komen
- Bij RNA als input (Corona)

=> RT-PCR

Nederlandstalig celbiologie boek? (Karien)

Bacteriofagen

Cees-Jan: Griep

Statistiek, literatuur en fake news => college 5

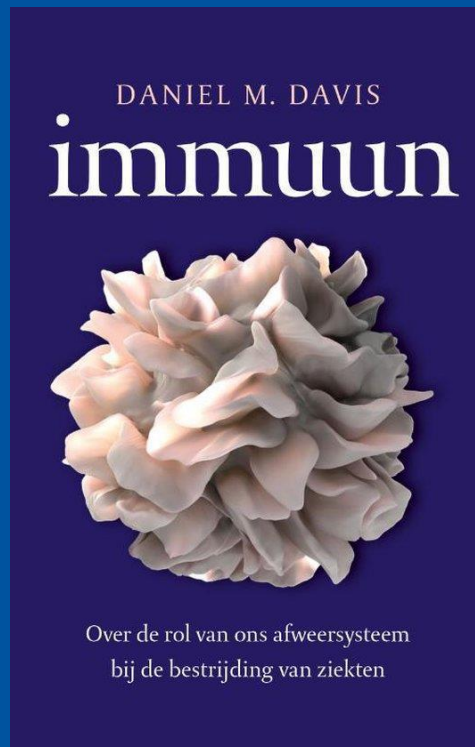
Cees: kwaliteit => college 5

NL Boek

Prof. dr. Jaap van Dissel
Nederlands
Paperback
9789073196919



Daniel Davis
Nederlands (vertaald)
Paperback
9789057125256



Kurzgesagt Bacteriofaag

The Deadliest Being on Planet Earth – The Bacteriophage



Ze zien er ook uit
alsof ze verzonnen zijn.

Our Best Stuff ► ALLES AFSPLEN

New here? Try these.



Why Alien Life Would be our Doom - The Great Filter
Kurzgesagt – In a Nutshell ✓
19 min. weergaven •
3 jaar geleden
Ondertiteling



Optimistisch Nihilisme
Kurzgesagt – In a Nutshell ✓
12 mln. weergaven •
3 jaar geleden
Ondertiteling



Wormgaten uitgelegd - de ruimtetijd breken
Kurzgesagt – In a Nutshell ✓
15 mln. weergaven •
2 jaar geleden
Ondertiteling



Eenzaamheid
Kurzgesagt – In a Nutshell ✓
16 mln. weergaven •
2 jaar geleden
Ondertiteling



De bijwerkingen van inentingen - Hoe hoog is het...
Kurzgesagt – In a Nutshell ✓
10 mln. weergaven •
1 jaar geleden
Ondertiteling

The Existential Crisis Playlist ► ALLES AFSPLEN



How Many People Did Nuclear Energy Kill? Nuclea...
Kurzgesagt – In a Nutshell ✓
4,6 mln. weergaven •
1 maand geleden
Ondertiteling



What If We Nuke the Moon?
Kurzgesagt – In a Nutshell ✓
7,4 mln. weergaven •
2 maanden geleden



What If Earth got Kicked Out of the Solar System? Rogue...
Kurzgesagt – In a Nutshell ✓
7,6 mln. weergaven •
3 maanden geleden
Ondertiteling



Geoengineering: A Horrible Idea We Might Have to Do
Kurzgesagt – In a Nutshell ✓
5 mln. weergaven •
4 maanden geleden
Ondertiteling

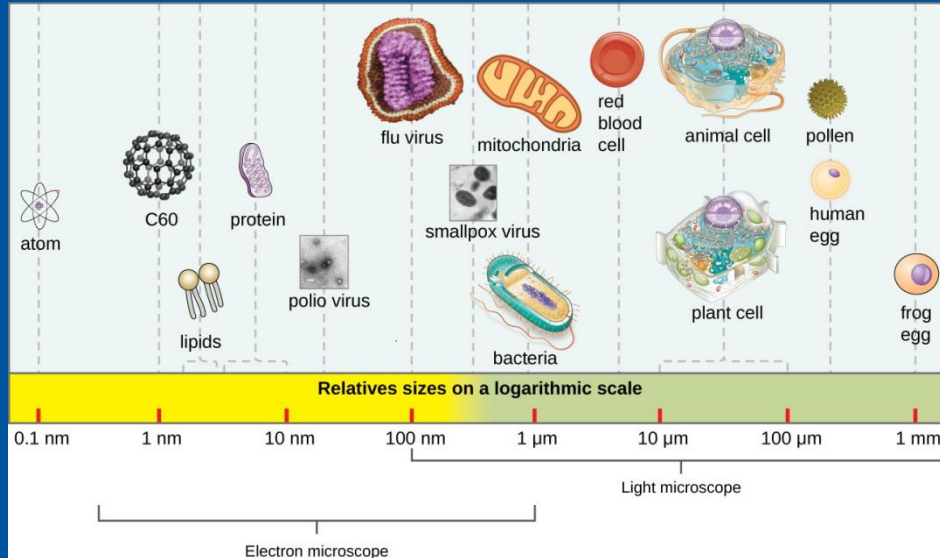


Toen de tijd geschiedenis werd - het menselijke tijdperk
Kurzgesagt – In a Nutshell ✓
5,4 mln. weergaven •
4 maanden geleden
Ondertiteling

<https://www.youtube.com/c/inanutshell>

https://www.youtube.com/watch?v=YI3tsmFsrOg&ab_channel=Kurzgesagt%E2%80%93InaNutshell

Bacteriofagen zijn virussen



Dieren (meestal meercellig)

Planten (vaak meercellig, maar ook algen)

Bacteriën (altijd eencellig)

Virussen (nog kleiner dan bacteriën)

Virussen infecteren dieren, planten en bacteriën (=> bacteriofaag, of phage).

<https://nl.wikipedia.org/wiki/Bacteriofaag>

Om bacteriën te bestrijden worden daarom soms ook bacteriofagen gebruikt

How COVID-19 is changing the cold and flu season

Measures meant to tame the coronavirus pandemic are quashing influenza and most other respiratory diseases, which could have wide-ranging implications.

=> kans!

Despite humanity's long history with colds and flu, the viruses that cause them still hold many mysteries. Scientists hope this year's disrupted seasons could reveal new information about the transmission and behaviour of these unwelcome annual guests: how these viruses respond to health measures, how they interact and what that might mean for long-term disease burdens. "This is a natural experiment for so many respiratory viruses," says Sonja Olsen, an epidemiologist at the National Center for Immunization and Respiratory Diseases, part of the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia.

<https://www.nature.com/articles/d41586-020-03519-3>

Coronabeleid gaf griep de nekslag: nul officiële gevallen

Terwijl de coronapandemie voortwoekert, kreeg de griep deze winter in Nederland geen voet aan de grond. Er zijn precies nul officiële gevallen. Volgens experts toont dat aan dat ook griepdoden met maatregelen te voorkomen zijn. Of dat wenselijk is, is een tweede.

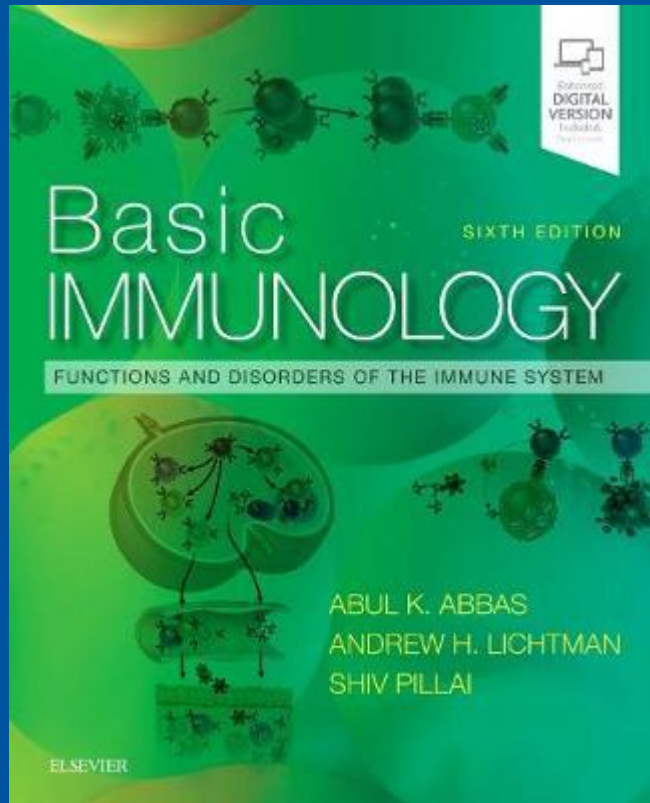
=> Volgende winter extra veel griep?

⇒ Maatregelen om griep te voorkomen (ook 5000 doden per jaar)?

NB Corona is dus besmettelijker, en erger.

Maar, waarom wel maatregelen tegen Corona en niet tegen griep => ethiek.

Volgende week college 5



1. Onderdelen van het afweersysteem
cellen, signaalstoffen, antilichamen
2. Hoe leert het afweersysteem
memory, (RNA-)vaccins
3. Intracellulaire afweer
RNA detectie, PCR (tests)
4. Ziekte en veroudering
virussen en leven => wat maakt corona bijzonder
5. Vragen en ethiek
ingrijpen in het leven

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

<https://youtu.be/7g0fkC3CywM>

Verspreiding al voor je ziek bent

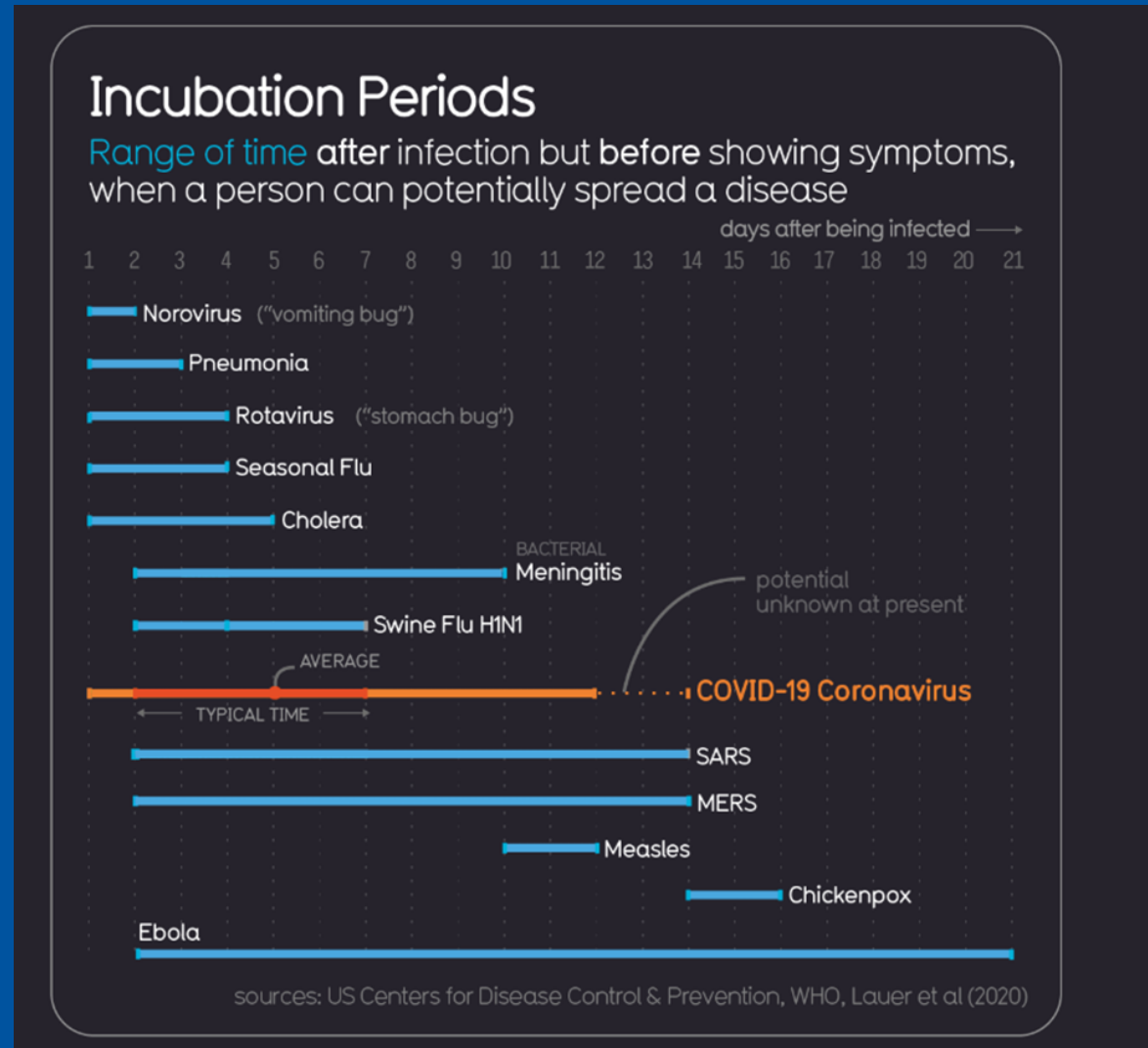
- Corona is ook een probleem omdat dit virus zich al kan verspreiden voor je ziek bent (Interferon respons)

=> Belang mondkapje

=> Het is ook gewoon een gemeen virus

NB Als besmetting optreedt voor ziekte is evt. overlijden niet meer relevant (maar meestal nog besmetting tijdens ziekte)

=> Aanpassing van virus is dan ook niet meer relevant (vraag Koos)



Wat bepaalt de besmettelijkheid?

- Besmettelijkheid gedurende incubatie periode
 - Receptor abundance; ACE komt voor op veel cellen
 - Receptor binding => Britse variant?
 - One preprint manuscript, found N501Y is associated with increased binding of the virus to a receptor found on the surface on many of our cells, called “ACE2”. This could mean the variant is even more efficient at entering our cells.
 - Viral load: Hoeveel deeltjes verspreid iemand, en hoeveel daarvan krijg je binnen.
 - Zonder klachten nauwelijks besmettelijk, maar uiteindelijk komt 60% van de nieuwe besmettingen toch van mensen zonder klachten
 - Superspreaders zijn mensen die veel deeltjes produceren.
 - Superspread events: waar veel mensen bij elkaar komen (waar evt. een superspreader bij is => zangkoren)
 - Sociale superspreader; een “mensen-mens”
- ⇒ Belang mondmasker
- ⇒ Biologische en sociale factoren

Sociale aspecten waar ziekmakers van profiteren:

- Steden
 - Slechte woonomstandigheden
 - Gezelligheid
 - Aanraking => huidhonger
 - Seks
-
- Veel kunnen we tijdelijk beperken, maar niet de hele tijd
 - Net als elke andere impuls (snacks)
-
- **Levensbehoefte.** De vraag breder gesteld: wat doet dat met een primate? Bioloog en **primatoloog Frans de Waal** deed hier onderzoek naar. “Fysiek contact is altijd belangrijk voor de primaten. Ze vlooien elkaar, spelen, zitten vaak tegen elkaar aan,” legt De Waal uit. “We weten ook dat het stresshormoon cortisol daalt en het ‘knuffelhormoon’ oxytocine stijgt als gevolg van contact. Lichamelijk contact wordt dan ook gebruikt in verzoeningen en natuurlijk tussen moeder en kind. Als een jonge aap ergens van schrikt of een ruzie heeft verloren, dan rent ie naar moeder om een tepel in de mond te nemen en tegen haar aan te zitten, hetgeen kalmering brengt.”

The word *quarantine* comes from *quarantena*, meaning "forty days", used in the 14th-15th-century Venetian language and designating the period that all ships were required to be isolated before passengers and crew could go ashore during the Black Death plague epidemic

Pest, kwam ook al uit (centraal) Azie, verspreid via handelaren

An early mention of isolation occurs in the Biblical book of Leviticus, written in the seventh century BC or perhaps earlier, which describes the procedure for separating out infected people to prevent spread of disease under the Mosaic Law:

=> Al belangrijk sinds de landbouwrevolutie en de eerste steden

⇒ virussen, en hun aanpak zijn al lang onderdeel van het leven van mensen

⇒ **Infecties bij de mens gedragen zich nog steeds hetzelfde**

⇒ Verspreid via reizigers

⇒ Stop met reizen, met name vliegen!

⇒ Virussen hebben het nu alleen maar makkelijker.

Ziekmakers en symbiose

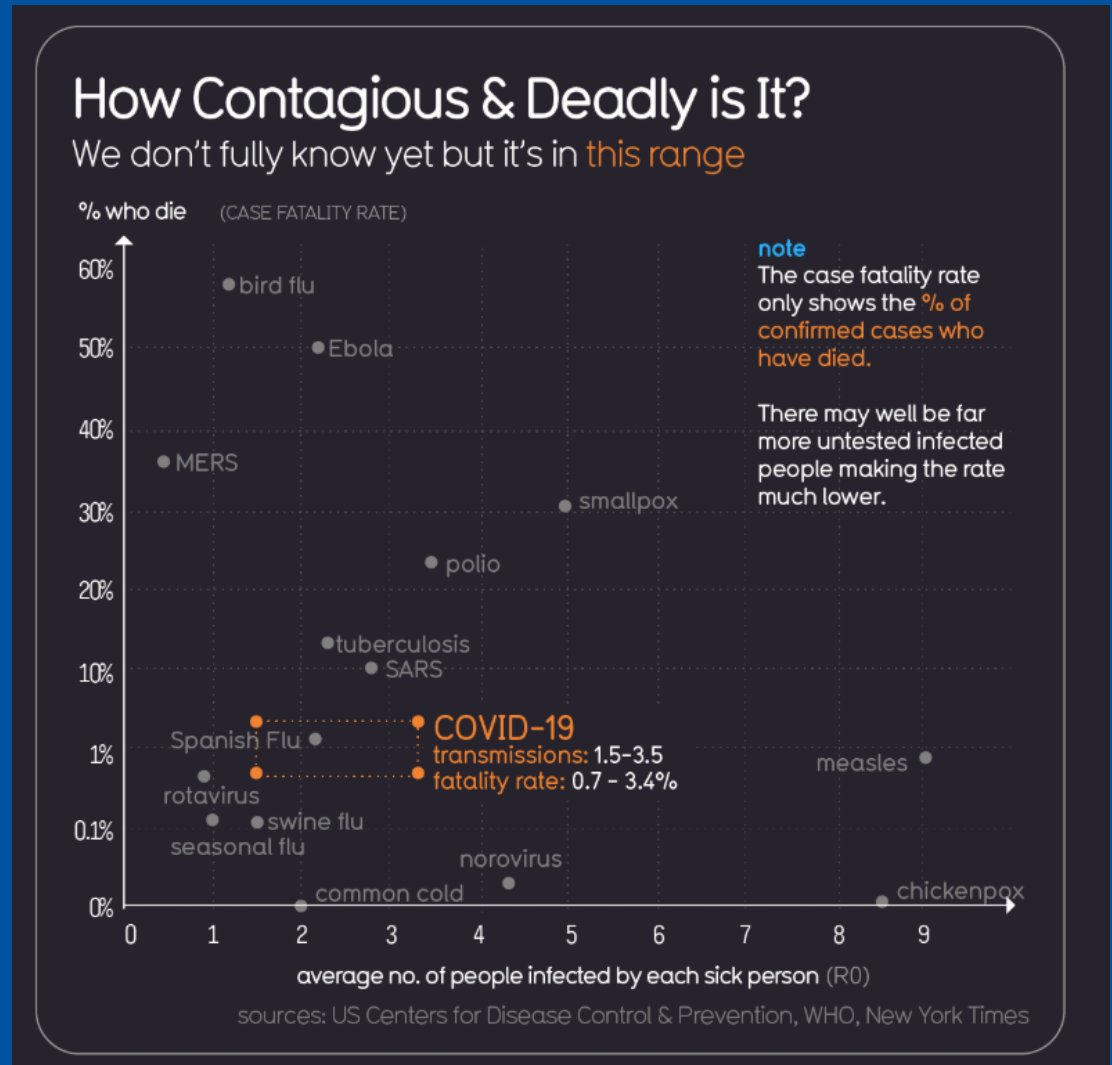
- Ziekmakers zijn de belangrijkste drijver van evolutie.
- Iedereen heeft een eigen repertoire tegen ziekmakers, en er vindt selectie plaats => ziekmaker wordt (meestal) minder virulent.
- Selectie vindt plaats op “grote” gebeurtenissen, als HIV / Ebola.
- Wij zijn de nazaten van mensen die virussen hebben overleefd.
- Al miljarden jaren samenleven ziekmakers en andere organismen !
- In dit systeem zijn individuen uitwisselbaar.

Corona gegevens: Information is beautiful

Hoe besmettelijk is het;
Valt wel mee

⇒ Waarom is de
infectie dan zo'n
groot probleem?

<https://informationisbeautiful.net/visualizations/covid-19-coronavirus-infographic-datapack/>



Virulentie sweet-spot? R_0 veranderd maar niet

Veel ziekmakers passen zich aan aan (nieuwe) gastheer.

Maar Corona zit (al) in sweet-spot van besmettelijkheid en virulentie (hoe ziek wordt je er van, en blijf je in staat virus te verspreiden)?

Tegenargument:, TB, pest en Ebola blijven zeer dodelijk.

The adaptive evolution of virulence: a review of theoretical predictions and empirical tests

Why is it that some parasites cause high levels of host damage (i.e. virulence) whereas others are relatively benign?

The classic expression of parasite fitness, R_0 .

$$R_0 = \frac{\beta S}{\mu + v + \gamma}$$

Parasite fitness is the product of the rate at which new infections are caused by an infected host (βS) and the duration of infection $(\mu + v + \gamma)^{-1}$. In this formulation, β is the transmission rate, S is the density of susceptibles, γ is the rate at which an infected host clears the disease, μ is the background mortality rate and v is the mortality rate due to infection, often referred to as 'virulence'

=> als besmetting optreedt voor ziekte is evt overlijden niet meer relevant

=> vergelijking gaat ook op voor bacteriën schimmels etc.

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

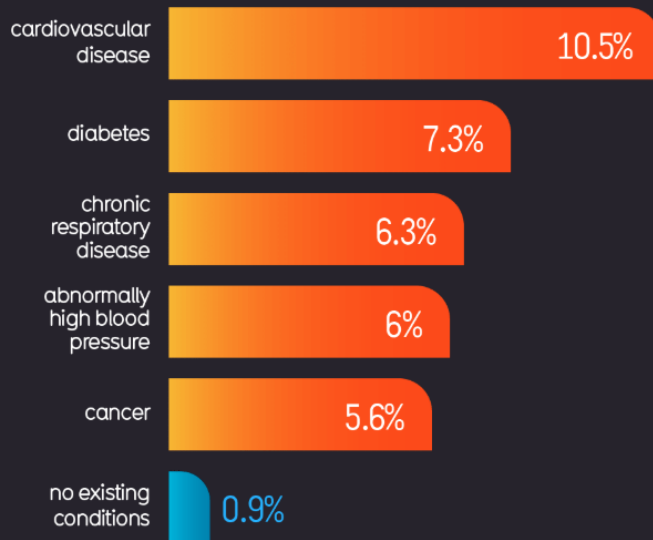
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4873896/>

Corona gegevens: Information is beautiful

99% van de mensen die overlijden hebben onderliggend lijden
=> Niet meer belangrijk voor verspreiding?

Especially Those with Existing Conditions

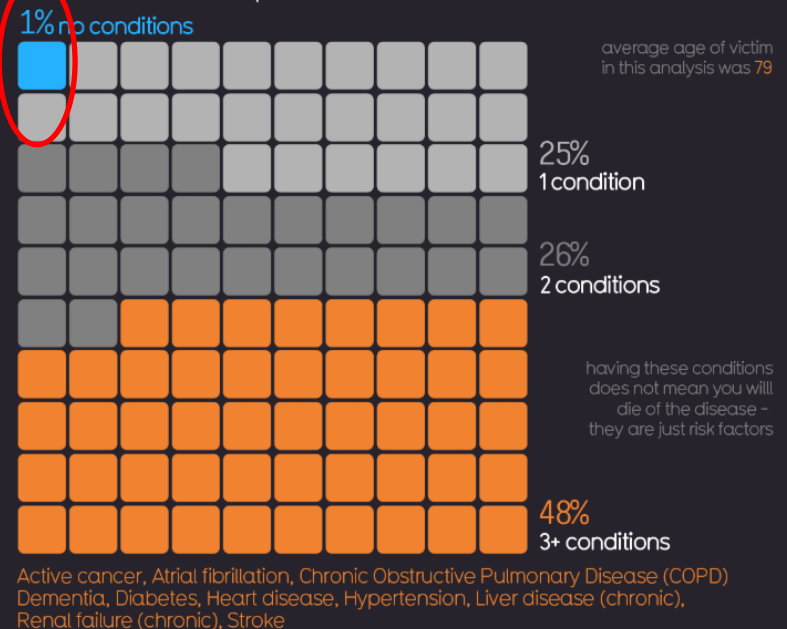
% with other **serious ailments** who die



study of 44,672 confirmed cases in Mainland China
sources: China Center for Disease Control & Prevention, Statista

Multiple Conditions Increase Risk

Serious conditions present in those who have died



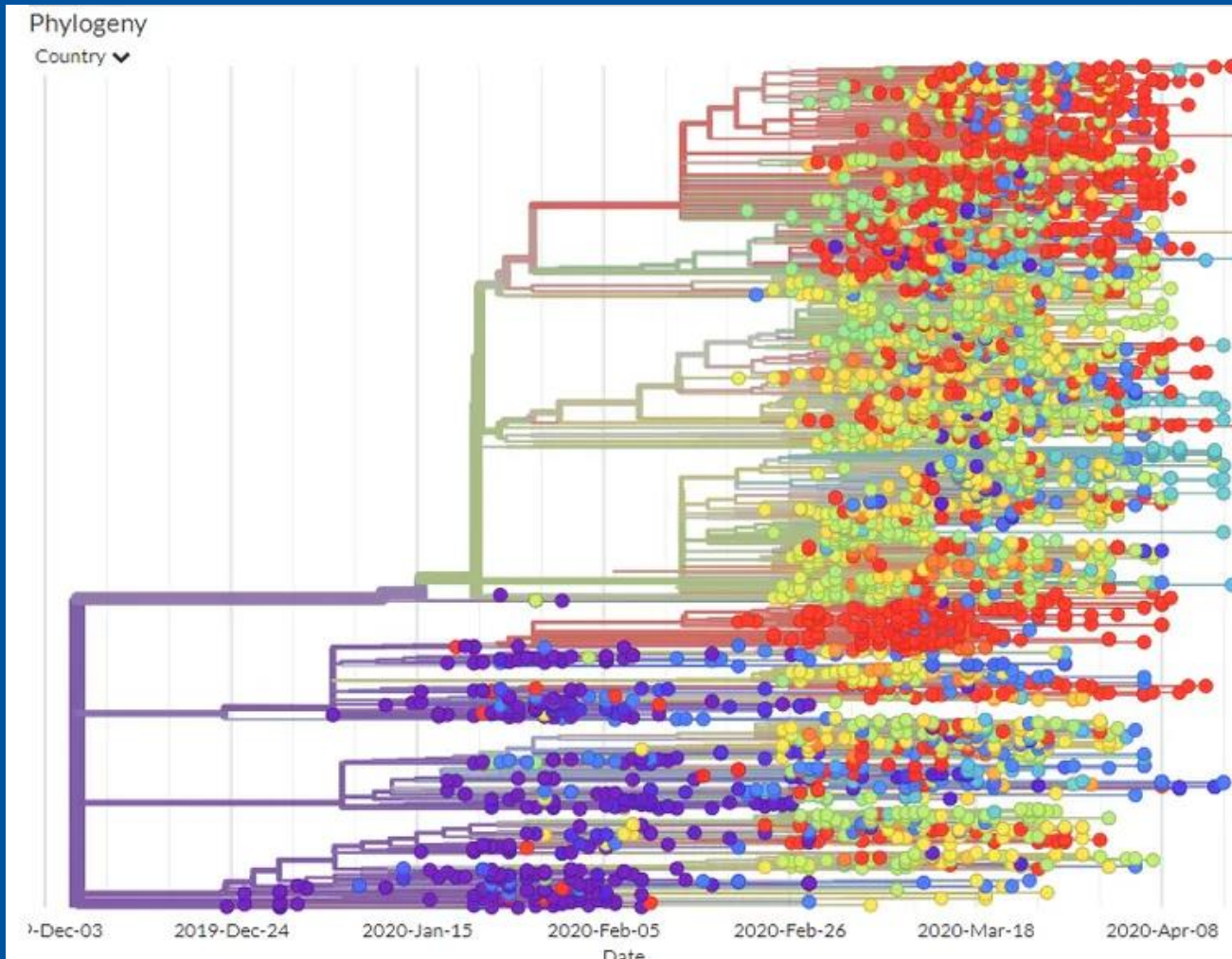
study of 355 deaths from 16,925 confirmed cases in Italy
source: Italian Portal of Epidemiology for Public Health

The emerging plasticity of SARS-CoV-2

- Viruses evolve as a result of mutation (misincorporations, insertions or deletions, and recombination) and natural selection for favorable traits such as more efficient viral replication, transmission, and evasion of host defenses. Newly selected traits may be linked in unpredictable ways and raise concern that virus spread and evolution could result in greater virulence (disease severity).
- Vaccine manufacturers are now testing potential booster vaccines against circulating SARS-CoV-2 variants, and more broadly active monoclonal antibodies are in development for therapy. Such proactive approaches are likely to be needed to ensure pandemic control and elimination.

<https://science.sciencemag.org/content/371/6536/1306>

The coronavirus genome is like a shipping label that lets epidemiologists track where it's been



The analysis of viral genomic sequences will continue to be a valuable tool for tracking and containing the spread of SARS-CoV-2.

For instance, sequencing the genome of a virus from a newly infected patient could tell you if it is a virus that has been circulating in the area for a while, or if it is a new introduction from elsewhere.

<https://theconversation.com/the-coronavirus-genome-is-like-a-shipping-label-that-lets-epidemiologists-track-where-its-been-136826>

Hoe twee dappere virologen de Chinese doofpot (

Reconstructie Hoe reageerde China toen het nieuwe coronavirus daar een jaar geleden de eerste slachtoffers maakte? Er was een breekijzer nodig om het land tot openheid te dwingen.

Op 11 januari 2020, om twee uur 's nachts Nederlandse tijd, post viroloog Eddie Holmes van de University of Sydney de genetische code van 29.903 letters van het virus op de openbare website van virological.org. Die genetische blauwdruk van het virus is ontcijferd door Zhang Yongzhen, een viroloog van de Fudan Universiteit in Shanghai, met wie Holmes al jaren samenwerkt. Tegen de wil van de Chinese overheid in besluiten Zhang en Holmes dat de wereld onmiddellijk moet weten welk nieuwe virus in Wuhan is uitgebroken.

<https://www.nrc.nl/nieuws/2020/12/18/china-een-jaar-geleden-twee-dappere-virologen-omzeilen-de-doofpot-a4024454>

<https://virological.org/t/novel-2019-coronavirus-genome/319>

The emergence of SARS-CoV-2 in Europe and North America

Viral genetic sequence data can provide critical information about whether viruses separated by time and space are likely to be epidemiologically linked.

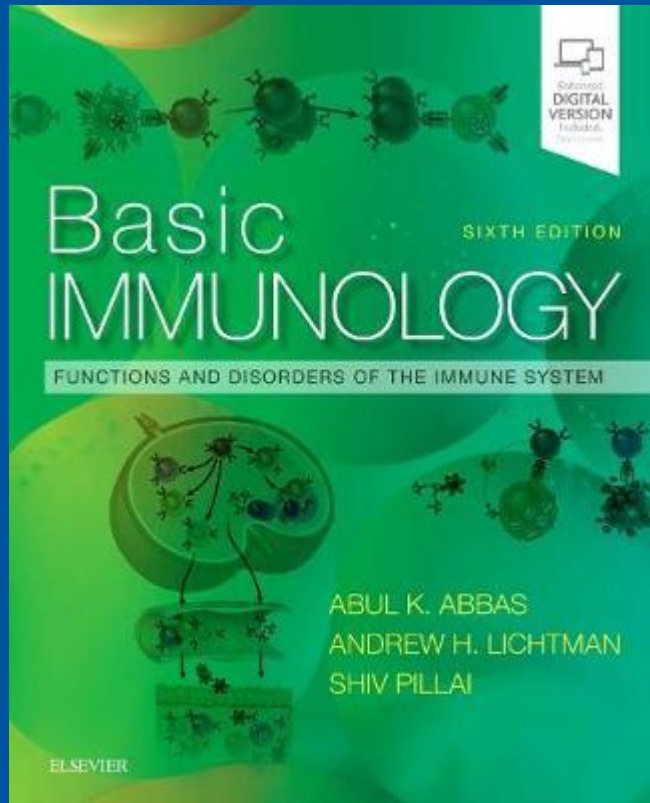
Early introductions into Germany and the west coast of the United States were extinguished by vigorous public health efforts, but these successes were largely unrecognized.

Unfortunately, several major travel events occurred in February, including **repatriations from China**, with lax public health follow-up.

=> KLM zorgde voor de 1^e golf ?

<https://science.sciencemag.org/content/370/6516/564>

Volgende week college 5

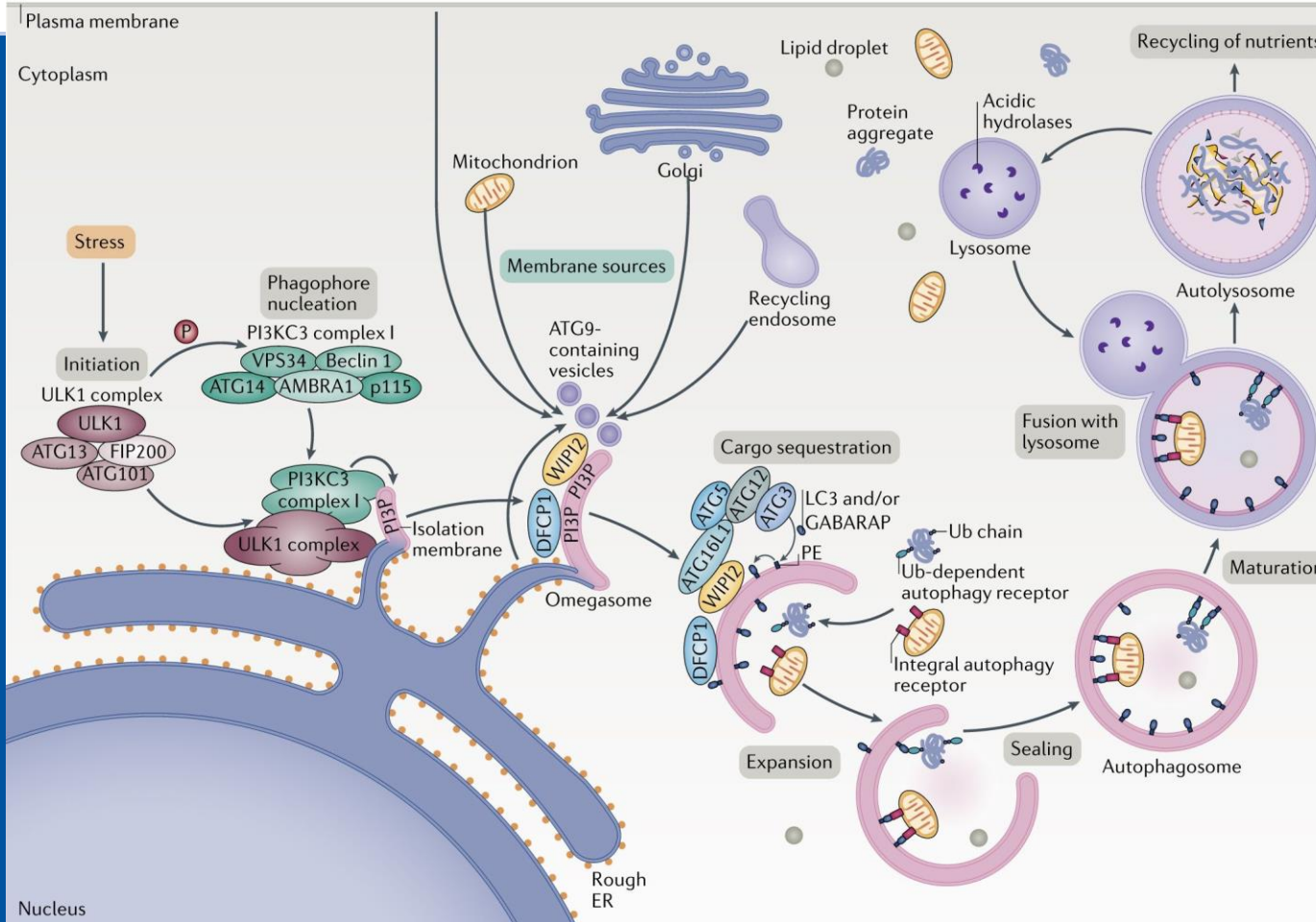


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Boek: Abbas, Basic Immunology.
Aanrader, maar **niet noodzakelijk**

<https://youtu.be/7g0fkC3CywM>

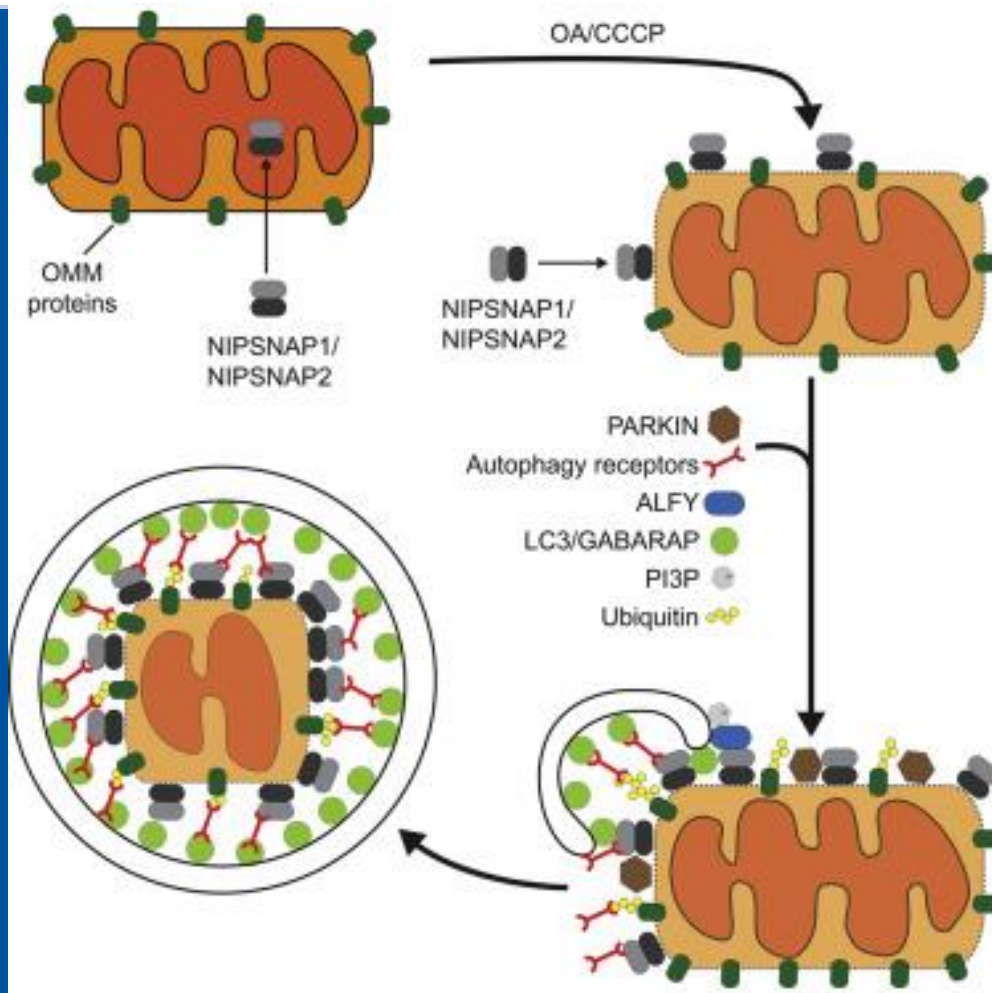
Autophagy



Autophagy (or *autophagocytosis*) is the natural, regulated mechanism of the cell that disassembles unnecessary or dysfunctional components. It allows the orderly degradation and recycling of cellular components.

Foute autophagy
=> Alzheimers?

“Eat Me” Signals for Mitophagy => vgl met fagocytose



The clearance of damaged or dysfunctional mitochondria by selective autophagy (mitophagy) is important for cellular homeostasis and prevention of disease.

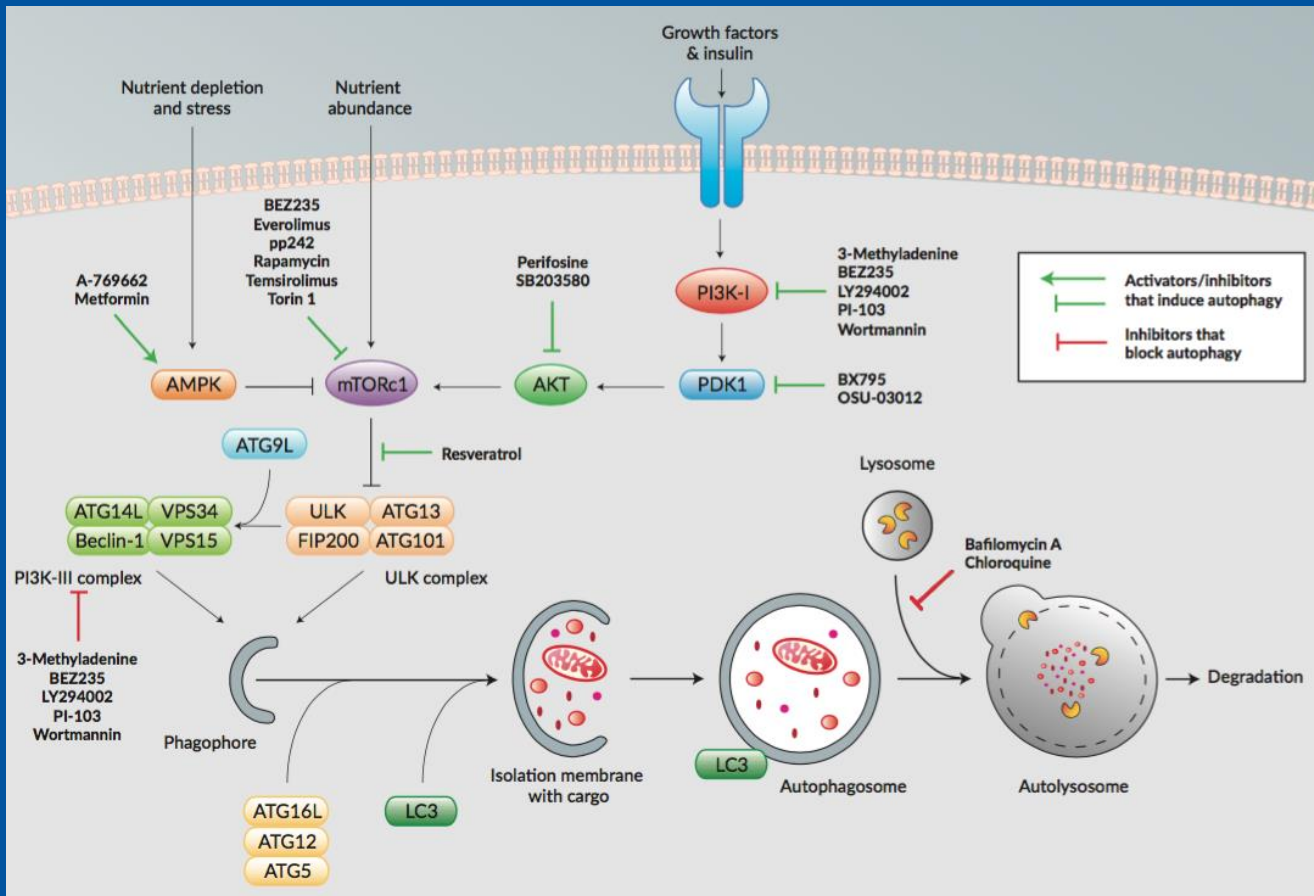
- The mitochondrial matrix proteins NIPSNAP1 and NIPSNAP2 accumulate on the mitochondria surface upon mitochondrial depolarization. There, they recruit proteins involved in selective autophagy, thereby functioning as an “eat me” signal for mitophagy. NIPSNAP1 and NIPSNAP2 have a redundant function in mitophagy and are predominantly expressed in different tissues. Zebrafish lacking a functional Nipsnap1 display reduced mitophagy in the brain and parkinsonian phenotypes.

CD22 blockade restores homeostatic microglial phagocytosis in ageing brains



- Published: 03 April 2019
- **Abstract**
- Microglia maintain homeostasis in the central nervous system through phagocytic clearance of protein aggregates and cellular debris. This function deteriorates during ageing and neurodegenerative disease, concomitant with cognitive decline. However, the mechanisms of impaired microglial homeostatic function and the cognitive effects of restoring this function remain unknown. We combined CRISPR–Cas9 knockout screens with RNA sequencing analysis to discover age-related genetic modifiers of microglial phagocytosis. These screens identified CD22, a canonical B cell receptor, as a negative regulator of phagocytosis that is upregulated on aged microglia. CD22 mediates the anti-phagocytic effect of $\alpha 2,6$ -linked sialic acid, and inhibition of CD22 promotes the clearance of myelin debris, amyloid- β oligomers and α -synuclein fibrils in vivo. Long-term central nervous system delivery of an antibody that blocks CD22 function reprograms microglia towards a homeostatic transcriptional state and improves cognitive function in aged mice. These findings elucidate a

Autophagy, nutrient sensing and longevity



yeasts, worms, flies and mice have demonstrated a broad requirement for autophagy-related genes in lifespan extension.

Selective types of autophagy may be crucial for longevity by specifically targeting dysfunctional cellular components and preventing their accumulation

Inflammaging

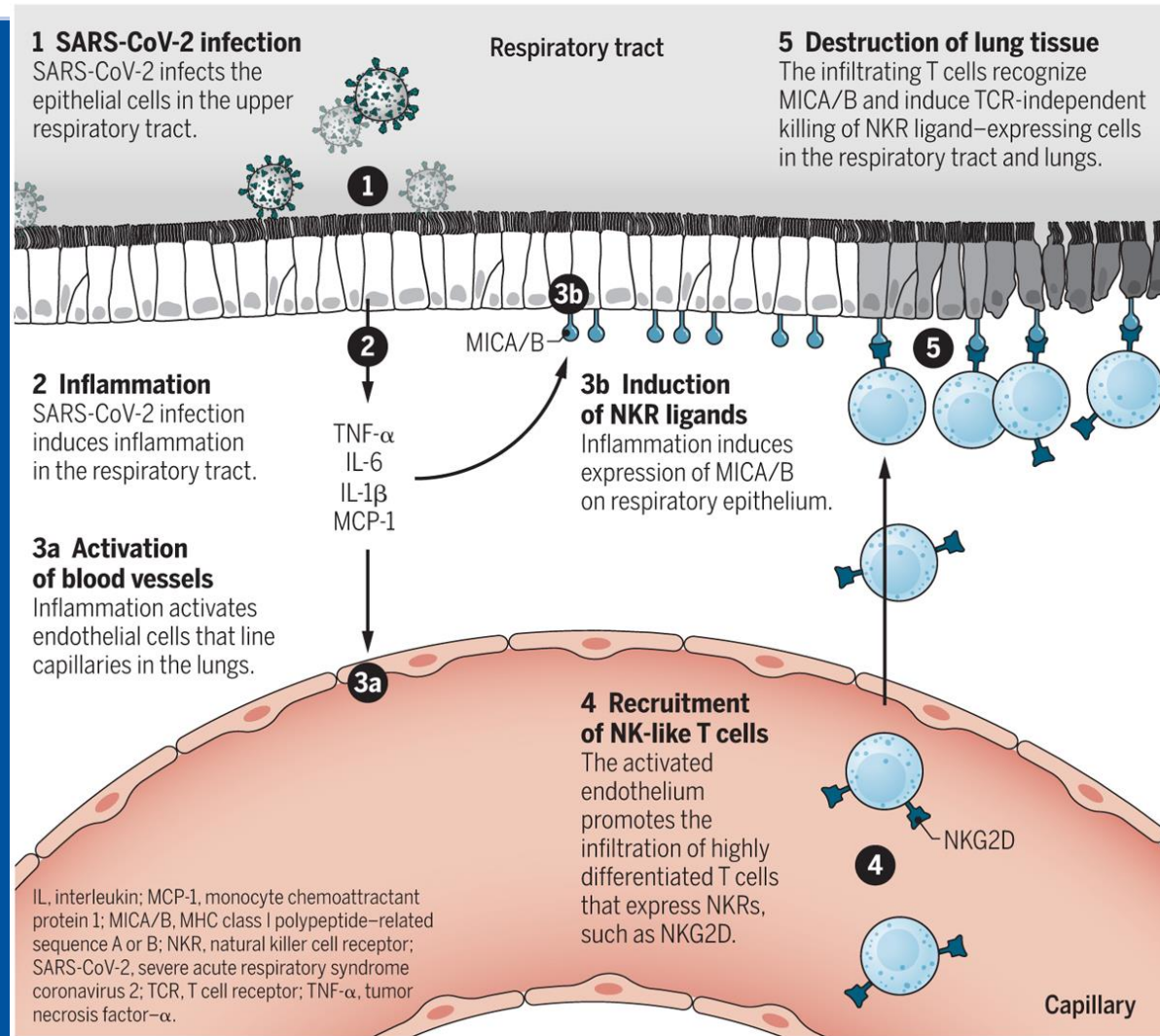
- The immune system declines as aging persists. This drastically affects an individual's adaptive immune system. It causes it to become less effective as the B and T lymphocyte numbers gradually reduce as time passes by. These cells can be seen in the bone marrow, thymus, and the mature lymphocytes found in the secondary lymphoid tissues. This was seen when the elderly were given **vaccinations. They were very much less effective.**
- While effectiveness of adaptive immune system declines, innate immune mechanisms become more active. This is represented by increased number of natural killer cells and increased production of pro-inflammatory cytokines. This chronic activation of innate immune system results in **a low-grade chronic inflammation** development in the elderly.
- Inflammaging is described as a low grade, chronic, controlled and asymptomatic inflammation which occurs in the absence of infection and is primarily driven by endogenous signals. Key molecules associated with inflammaging are elevated pro-inflammatory cytokines, especially **IL-6.**
- This chronic inflamed state has detrimental effect on health and contributes to biological ageing and development of age-related pathologies. Inflammaging was shown to help development and worsen course of Alzheimer's disease, atherosclerosis, **type II diabetes** and chronic heart diseases.

Aging immunity may exacerbate COVID-19

Older healthy individuals (60 years and above) exhibit chronic low-grade sterile inflammation (not caused by a pathogen) characterized by high baseline serum concentrations of C reactive protein (CRP) and cytokines, including interleukin-6 (IL-6), and IL-8. **Inflammaging** may arise as a result of multiple mechanisms, including the accumulation of misfolded proteins, compromised gut barrier function, and obesity (3). Senescent cells, which no longer divide, accumulate in every organ during aging and contribute to increased baseline inflammation

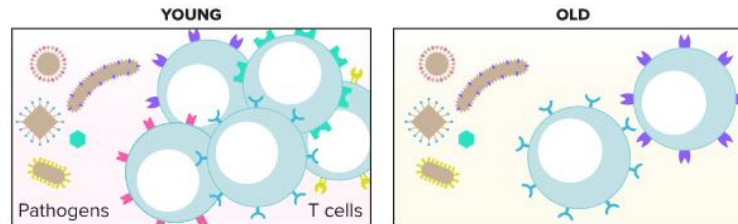
Aged immune responses to SARS-CoV-2 infection

Highly differentiated T cells in older individuals may induce damage in SARS-CoV-2-infected lungs, as hypothesized in the diagram.

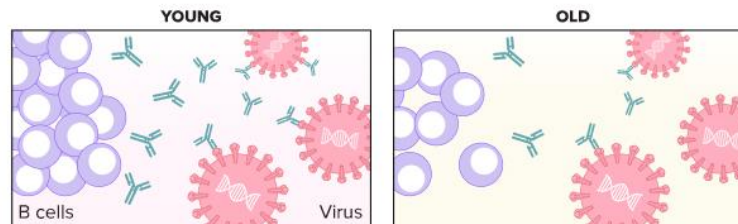


Immunity in the young and old

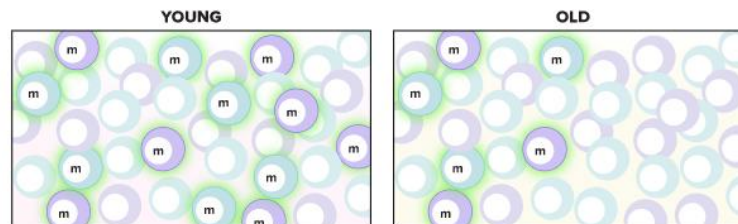
Scientists have discovered a number of specific changes that make an older person's immune system produce a less robust defense against infection or vaccines.



The ability to respond to a wide variety of disease-causing pathogens rests on the diversity of T cells, which carry receptors for specific pathogens. Older adults produce fewer new T cells than the young, which leads to less diversity.



Antibody responses to vaccination or infection are slower and less effective in older adults.



After a new exposure to a pathogen, older adults struggle to generate the long-term memory responses that are crucial to a vaccine's effectiveness or to protection against reinfection.

SOURCE: REPORTING BY J. WOsEN

KNOWABLE MAGAZINE

Afweer heeft
ook last van
veroudering

<https://knowablemagazine.org/article/health-disease/2020/aging-immune-system-and-vaccines>

Na-ijl effecten

Halfwaardetijd cellen

- Rode bloedcel 110 dagen
- Huidcel 21 dagen
- Darm epitheel 2 dagen
- Long epitheelcel 1 jaar

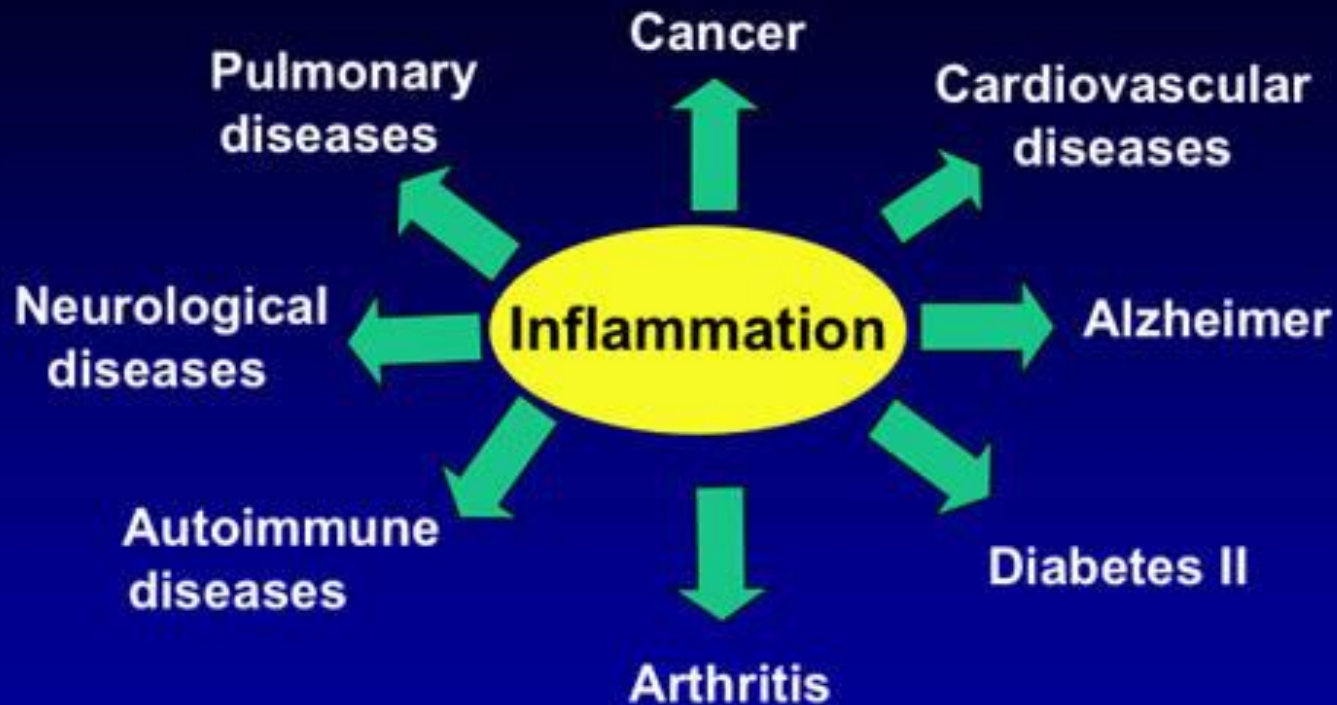
⇒ Vrijwel elke cel in het lichaam is vervangen na ~10 jaar

⇒ schip van Theseus (u bent informatie)

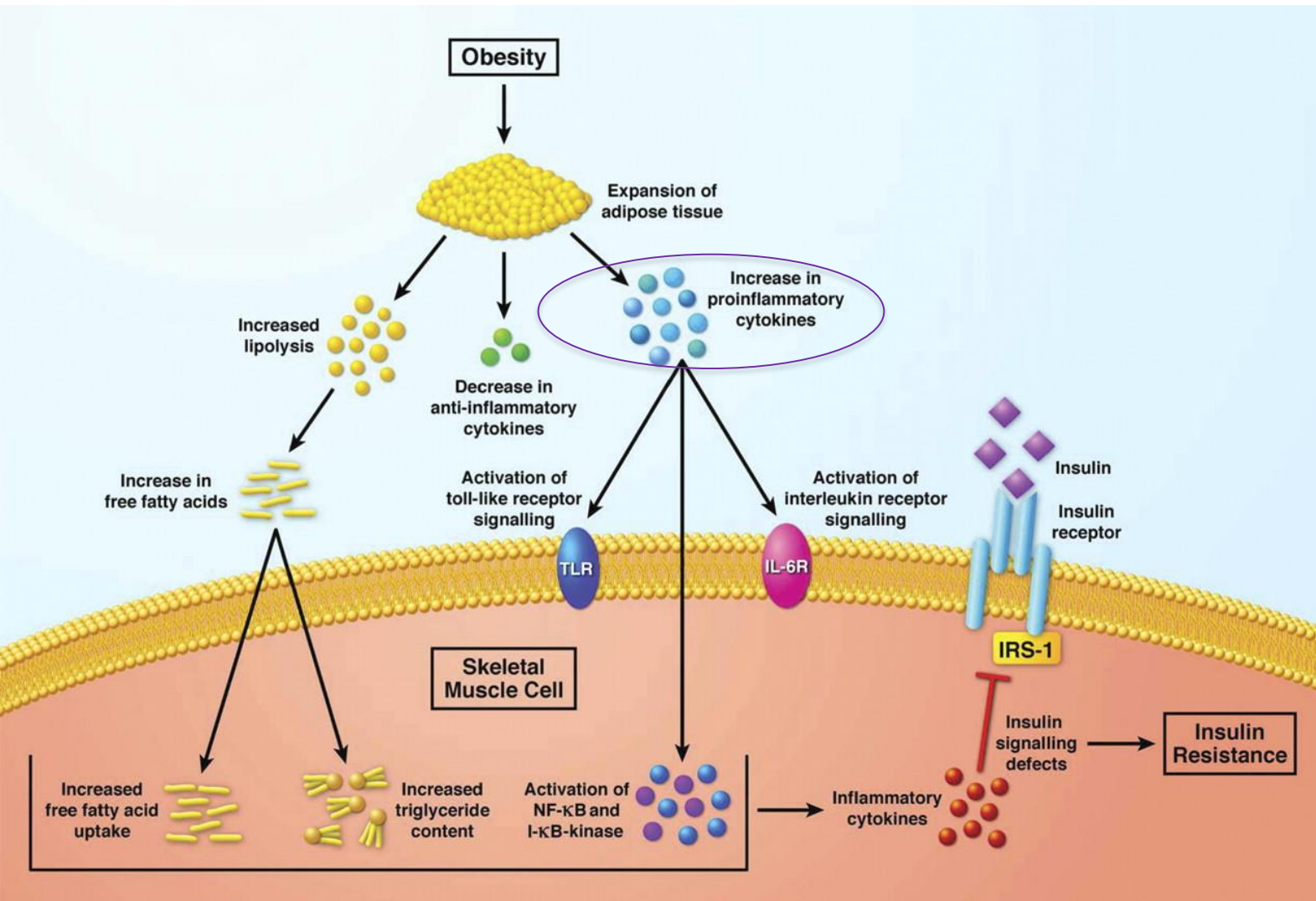
- Stamcellen, 10 jaar => nieuwe cellen en atomen.
- Vervangingsniveau's: atomen, cellen, **individu (nadruk)**, soort
- 70% effectief is heel normaal
- 92% (mRNA) 8% => toch een probleem.
- Jong => was mich nicht umbringt macht mich starker
- Oud => was mich nicht umbringt macht mich swacher

<http://www.uptodate.com/contents/red-blood-cell-survival-normal-values-and-measurement>
<https://www.goodreads.com/quotes/469374-was-mich-nicht-umbringt-macht-mich-st-rker>
https://nl.wikipedia.org/wiki/Schip_van_Theseus

Chronische ontsteking en ziekte



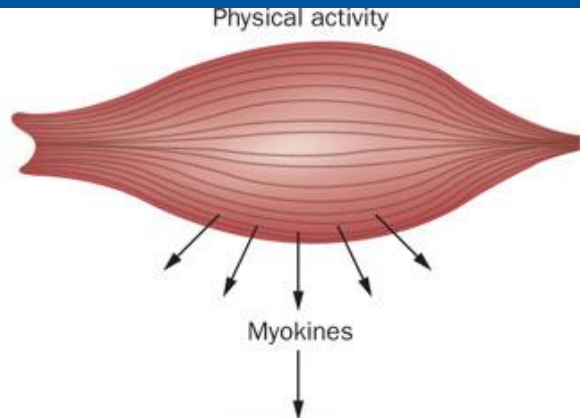
Celbio: Vet verstoord homeostase => Insuline resistentie en verstoorde afweer (chronic inflammation)



Wat we ons
mooie
lichaam
aandoen
met vet (of
roken, of
alcohol etc.)
is veel erger
dan een
vaccin

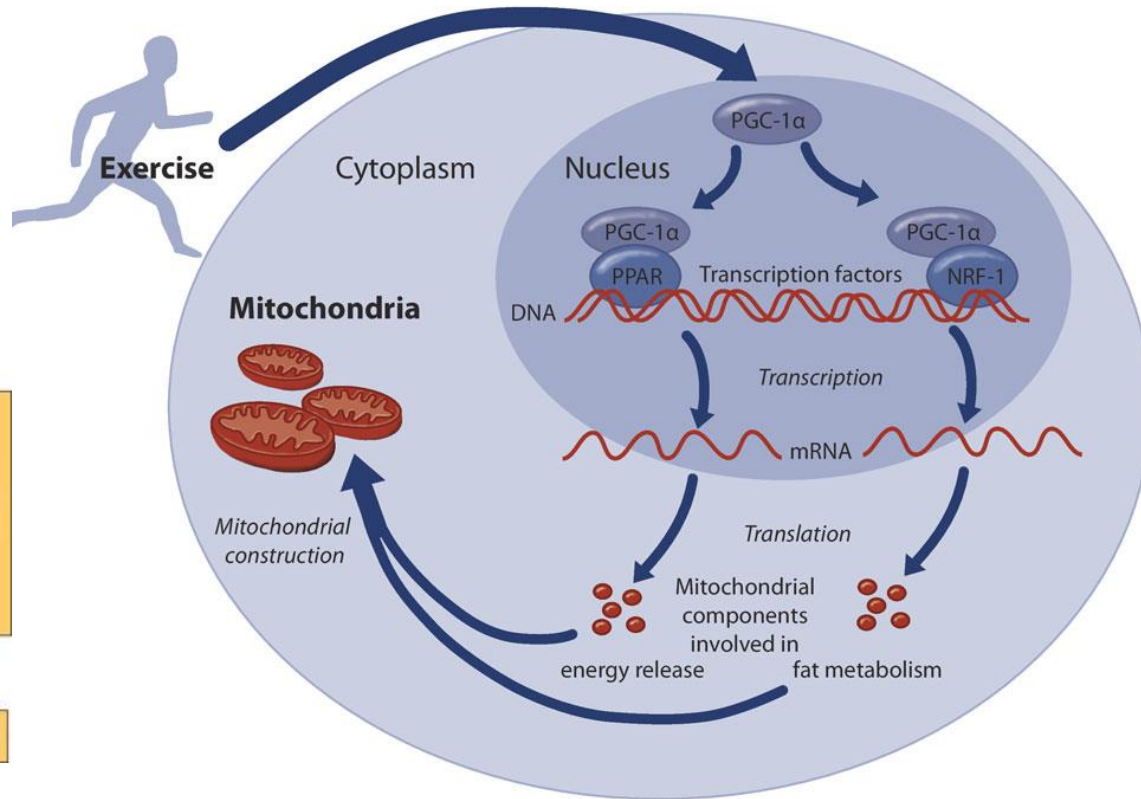
Celbio:

Activiteit, energiehouding en afweer



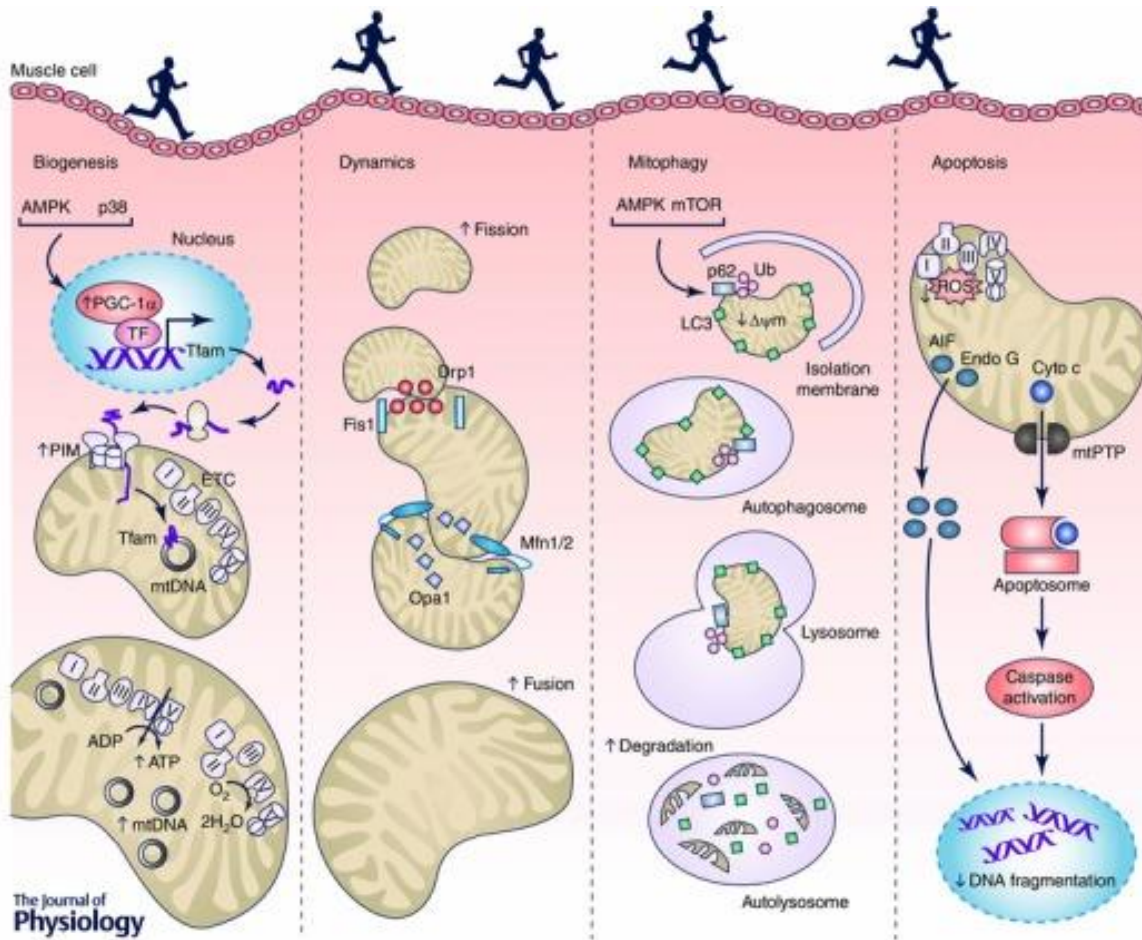
- ↑ Muscle hypertrophy (myostatin, LIF, IL-4, IL-6, IL-7, IL-15)
- ↑ Adipose tissue oxidation (IL-6, BDNF)
- ↑ Insulin sensitivity (IL-6)
- ↑ Osteogenesis (IGF-1, FGF-2)
- ↑ Anti-inflammation (IL-6)
- ↑ Anti-tumour defence (unidentified secreted factor(s))
- ↑ Pancreas function (unidentified secreted factor(s))
- ↑ Browning of fat (Irisin)

Decreased risk of chronic diseases and premature mortality



- 20min bewegen p/d
- Wordt niet gehaald !

Exercise may just be nature's best medicine



- Best example: Bone density increases with exercise
- Muscle and mitochondria (mitophagy)
- And Exercise improves wound healing by improved circulation

⇒ reductions in oxidative stress, and chronic low-grade inflammation?

<https://medlineplus.gov/ency/article/007165.htm>

<https://physoc.onlinelibrary.wiley.com/doi/full/10.1113/JP270659>

- Low grade inflammation as a common pathogenetic denominator in age-related diseases: novel drug targets for anti-ageing strategies and successful ageing achievement.

<http://www.ncbi.nlm.nih.gov/pubmed/20388068>

<http://healthletter.mayoclinic.com/editorial/editorial.cfm/i/163/t/Buzzed%20on%20inflammation/>

- What you can do, though, is make a point to avoid certain things that cause inflammation and are proven unhealthy like smoking, overeating (obesitas), sedentary life stile.
- But also things like treating gum infections.
- Or stress
- And exercise

Exercise generates immune cells in bone

- A specialized type of bone-cell progenitor has been identified in the bone marrow, and shown to support the generation of immune cells called lymphocytes in response to movement.

<https://www.nature.com/articles/d41586-021-00419-y>

Life-span v. Health span

Vroeger werden mensen maar ~35 jaar, door roofdieren, voedseltekort, veroudering en ziekmakers (=> natuurlijke selectie).

Tegenwoordig blijven we langer leven, maar vaak in slechte gezondheid.

=> Rol farmaceutische industrie

=> Heel fijn voor het individu, maar minder goed voor de samenleving

=> Als er dan een ziekmaker langs komt is er ineens een heel grote groep mensen extra vatbaar => crisis

=> **Investeer in gezonde mensen, niet perse in oude**

=> En in gezonde omgang met de natuur

=> Belasting op vet, en suiker (Coca cola, McDonalds) => laten betalen voor (deels) veroorzaken Corona.

=> Profits are private, costs are public (net als bij de kredietcrisis, en CO2-crisis)

Medicalisering van sociaal probleem

Insuline resistentie = lifestyle choice ?



Some scholars go as far as to claim that neither insulin resistance, nor obesity really are metabolic disorders *per se*, but simply adaptive responses to **sustained caloric surplus**, intended to protect bodily organs from lipotoxicity (unsafe levels of lipids in the bloodstream and tissues): "Obesity should therefore not be regarded as a pathology or disease, but rather as the normal, physiologic response to sustained caloric surplus

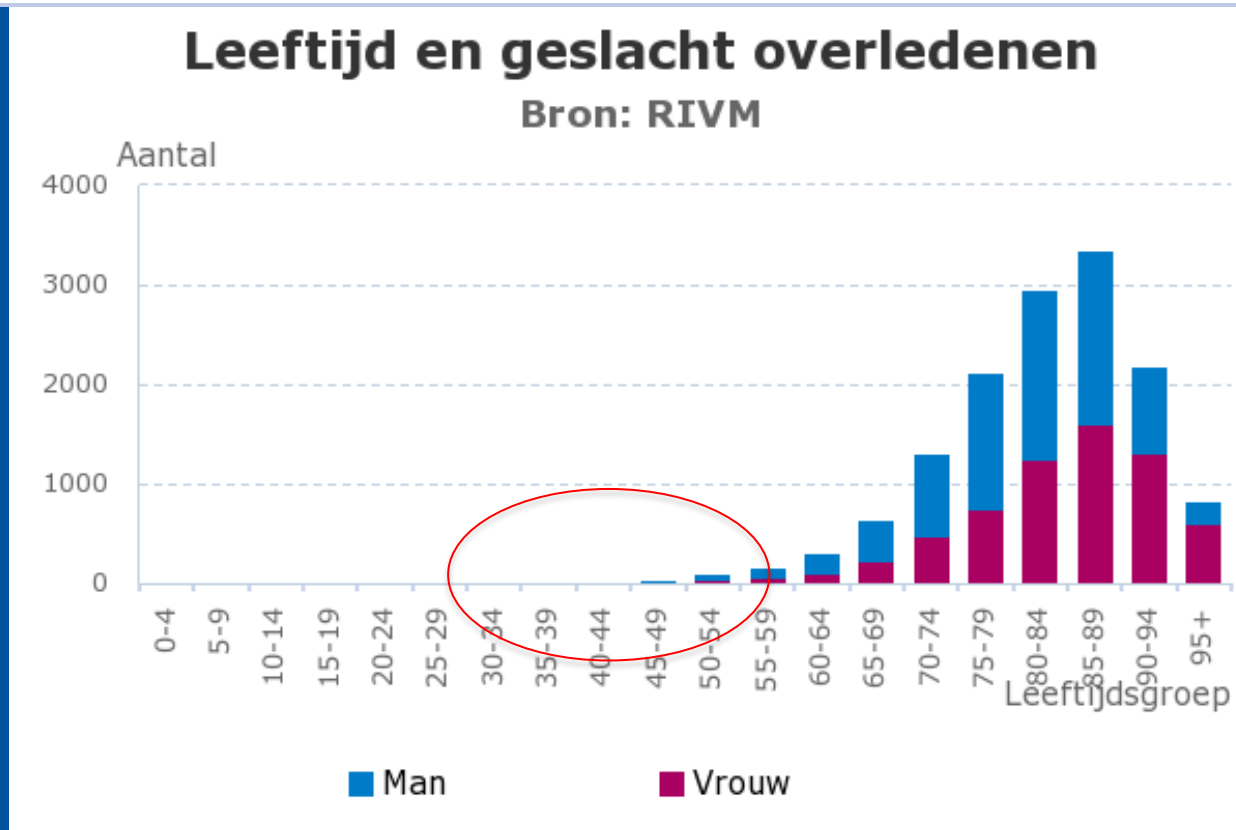
<https://www.youtube.com/watch?v=KY0V3RxwFD8>

Stelling:

Corona is een vervelend virus, maar de problemen zijn vooral maatschappelijk.

Meestal geen oorzaak, maar aanleiding van overlijden

Nederlandse data feb.2021



We hebben een relatief oude populatie => toch veel doden.

7 miljoen 50+ => 70.000 doden potentieel (CFR 1,0)

=> CFR is voor de gehele populatie, ligt voor ouderen 2x hoger

=> **140.000 doden?**

NB verspreiding vooral via 30-40 jarigen?

NB Binnen zitten is makkelijker als je met pensioen bent.

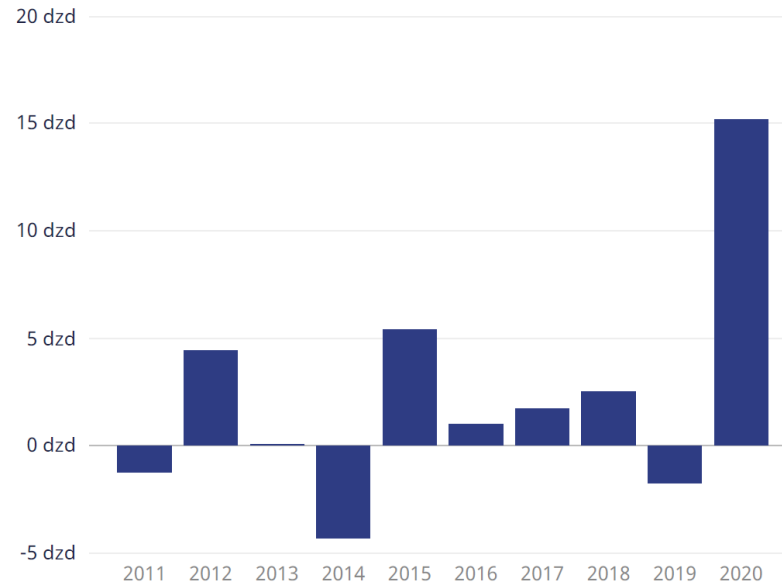
2,6 miljoen Nederlanders zouden besmet zijn geweest

Gegevens van Sanquin helpen inschatten hoeveel mensen werkelijk besmet zijn geraakt. Volgens de laatste stand, van half februari, heeft 15 procent van de donoren het virus gehad. Dat komt neer op 2,6 miljoen mensen, als wordt aangenomen dat een net zo groot deel van de hele bevolking besmet is geweest.

NB Veel mensen ontwikkelen niet eens antilichamen

=> aantal mensen dat corona heeft “gezien” is nog veel hoger

Het aantal personen dat meer is overleden dan verwacht (oversterfte) per jaar (x 1.000) | Negatief cijfer = minder sterfgevallen dan verwacht



Grootste aantal sinds 2^e wereldoorlog.

NB Watersnoodramp 1863 doden => deltaplan

Wat gaan we doen met deze ramp?

=> **Deltaplan gezondheid?**

<https://www.nu.nl/uitleg-over-het-coronavirus/6118920/een-jaar-bevestigd-corona-in-nederland-de-ziektecijfers-op-een-rij.html>

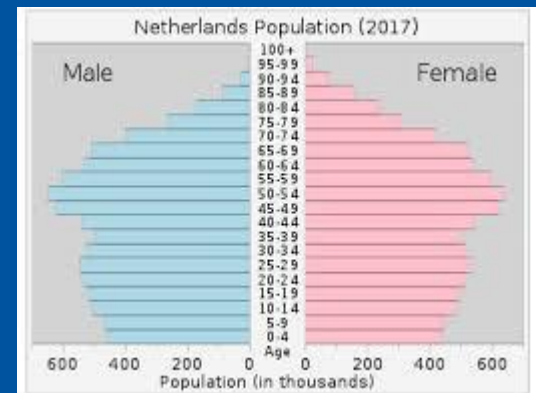
Why did the world's pandemic warning system fail when COVID hit?

- Nearly one year ago, the World Health Organization sounded the alarm about the coronavirus, but was ignored.
- <https://www.nature.com/articles/d41586-021-00162-4>
- The USA's response to the 2014 Ebola outbreak could have informed its COVID-19 response
- <https://www.sciencedirect.com/science/article/pii/S0140673621004335>

Controle van Corona door een landje bij de zee

Early preparedness, contact tracing, isolation and testing, coupled with timely border closure, physical distancing and community adherence, have been key measures in controlling COVID-19 in **Vietnam**.

- ⇒ Effectieve overheid
- ⇒ Meer vertrouwen in de overheid?
- ⇒ Eerdere ervaring met SARS
- ⇒ Andere bevolkingsopbouw



COVID-19 control in Vietnam

<https://www.nature.com/articles/s41590-021-00882-9>

Teveel nadruk op het redden van een individu?

Wat mag een mensenleven kosten?

Stelling: Zodra er een getal is geen chantage mogelijkheden meer door farmaceuten. Dan pas echte concurrentie en dalende ziektekosten ??

At the EPA's \$10 per micromort, it would be worth spending \$100,000 to prevent a single infection with Covid-19.

⇒ Zonder maatregelen 10 miljoen geïnfecteerden

⇒ 10 miljoen x 0,1 miljoen euro = 1 miljard schade = OK

Financial Times

<https://www.ft.com/content/e00120a2-74cd-11ea-ad98-044200cb277f>

Gezondheid levert ook geld op

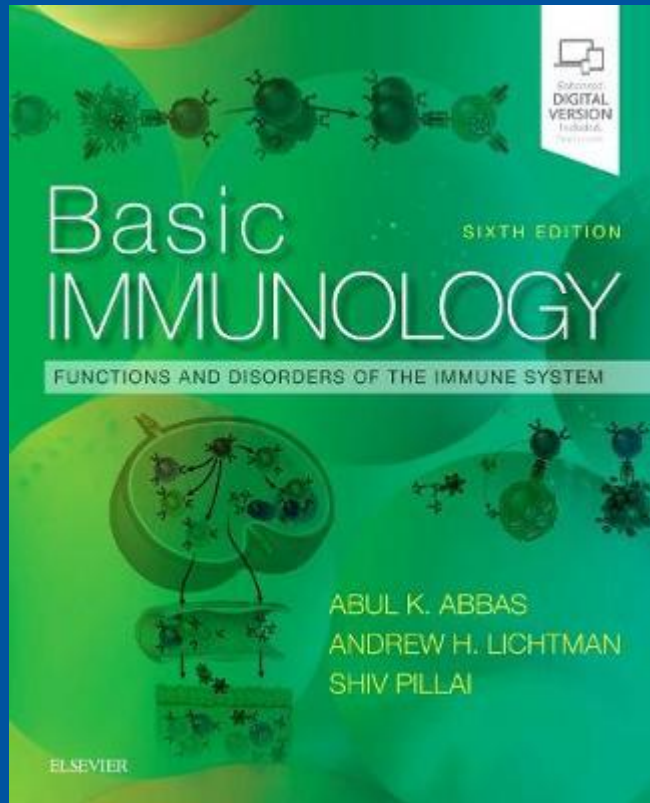
⇒ Investeer daar dan ook in

⇒ Of in ieder geval in bestrijding van virussen

Fossil fuels caused 8.7m deaths globally in 2018

- The 8.7m deaths in 2018 represent a “key contributor to the global burden of mortality and disease”, states the study, which is the result of collaboration between scientists at Harvard University, the University of Birmingham, the University of Leicester and University College London. The death toll exceeds the combined total of people who die globally each year from smoking tobacco plus those who die of malaria.
- Scientists have established links between pervasive air pollution from burning fossil fuels and cases of heart disease, respiratory ailments and even the loss of eyesight. **Without fossil fuel emissions**, the average life expectancy of the world’s population would increase by more than a year, while global economic and **health costs would fall by about \$2.9tn**.
- <https://www.theguardian.com/environment/2021/feb/09/fossil-fuels-pollution-deaths-research>

Volgende week college 5

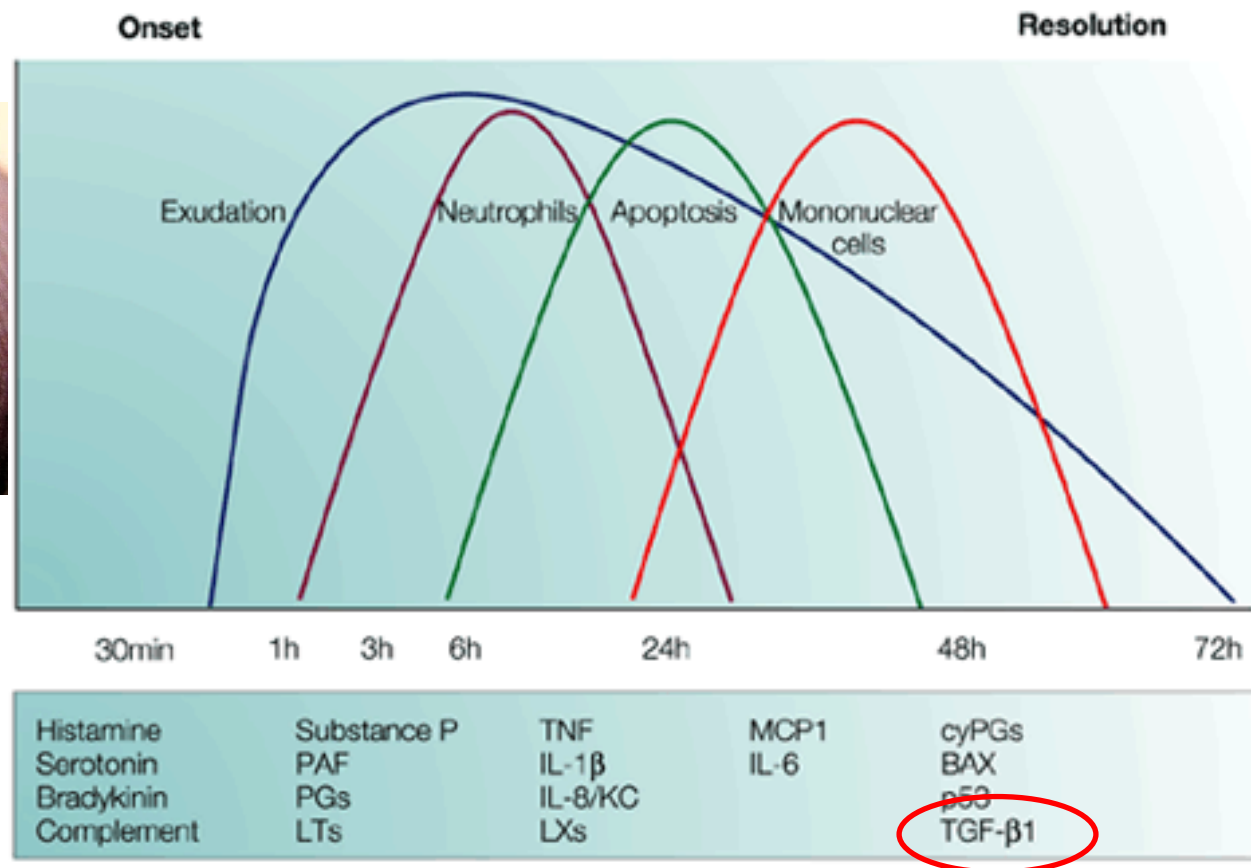


1. Onderdelen van het afweersysteem
cellen, signaalstoffen, antilichamen
2. Hoe leert het afweersysteem
memory, (RNA-)vaccins
3. Intracellulaire afweer
RNA detectie, PCR (tests)
4. Ziekte en veroudering
virussen en leven => wat maakt corona bijzonder
5. Vragen en ethiek
ingrijpen in het leven

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

<https://youtu.be/7g0fkC3CywM>

Ontsteking: Cytokines stimuleren herstel



Nature Reviews | Immunology

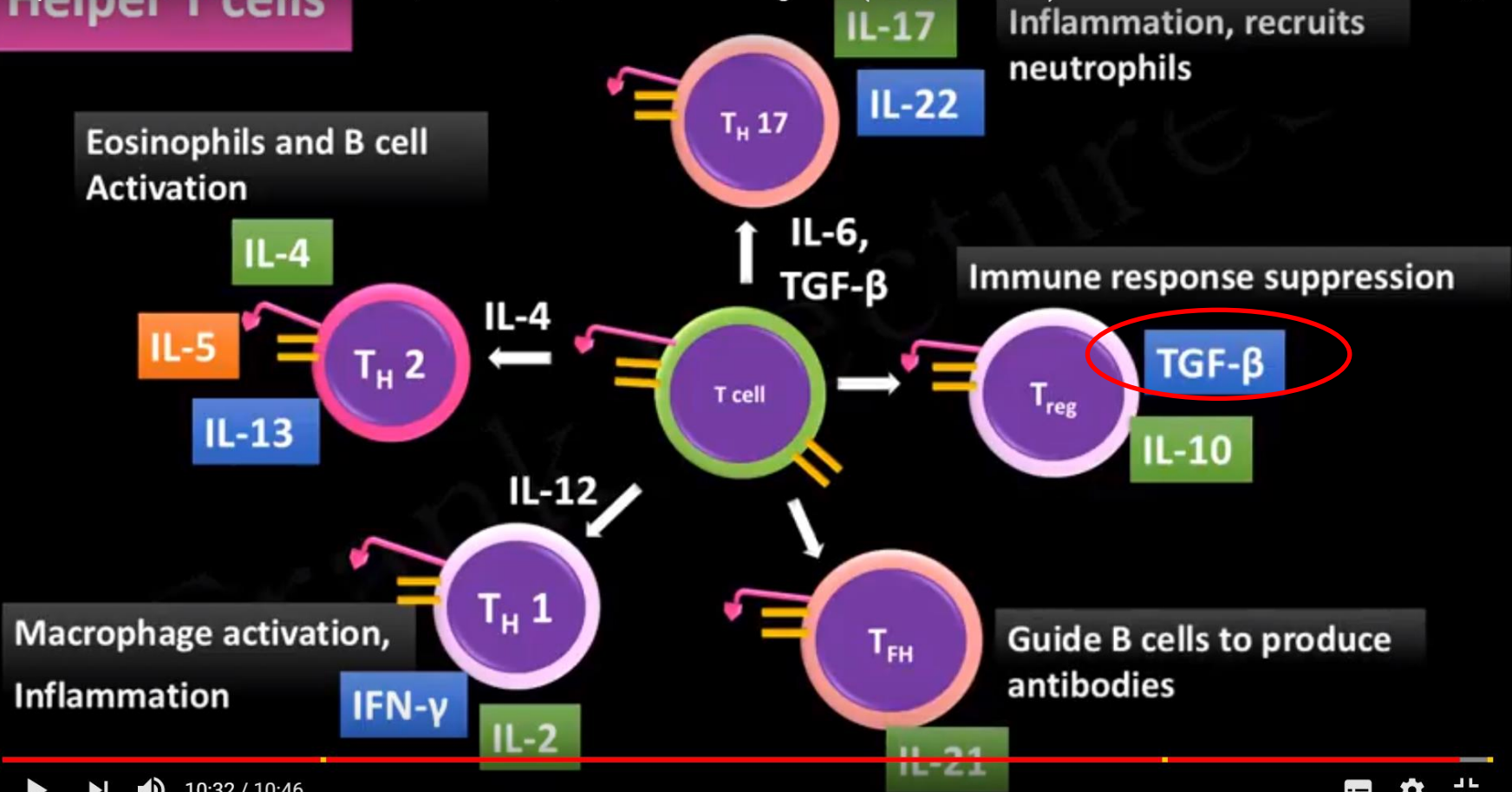
Herstel => stamcellen => differentiatie => epigenetica => miRNA => CRISPR

Thelper

<https://www.youtube.com/watch?v=Qs1H5P0SaLU>

Helper T Cells: TH1 cells, TH2 cells, TH17 cells, TFH cells and Treg cells (FL-Immuno/32)

Helper T cells

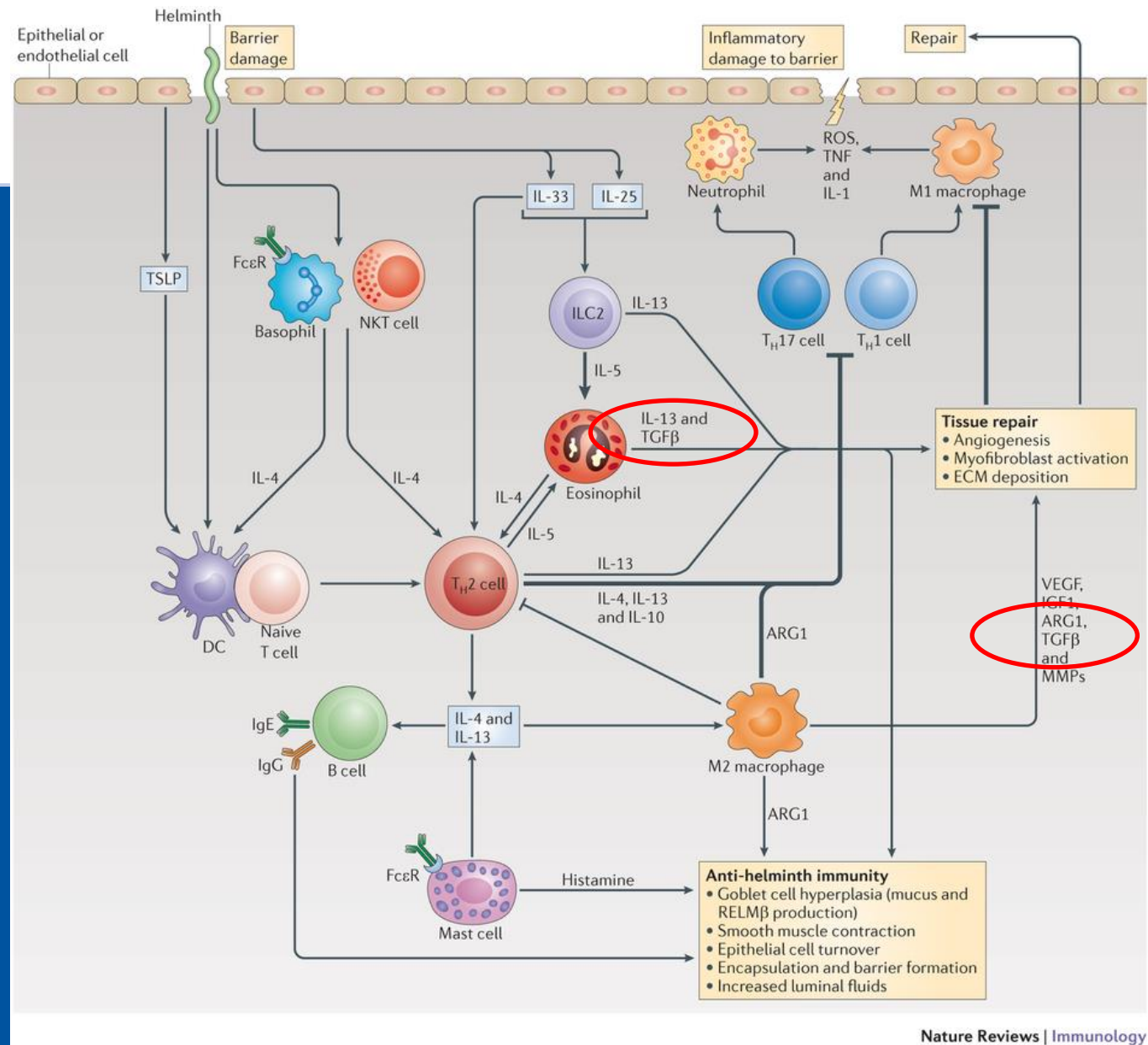


https://www.nature.com/nri/posters/tregcells/nri1001_treg_poster.pdf

Afweer en herstel

Herstel via Treg,
macrofagen,
eosinofielen etc.

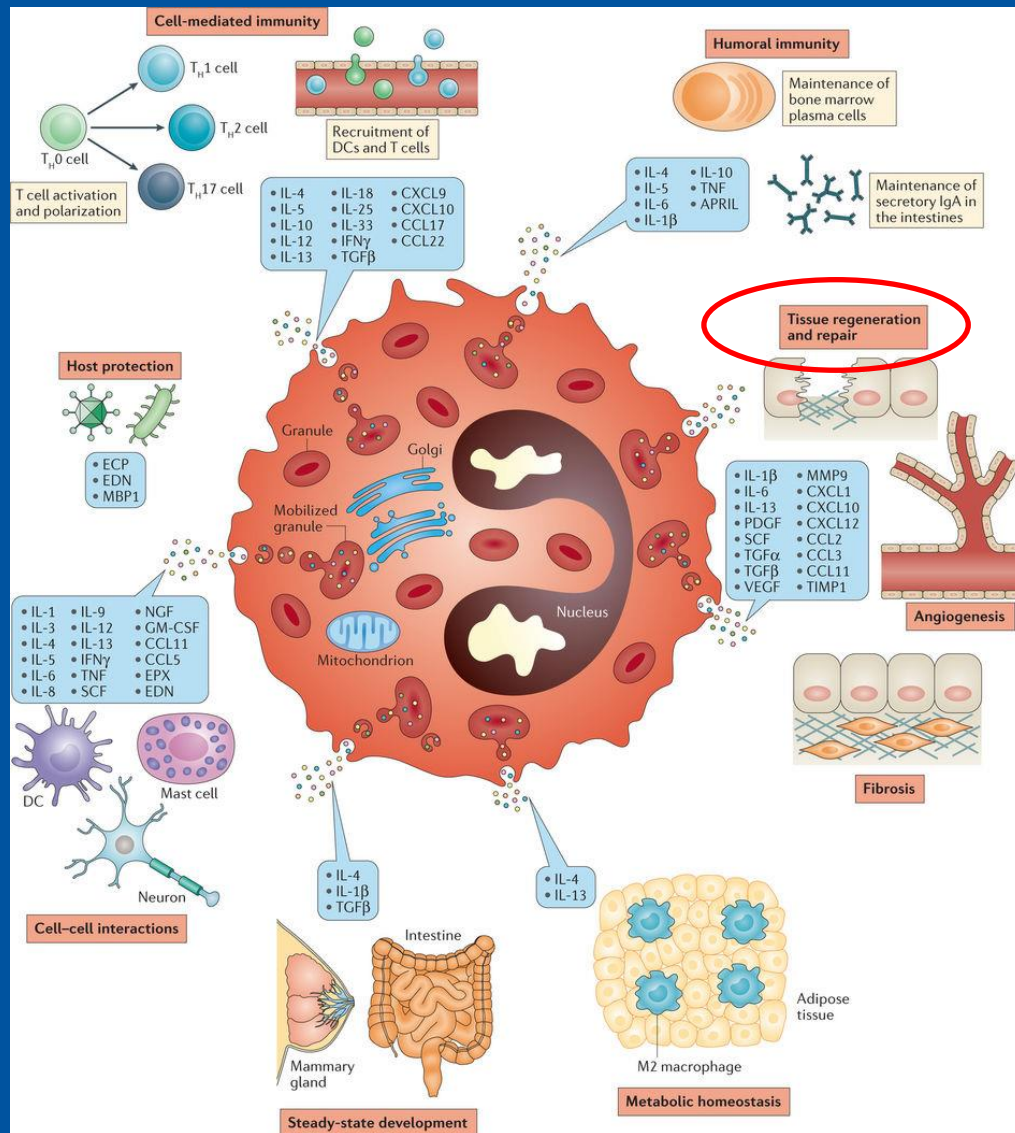
Bij verdwijnen
van infectie =>
omschakeling
van cellen van
pro naar anti-
inflammatoir



Nature Reviews | Immunology

Eosinophils can also be recruited by danger signals released by pathogen infections or tissue injury, inducing host defense against parasitic, fungal, bacterial or viral infection or promoting tissue repair and remodeling.

eosinofiel

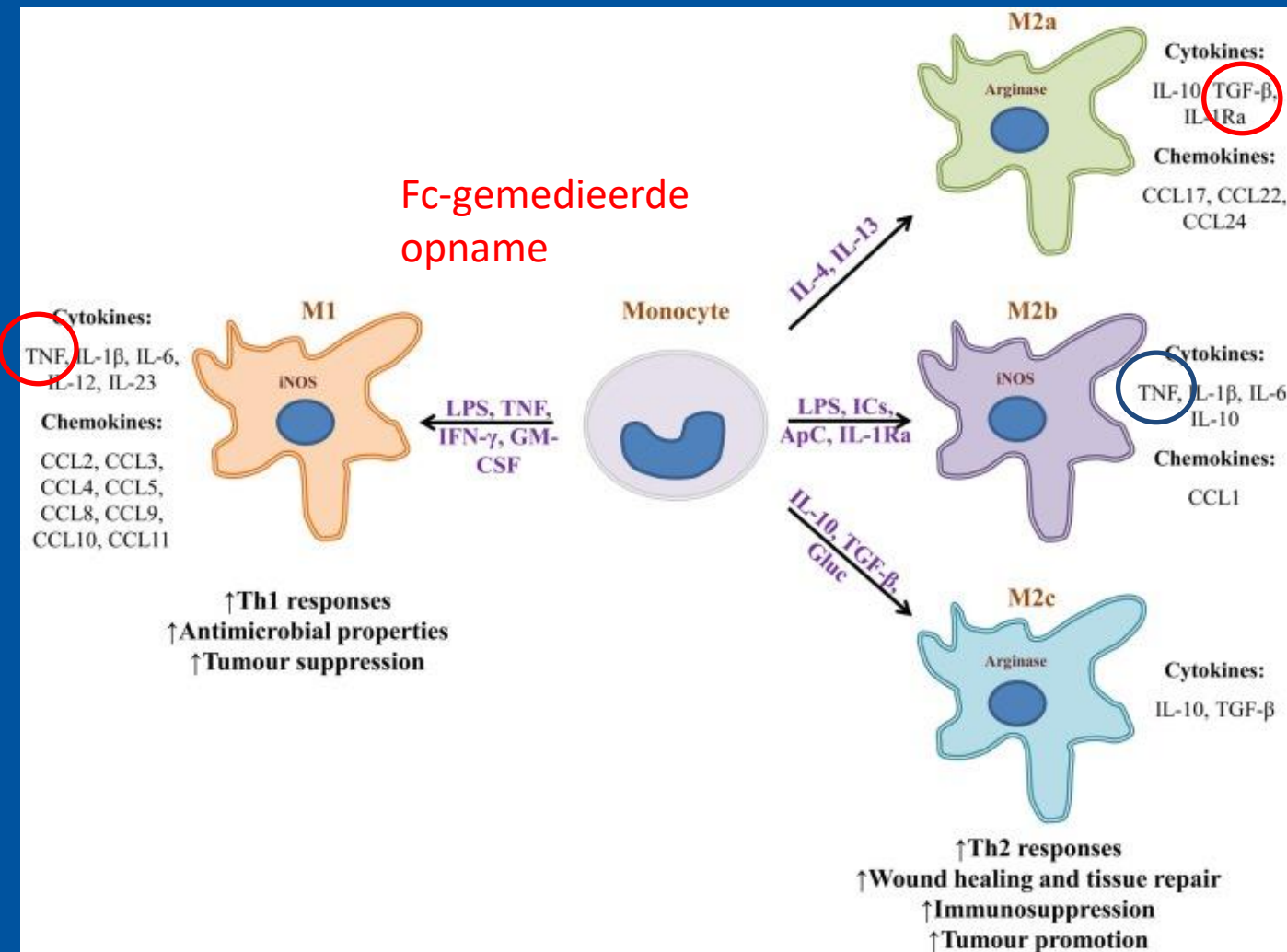


• Lijkt overal bij betrokken
=> immunologie is ingewikkeld

• Origineel bekend van
apecifieke (innate) reactie
tegen beestjes

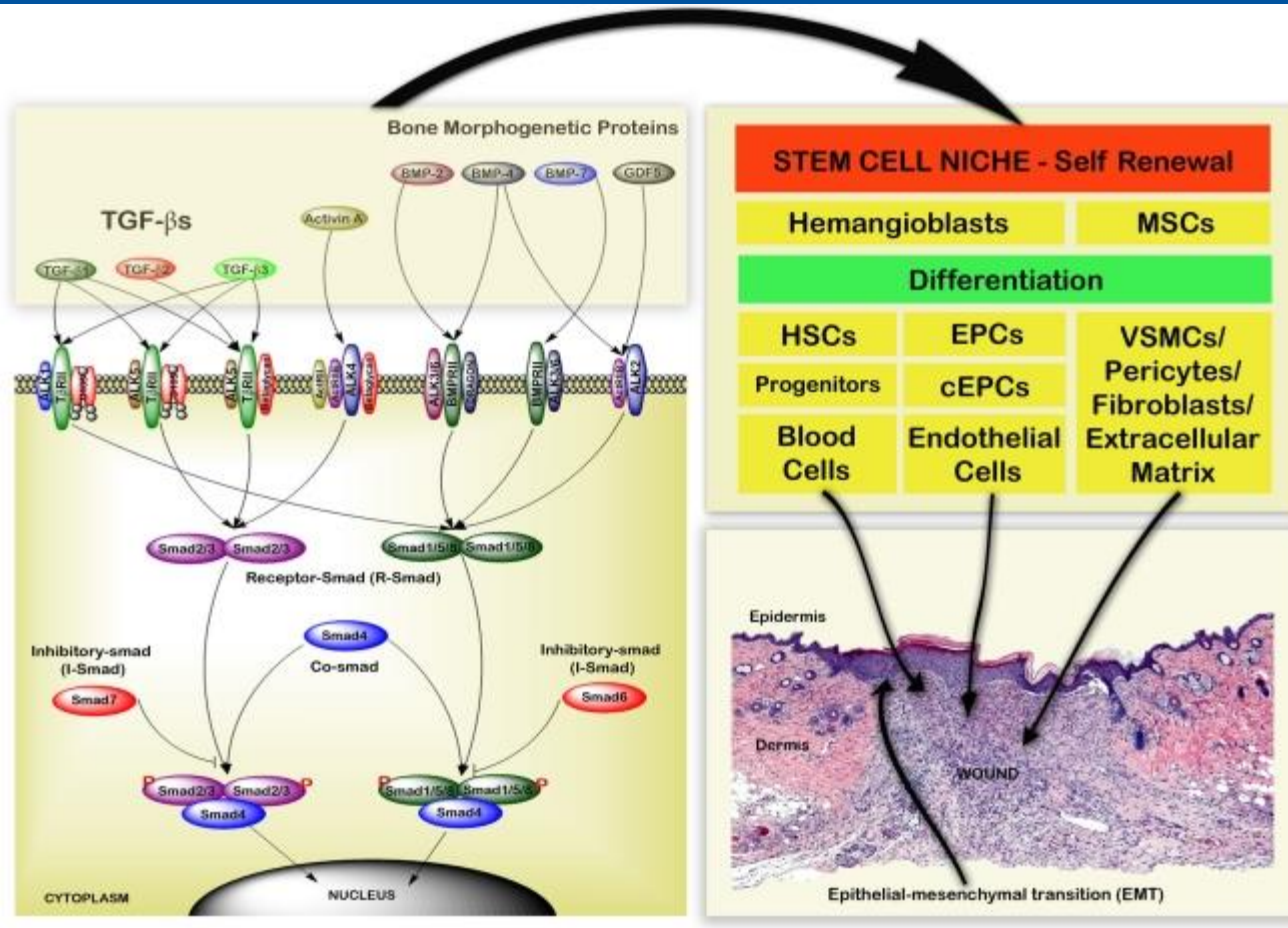
- Netwerk
- Beïnvloedbaar
- Vgl met stamcel

Potentiele cytokineprofielen van macrofagen



Monocytes can become phenotypically distinct macrophages. Upon encountering different stimuli, monocytes turn into highly microbicidal (M1), or into immunosuppressive macrophages (M2). It is important to note that macrophage bias is a spectrum and is reversible. IC, immune complexes; ApC, apoptotic cells; Gluc, glucocorticoids.

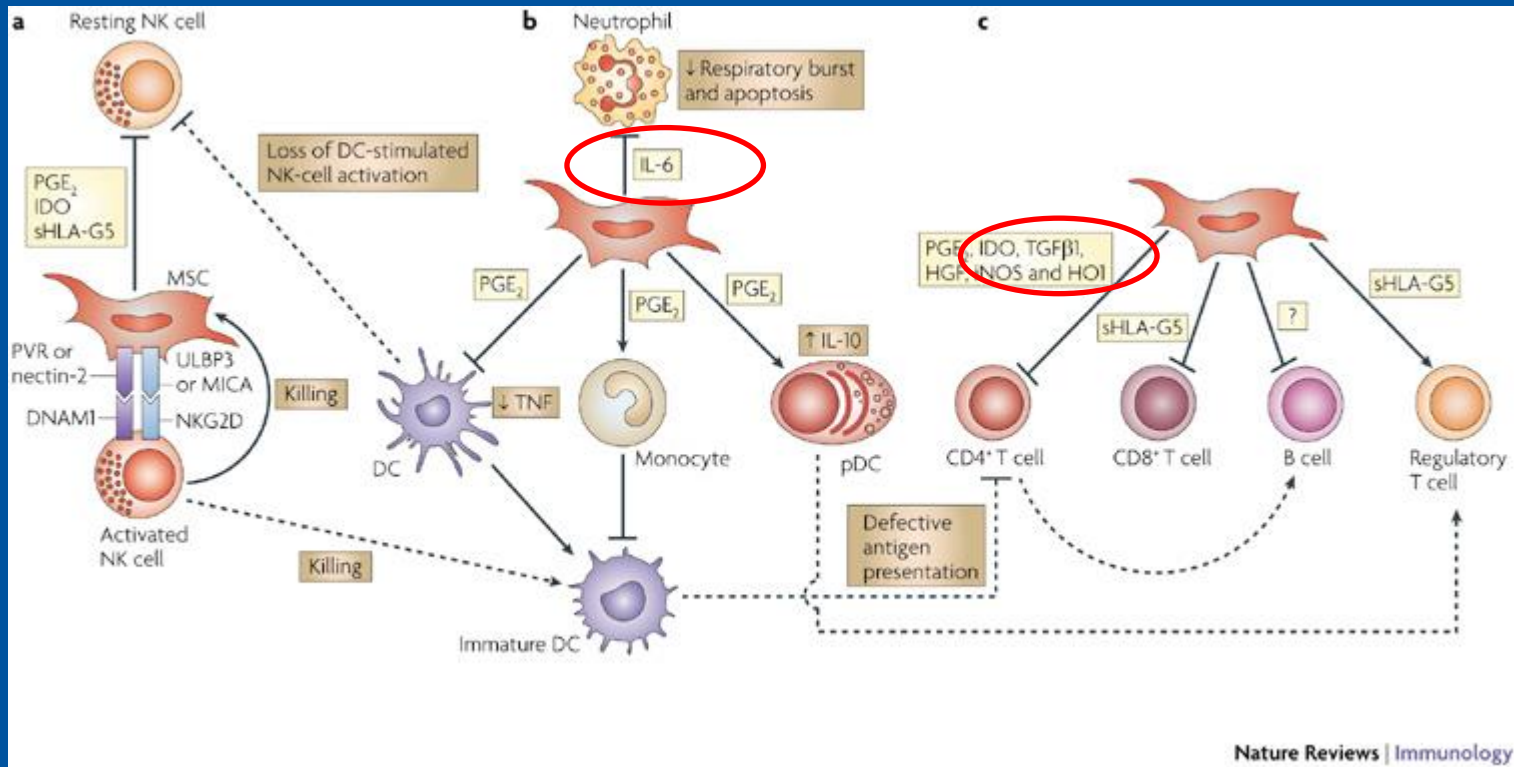
Herstel: TGF- β Signaling in Stem Cell Regulation



The transforming growth factor- β (TGF- β) family of cytokines, including TGF- β , bone morphogenic proteins (BMPs), and activin/nodal, is a group of crucial morphogens in embryonic development, and plays key roles in modulating stem/progenitor cell fate.

Herstel en Afweer (andersom)

- Cytokines van het afweersysteem stimuleren stamcellen
- Stamcellen produceren cytokines met ontstekingsremmende effecten



Nature Reviews | Immunology

=> Aflopen ontsteking en herstel van het weefsel

Immunomodulatory properties of mesenchymal stem cells

- Cytokines and factors such as members of the transforming growth factor superfamily (transforming growth factor- β), hepatic growth factors (HGF), prostaglandin E2 (PGE2), IL-10, indolamine 2,3-dioxygenase (IDO), nitric oxide (NO), heme oxygenase-1 (HO-1), and human leukocyte antigen-G (HLA-G) that are involved in immunomodulatory of MSCs.
- Prostaglandin E2 Indicates Therapeutic Efficacy of Mesenchymal Stem Cells in Experimental Traumatic Brain Injury
=> natuurlijke aspirine

Ontstekingsreactie helpt bevalling op gang

- The glucocorticoid cortisol has anti-inflammatory effects in many tissues of the body. However, in fetal membranes during labor, cortisol is associated with increased activity of the inflammatory enzyme COX-2, which produces prostaglandins that promote reproductive smooth muscle changes in the mother that enable delivery.
- Using primary human amnion fibroblasts from full-term births from patients who delivered after active labor or through nonlabor cesarean sections, Wang *et al.* found that the interaction of the glucocorticoid receptor and the transcription factor STAT3 at the gene encoding COX-2 mediates an autocrine feed-forward loop that amplifies cortisol-triggered prostaglandin production. The findings identify a mechanism linking cortisol to inflammatory prostaglandin production in the amnion.
- <http://stke.sciencemag.org/content/8/400/ra106.abstract>

Celbiologie: COX inhibitie

Medscape®

www.medscape.com

Aspirin: irreversible inhibition of COX-1 and COX-2

Nonspecific NSAIDs: reversible inhibition of COX-1 and COX-2

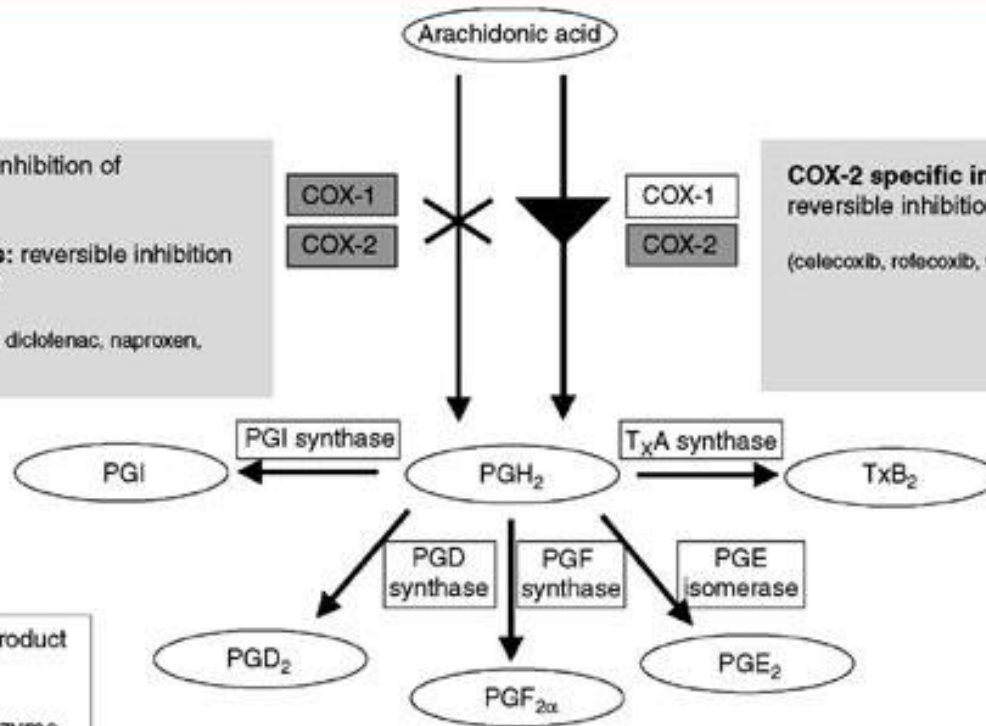
(indomethacin, ibuprofen, diclofenac, naproxen, nambutone)

COX-1
COX-2

COX-1
COX-2

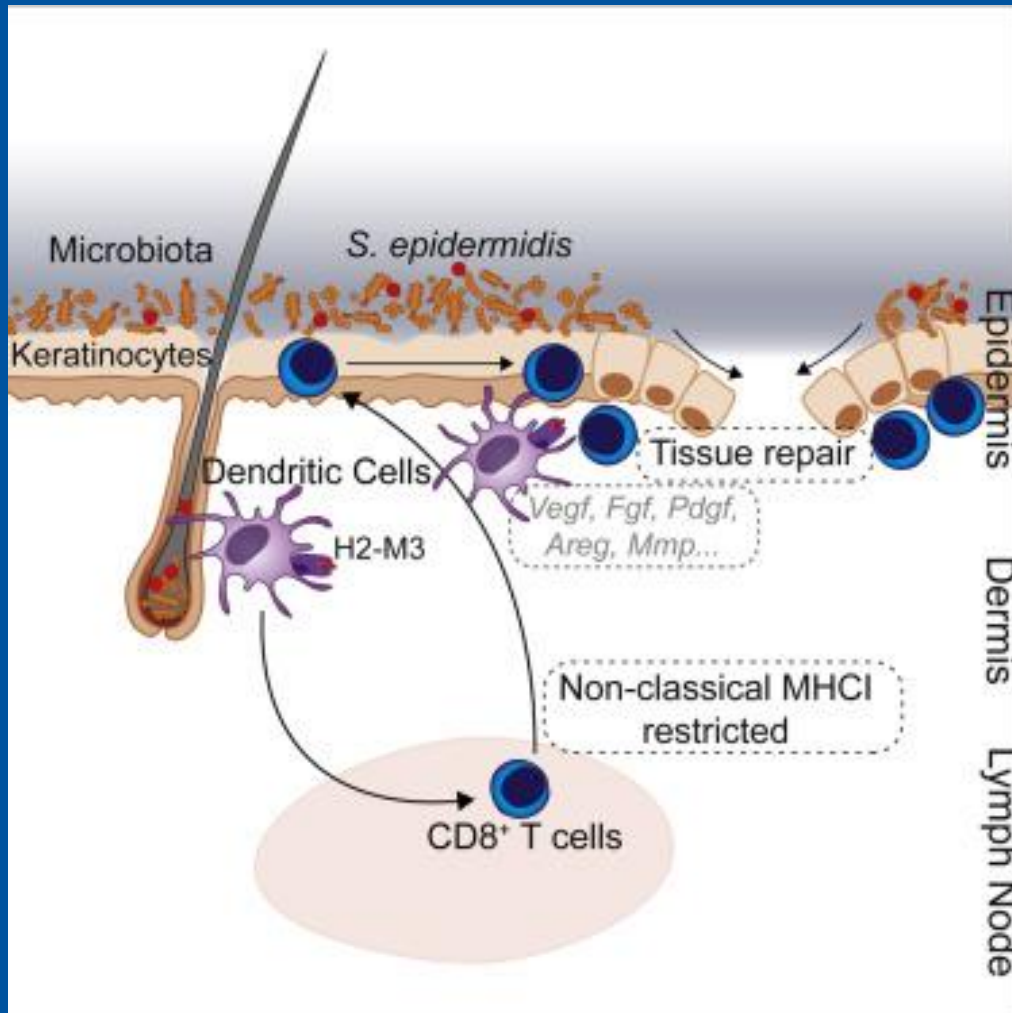
COX-2 specific inhibitors:
reversible inhibition of COX-2

(celecoxib, rofecoxib, valdecoxib)



Source: Cardiovasc Rev Rep © 2003 Le Jacq Communications, Inc.

Non-classical immunity:
Perifere tolerantie voor commensalen (microbiota)
En weefsel herstel



- [http://www.cell.com/cell/fulltext/S0092-8674\(17\)31513-1](http://www.cell.com/cell/fulltext/S0092-8674(17)31513-1)

non-classical MHC I-restricted commensal-specific immune responses not only promoted protection to pathogens, but also accelerated skin wound closure. Thus, the microbiota can induce a highly physiological and pleiotropic form of adaptive immunity that couples antimicrobial function with tissue repair. Our work also reveals that non-classical MHC class I molecules, an evolutionarily ancient arm of the immune system, can promote homeostatic immunity to the microbiota.

The hologenome concept of evolution

- The host with its microbiome, the holobiont, functions generally as a distinct biological entity anatomically, metabolically, immunologically, during development and in evolution
- Half of you is not actually you

<https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-018-0457-9>

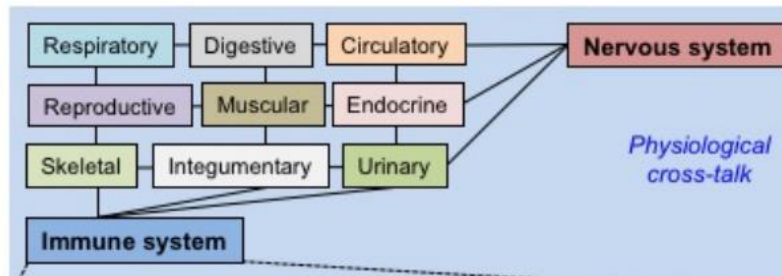
Towards a General Theory of Immunity?

We propose to combine different models to develop a unifying theory of immunity which situates immunology in the wider context of physiology.

<https://hal.archives-ouvertes.fr/hal-01673352/document>

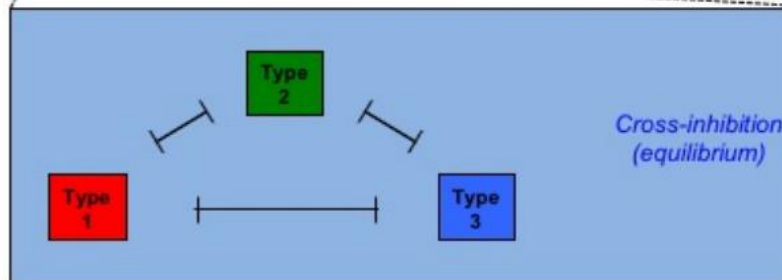
Level III – Integration

Immune responses are embedded in the organism and connected to the other vital systems. The nervous system and the immune system play major roles in the global integration of the other systems to maintain homeostasis at the organism level



Level II – Regulation

Three types of mutually inhibitory immune responses are induced by distinct types of changes, establishing an equilibrium, maintaining immune homeostasis and regulating the amplitude of immune reactions



Level I – Activation

Molecular and cellular pathways of the immune system react to changes induced to cells and tissues, as consequences from infections, tumors and injuries

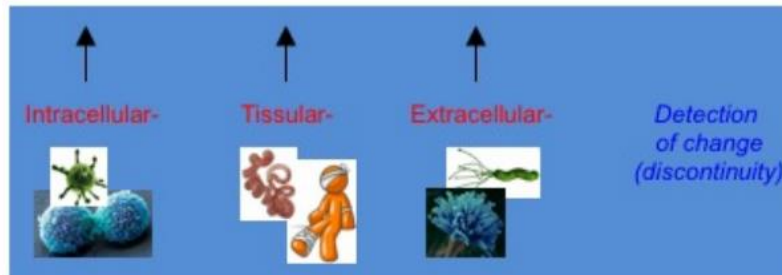


Figure 1. The immune system, as any other system, functions at different levels (or scales) in order to maintain homeostasis of the organism. As a consequence, immune responses are regulated, by different mechanisms, at each of these levels.

Immunity as a continuum of archetypes

<http://science.sciencemag.org/content/364/6435/28>

Accommodation archetypes

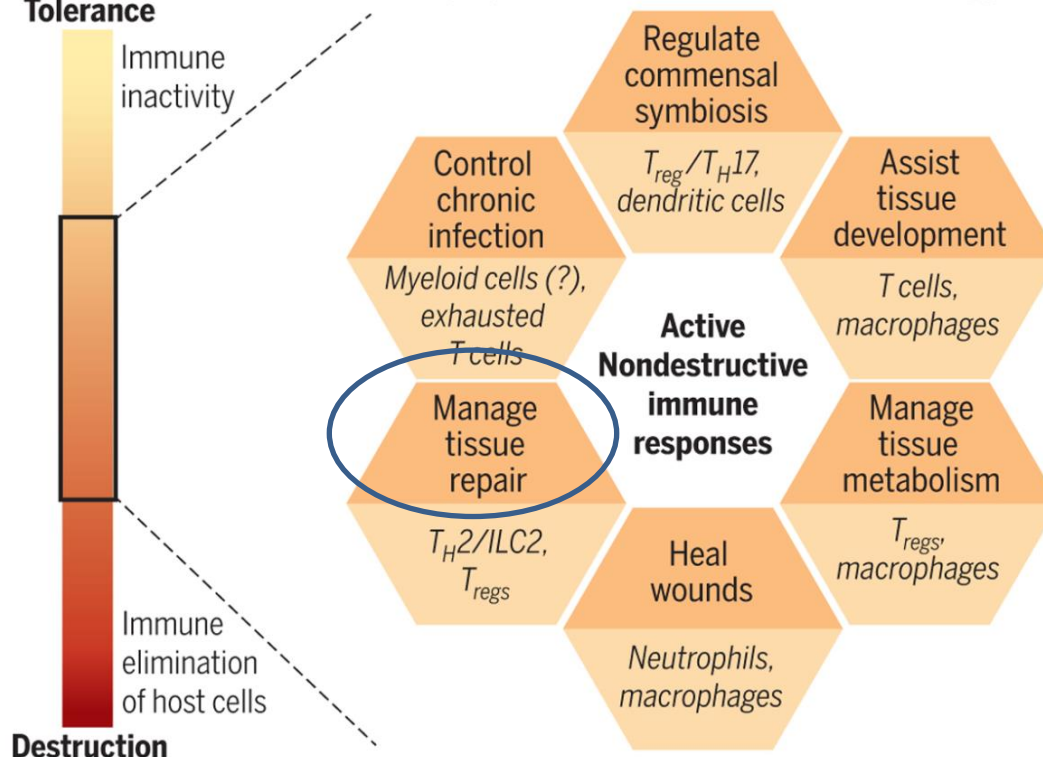
Traditional perspectives often reduce immune responses to tolerance and destruction. Emerging data show that the immune system has a larger palette of modular archetypes that accommodate healthy tissue. These archetypes can contribute to disease when dysregulated and/or dysfunctional.

Classical spectrum of immune reactivity

Tolerance

Immune inactivity

Emerging immune “accommodation” archetypes



Immunity has additional distinct roles in normal tissue biology, contributing to tissue development and maintenance.

=> Afweer 5/6

Hersenen

Niet alleen neuronen

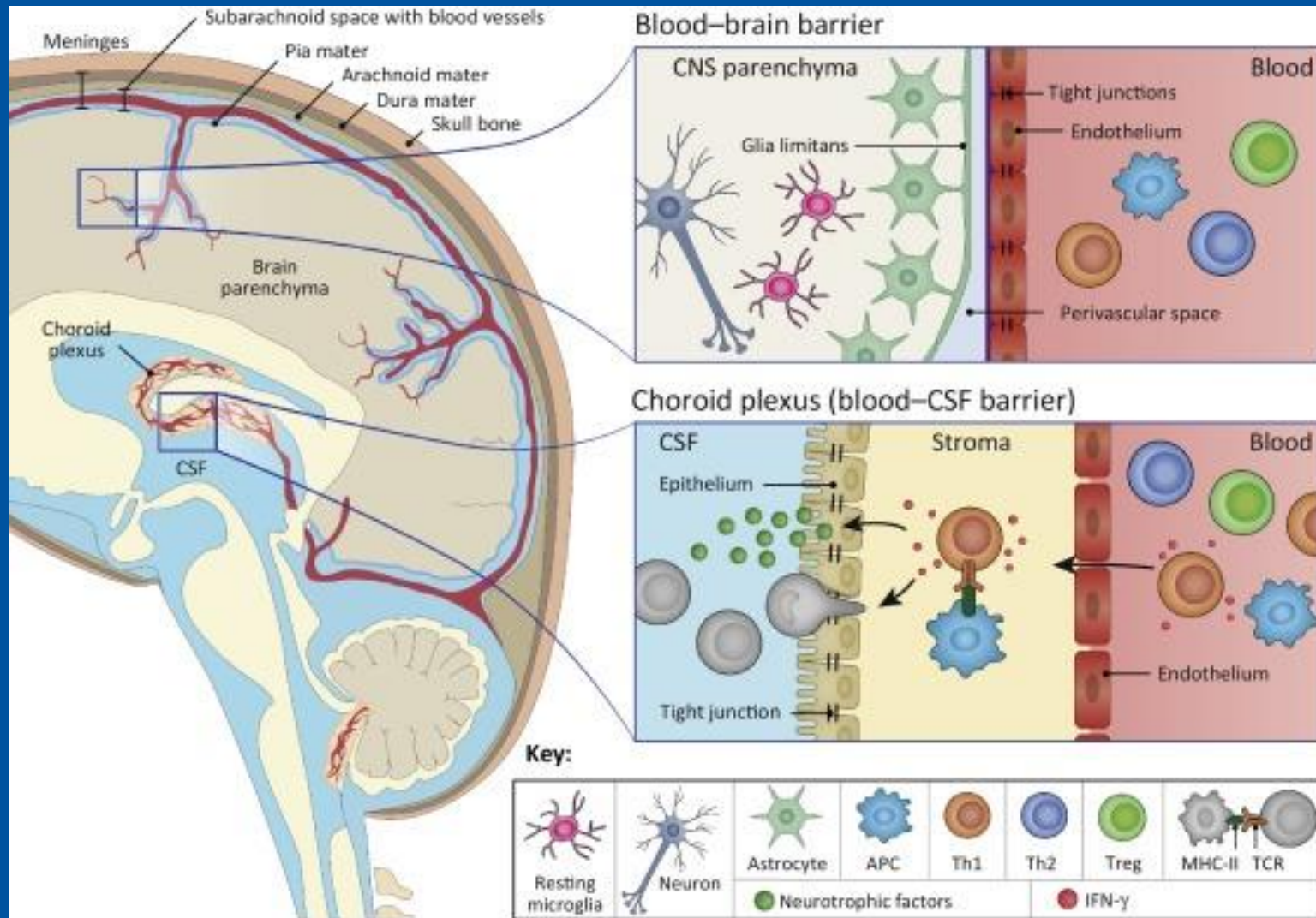
- Glia
- Microglia: lokale macrofaag, ~10% van de hersencellen!
- Macroglia (Oligodendrocyt): steuncel, maakt oa myeline
- Astrocyten: ondersteuning, stamcel?, signalen?
- Immune privileged site
- Bloed-hersen-barriere

Immune privileged sites:

- hersenen, oog, knie, baarmoeder
- Certain sites of the human body have **immune privilege**, meaning they are able to tolerate the introduction of antigens without eliciting an inflammatory immune response.
- Immune privilege is thought to be an evolutionary adaptation to protect vital structures from the potentially damaging effects of an inflammatory immune response. Inflammation in the brain or eye can lead to loss of organ function, while immune responses directed against a fetus can lead to miscarriage.

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

Blood brain barrier

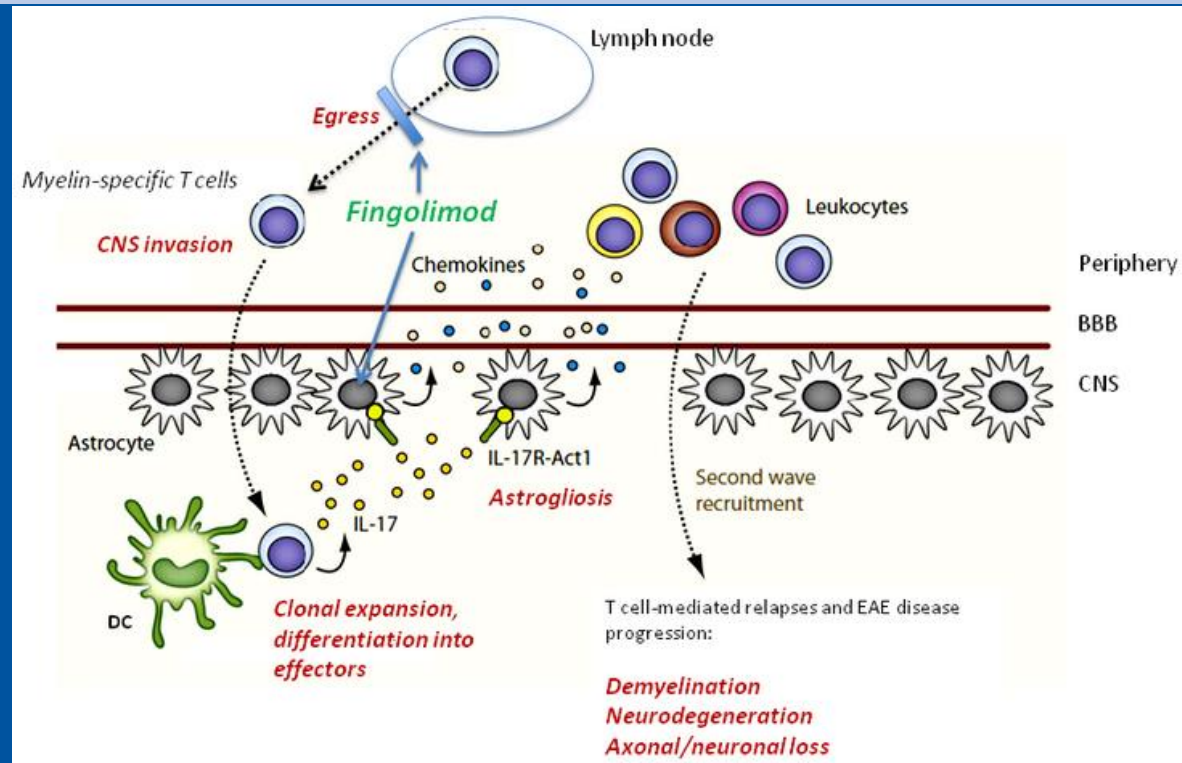


experimental allergic encephalomyelitis (EAE)

An animal model of brain inflammation (MS, ALS)

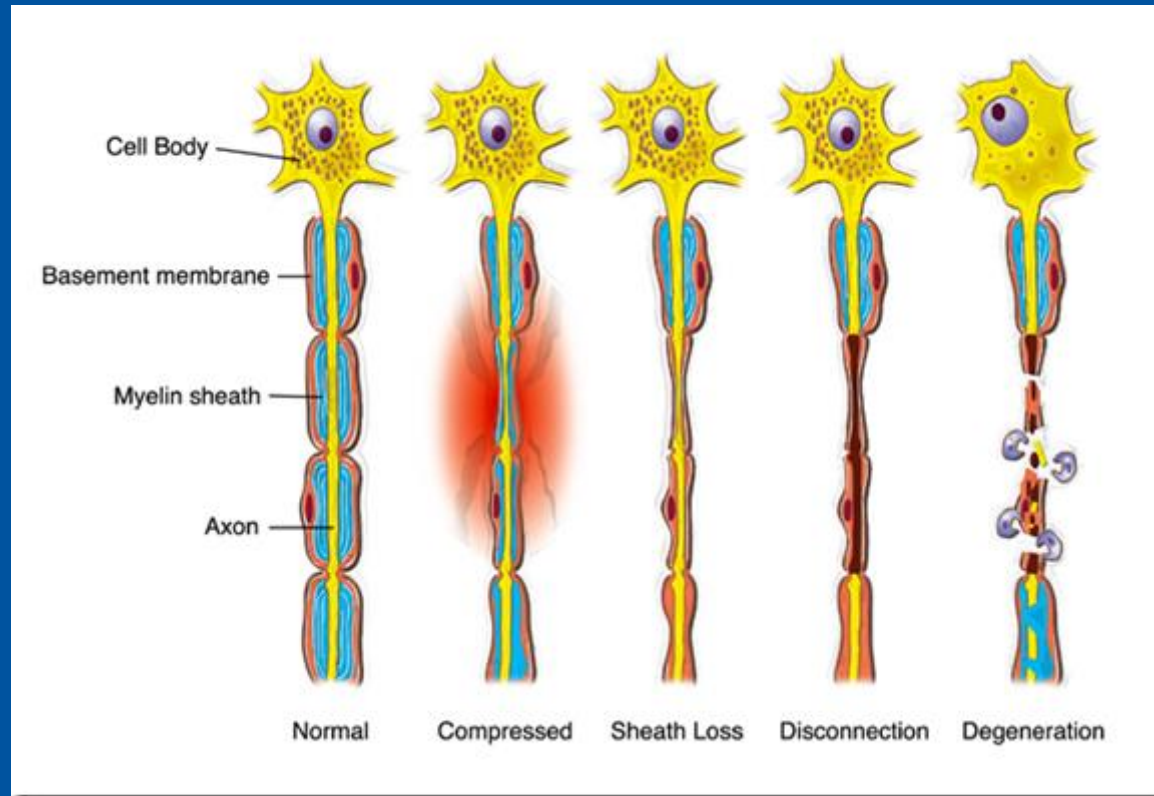
Myeline komt niet voldoende tot expressie in de Thymus
=> Geen goede negatieve selectie

EAE is the prototype for T-cell-mediated autoimmune disease in general and works by injection of purified myelin in the bloodstream

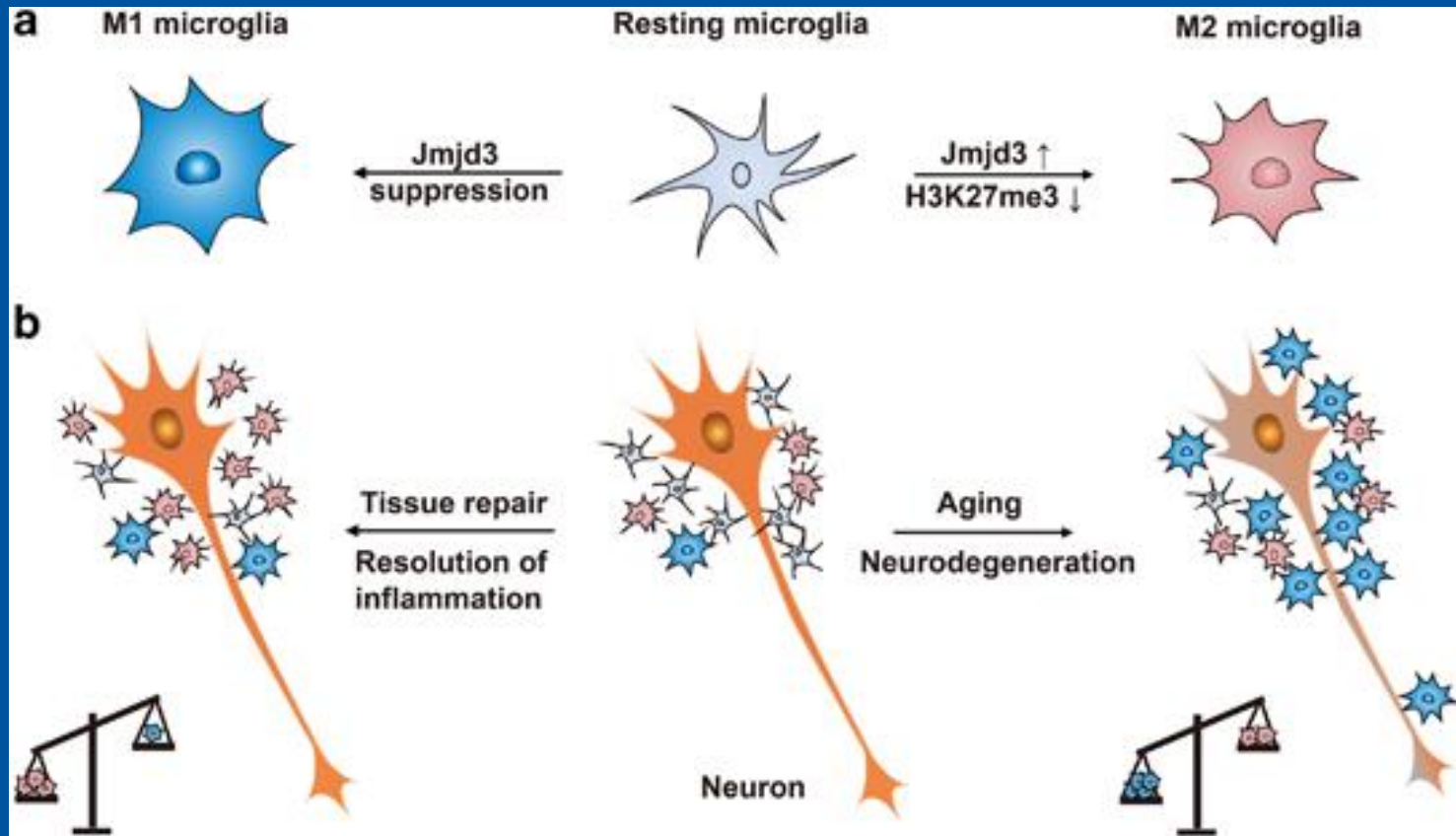


MS

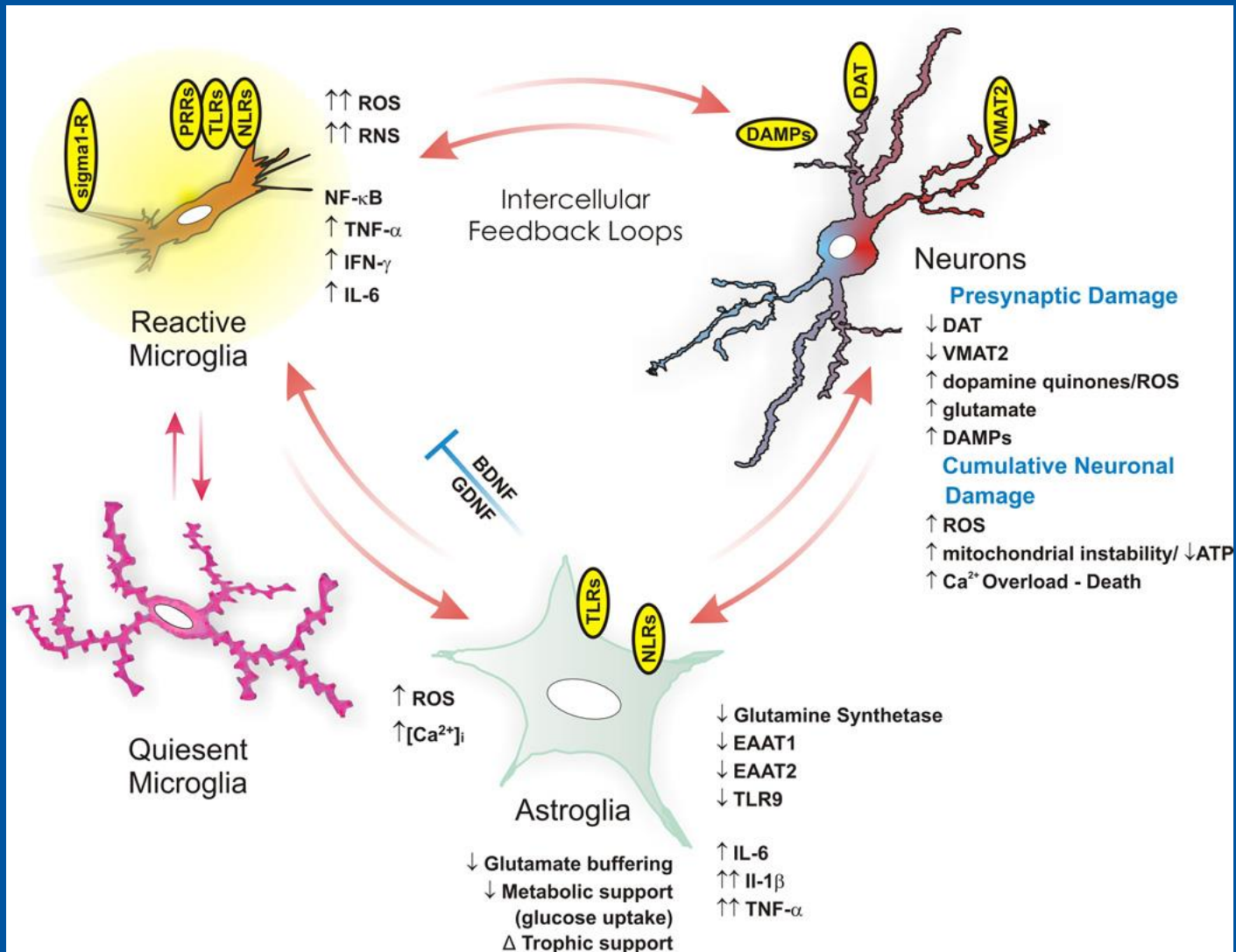
Neuroinflammatory degradation of myelin



Inflammation in the brain Vgl met macrofagen



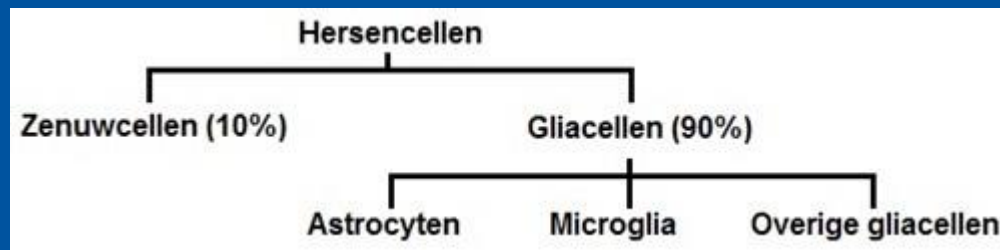
Neuro-immunology



Oorzaak of gevolg ?

Amyloid, buiten de cel

Tau, in de cel



Ontstekingscellen spelen een rol (microglia)

Neurotoxicity: roken, alcohol, metalen (Al), zuurstofradicalen

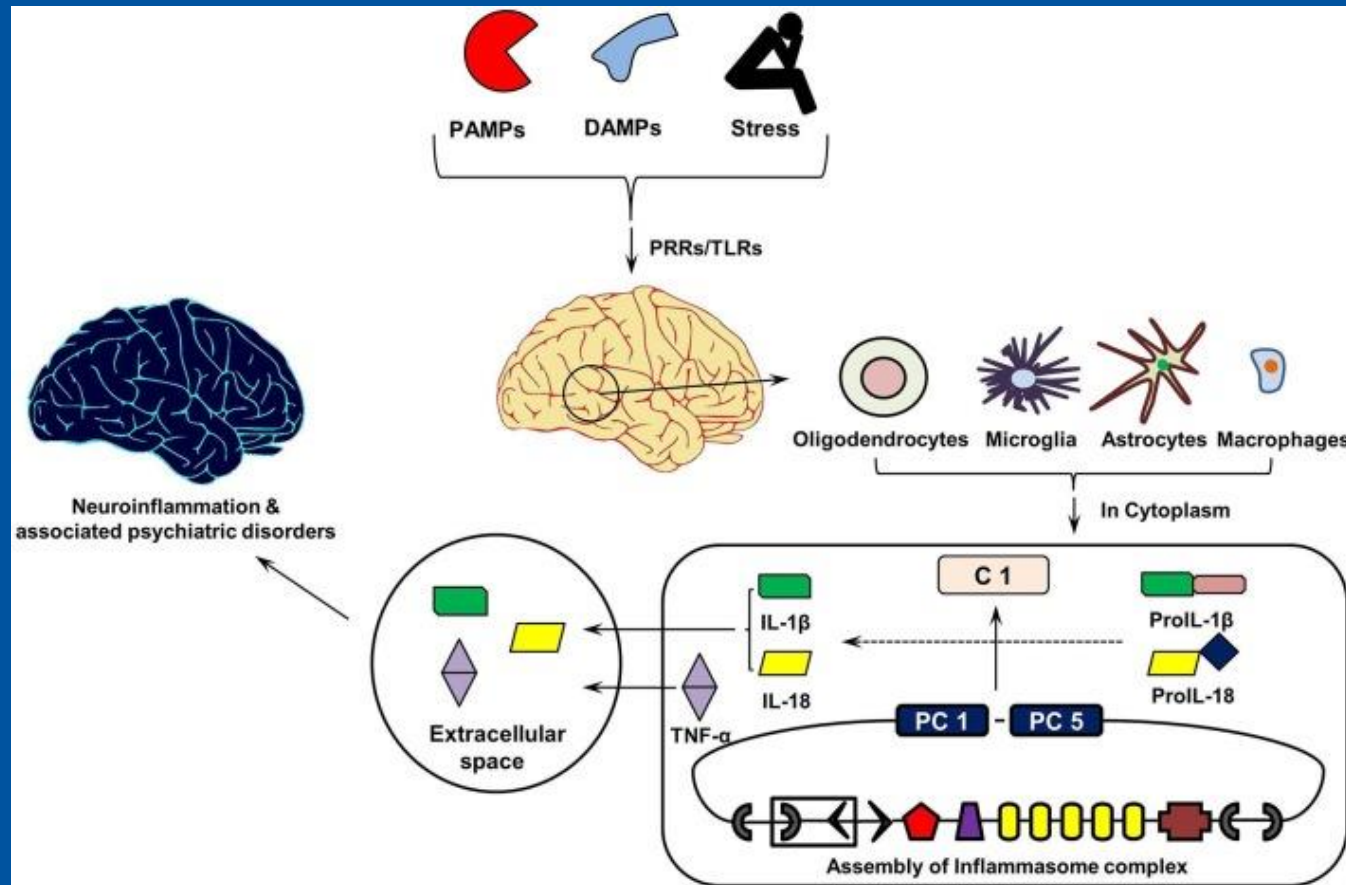
http://www.nature.com/nrn/posters/ad/nrn_ad_posters.pdf

<https://www.youtube.com/watch?v=yJXTXN4xrI8>

Inflammasomes Cascade in Brain

Initiate inflammatory reaction in the extracellular space

On recognizing pathogen associated molecular patterns (PAMPs, found in phagocytized microorganisms) and damage associated molecular patterns (DAMPs, e.g., nuclear and cytosolic proteins), intracellular pathogen recognition receptors (PRRs) and Toll-Like Receptors (TLRs) initiates assembly of cytosolic inflammasome complex. In turn, this activates the innate and acquired immune responses involving Interleukin (IL)-1 cytokines



<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4188030/pdf/fnis-08-00315.pdf>

Acta Neuropathol. 2013 Oct;126(4):479-97.

**The amyloid cascade-inflammatory hypothesis of Alzheimer disease:
implications for therapy**

<http://www.ncbi.nlm.nih.gov/pubmed/24052108>

**Kan in ieder geval helpen te remmen, en vroeg genoeg begonnen
misschien voorkomen.**

Misschien zelfs oorzaak (autoimmuun en/of mimicry)

Dementia is not a specific disease. It's an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. Alzheimer's disease accounts for 60 to 80 percent of cases. Vascular dementia, which occurs after a stroke, is the second most common dementia type. But there are many other conditions that can cause symptoms of dementia, including some that are reversible, such as thyroid problems and vitamin deficiencies.

The greatest known risk factor for Alzheimer's is advancing age.

For example, while one of nine people age 65 or older has Alzheimer's, nearly one of three people age 85 or older has the disease. One of the greatest mysteries of Alzheimer's disease is why risk rises so dramatically as we grow older.

Ouderdomsziekte => accepteren?

Ouderdom is verzameling ziektes: alles genezen => geen veroudering