





A pneumonia outbreak associated with a new coronavirus of probable bat origin



- Nature: 03 February 2020, Peng Zhou et al.,
- Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago, a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats 1,2,3,4. Previous studies have shown that some bat SARSr-CoVs have the potential to infect humans 5,6,7. Here we report the identification and characterization of a new coronavirus (2019-nCoV), which caused an epidemic of acute respiratory syndrome in humans in Wuhan, China. The epidemic, which started on 12 December 2019, had caused 2,794 laboratory-confirmed infections including 80 deaths by 26 January 2020. Fulllength genome sequences were obtained from five patients at an early stage of the outbreak. The sequences are almost identical and share 79.6% sequence identity to SARS-CoV. Furthermore, we show that 2019-nCoV is 96% identical at the whole-genome level to a bat coronavirus. Pairwise protein sequence analysis of seven conserved non-structural proteins domains show that this virus belongs to the species of SARSr-CoV. In addition, 2019-nCoV virus isolated from the bronchoalveolar lavage fluid of a critically ill patient could be neutralized by sera from several patients. Notably, we confirmed that 2019-nCoV uses the same cell entry receptor—angiotensin converting enzyme II (ACE2)—as SARS-CoV.

Quarantaine Sinds de landbouwrevolutie en de eerste steden



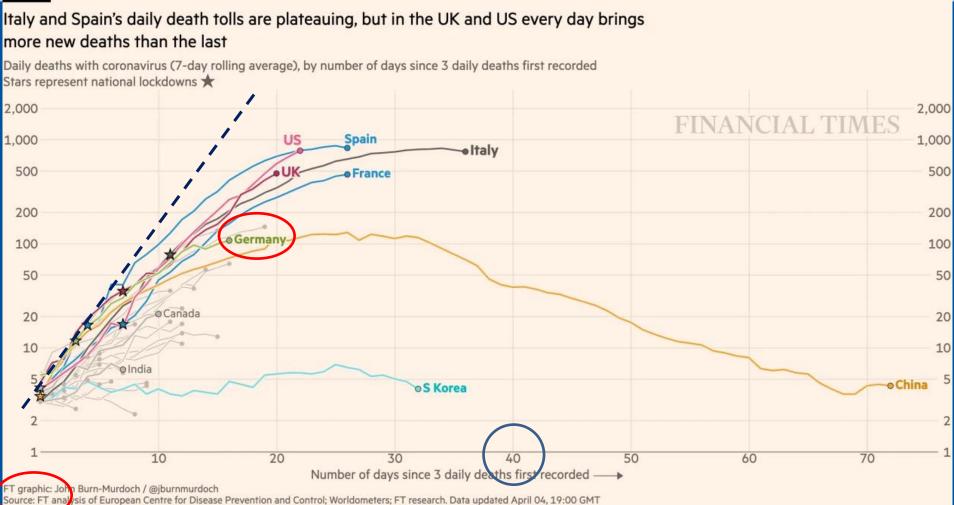
The word *quarantine* comes from *quarantena*, meaning "forty days", used in the 14th-15th-century <u>Venetian language</u> and designating the period that all ships were required to be isolated before passengers and crew could go ashore during the <u>Black Death</u> plague <u>epidemic</u>; it followed the *trentino*, or thirty-day isolation period, first imposed in 1377 in the <u>Republic of Ragusa</u>, <u>Dalmatia</u> (modern <u>Dubrovnik</u> in Croatia). [1][2][3][4] For more, see the <u>medieval history paragraph</u>.

An early mention of isolation occurs in the Biblical <u>book of Leviticus</u>, 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 <u>Mosaic Law</u>:

- ⇒ virussen, en hun aanpak zijn al lang onderdeel van het leven van mensen
- ⇒ Infecties bij de mens gedragen zich nog steeds hetzelfde
- ⇒ 40 dagen is het ergste hopelijk voorbij

Corona special:
Log charts
(rechte stippellijn is exponentiele toename, zonder maatregelen)

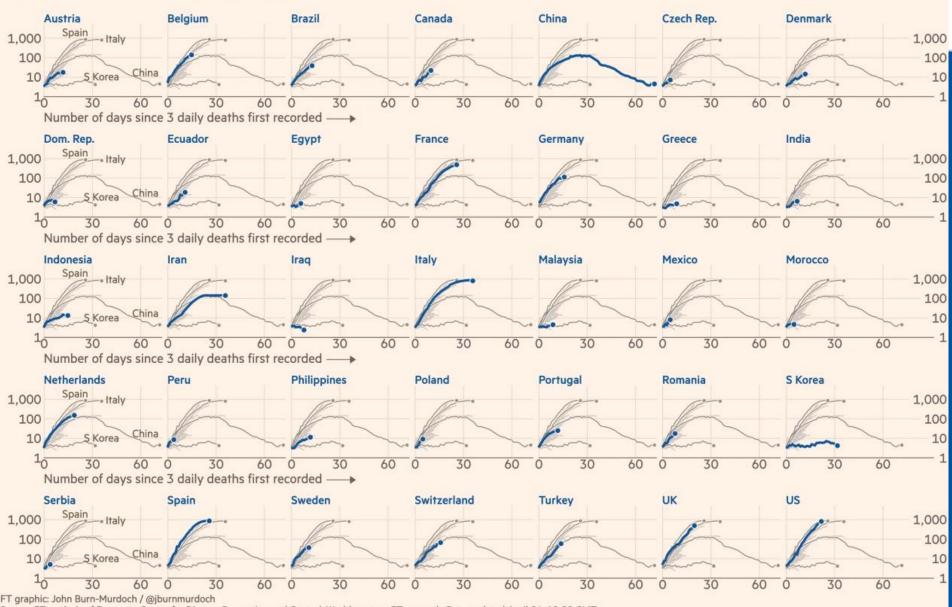




Of misschien doen we het wel slechter dan vroeger? Nog meer mensen op een kluitje, meer reizen etc.

Daily death tolls are still accelerating in most countries

Daily deaths with coronavirus (7-day rolling average), by number of days since 3 daily deaths first recorded



Source: FT analysis of European Centre for Disease Prevention and Control; Worldometers; FT research. Data updated April 04, 19:00 GMT

© FT

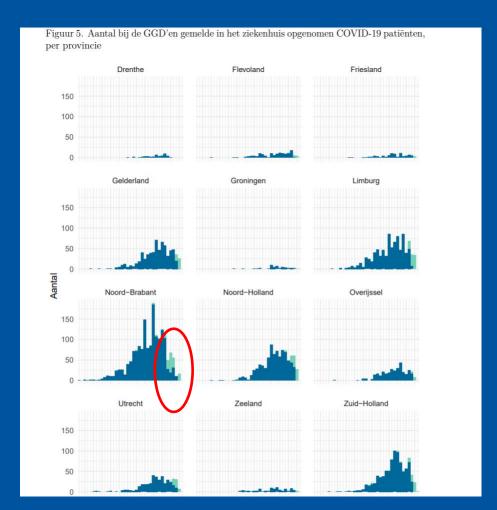
Corona gegevens: RIVM



Ergens diep verborgen in een pdf van het RIVM met alle gegevens over de Corona epidemie staan de meest interessante grafieken.

Deze zie je niet op het nieuws, maar vertellen het meest.

IC en sterftecijfers zijn belangrijk, maar het verloop van de epidemie haal je uit de ziekenhuisopnames, uitgesplitst naar provincie.



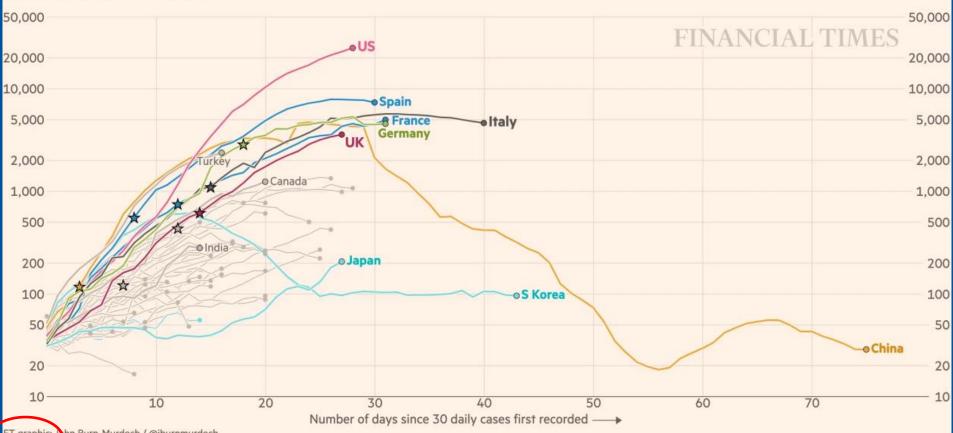
https://www.rivm.nl/actuele-informatie-over-coronavirus/data

Corona special: New cases



Italy has turned the corner, with numbers of new cases now in decline, following in China's footsteps

Daily confirmed cases (7-day rolling average), by number of days since 30 daily cases first recorded Stars represent national lockdowns *

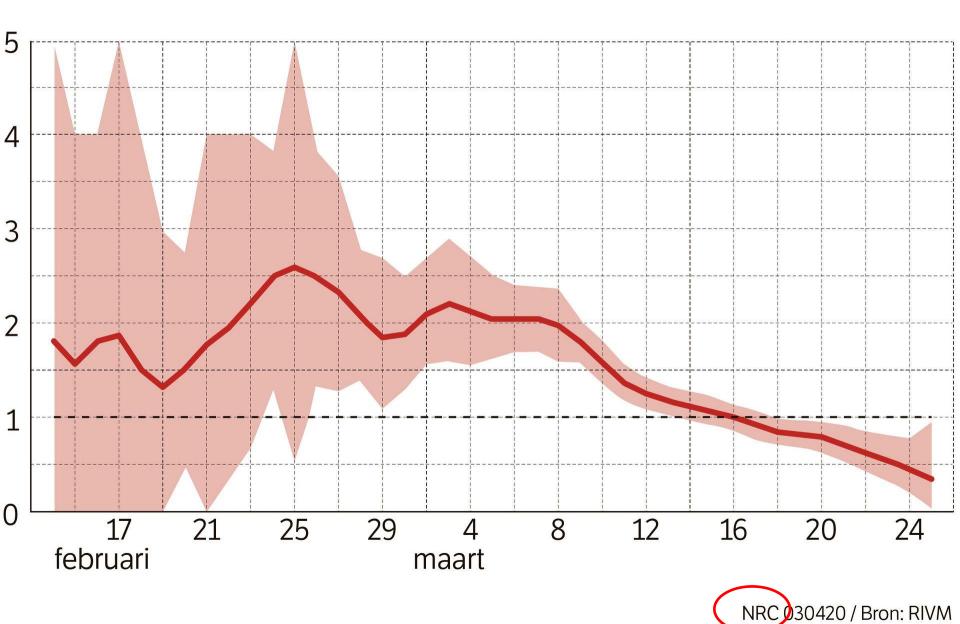


FT graphic: John Burn-Murdoch / @jburnmurdoch

Source: FT analysis of European Centre for Disease Prevention and Control; Worldometers; FT research. Data updated April 04, 19:00 GMT

OFT

Ontwikkeling van de R0 (hoeveel mensen besmet één zieke?)



Informatie: Betrouwbaarheid



Paper (Article): peer review

Summary door auteurs

Review door andere wetenschapper

Opinion editorial (Op-ed) door blad

News paper door redacteur

Website

Wikipedia selectie Ziekenhuis redactie

Bioplek docenten

Facebook elke halve zool

Wetenschap is de meest betrouwbare bron van informatie. Maar, er moet wel vertrouwen zijn in het systeem. Betrouwbaarheid (en moeilijkheidsgraad)

NB Wetenschappers maken ook fouten, en sommige facebook content is OK

Wetenschappelijke literatuur



Science

http://science.sciencemag.org/

Nature

http://www.nature.com/nature/index.html

Cell

http://www.cell.com/cell/current

Pubmed

https://www.ncbi.nlm.nih.gov/pubmed

Google scholar

https://scholar.google.nl/

Wetenschappelijk woordenboek

https://en.oxforddictionaries.com/

Tientallen corona virussen in vleermuizen



- Extensive diversity of coronaviruses in bats from China
- 32 alpha-CoVs and 41 beta-CoVs were identified in bats sampled from China.
- ⇒ We gaan dus nog niet af zijn van zoonosen
- ⇒ Een zoonose is vooral gevaarlijk omdat de nieuwe gastheer nog geen balans heft gevonden met de ziekmaker => virulentie is vaak hoog
- ⇒ Zoonosen door samenleven met dieren
- ⇒ Ook in Nederland (Q-koorts, vogelgriep, varkenspest)
- ⇒ Niet alleen in China is intensieve veehouderij een probleem

https://www.sciencedirect.com/science/article/pii/S0042682217301009

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



Ziekmakers en symbiose



- ledereen heeft een eigen repertoire tegen ziekmakers, en er vind selectie plaats => ziekmaker wordt minder virulent.
- Al miljarden jaren samenleven ziekmakers en andere organismen!
- ⇒ er mee om gaan, en geen oorlog tegen voeren
- ⇒ "Half of you is not actually you". We bestaan voor de helft uit bacterien (darmen, huid) en virus resten (transposons in het genoom), waar we ook voordeel van hebben => symbiose
- Het probleem zijn Zoonosen, waarbij een ziekmaker overspringt
- Normaal hebben we altijd al een beetje weerstand (Memory) voor een nieuwe virus variant
- Maar niet tegen een heel nieuw virus (Vogelgriep, Q-koorts, Corona)
- ⇒ Selectie vindt nu keihard plaats.
- ⇒ Mede door onnatuurlijk contact (dierenmarkt, bioindustrie)

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.

- ⇒ Heel fijn voor het individu, maar minder goed voor de samenleving
- ⇒ Als er dan een ziekmaker langs komt is er in ineens een heel grote groep mensen extra vatbaar => crisis
- ⇒ Investeer in gezonde mensen, niet in oude
- ⇒ En in gezonde omgang met de natuur

Corona special:

How do we value a (statistical) life?



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 geinfecteerden
- \Rightarrow 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

Vaccin: Verzwakte ziekmaker, of delen hiervan



- Voorkomt niet de infectie
- Maakt memory T en B cellen
- => Snelle, en vaak subklinische, reactie
- => Elk jaar miljoenen mensen niet dood
- Heel kosteneffectief
- Heel weinig bijwerkingen, al zijn die niet nul (autisme? allergie?)
- Normaal is ziek worden niet zo'n probleem, en voor jonge kinderen zelfs nuttig (=> minder allergie)
- De meeste mensen gaan dood door slechte algemene gezondheid
- Voor sommige ziekmakers geld dit niet (zie tabel) => vaccinatie
- Ook voor risicogroepen verstandig (ouderen, zieken) => <u>griepprik</u>

Effectiveness of Vaccines for Some Common Infectious Diseases

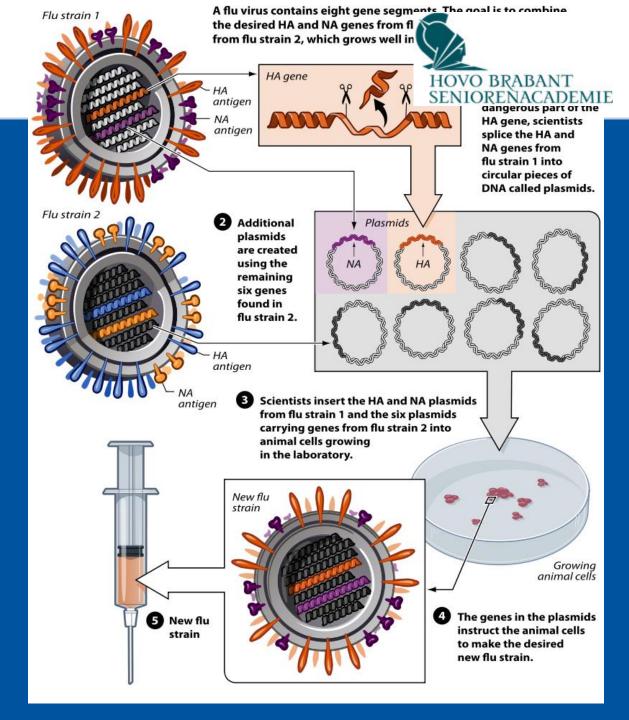
Disease	Maximum number of cases (year)	Number of cases in 2004	Percent change
Diphtheria	206,939 (1921)	0	-99.99
Measles	894,134 (1941)	37	-99.99
Mumps	152,209 (1968)	236	-99.90
Pertussis	265,269 (1934)	18,957	-96.84
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	12	-99.98
Tetanus	1,560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

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

Vaccin

Moleculaire biologie! (Knippen/plakken van DNA)

=> Cursus biotechnologie



Vaccins zijn (te) goedkoop: Een cynisch verhaal



- ⇒ Wordt niet veel aan verdiend door de industrie
- ⇒ Waarom zou je iets maken dat geneest. Alleen iets dat je een heel leven lang moet slikken (bloeddrukverlagers, anti-depressiva, cholesterolverlagers) levert het echte geld op.
- ⇒ Industrie is niet uit op beter maken, maar op ziek houden
- ⇒ Crisis op crisis
- ⇒ nauwelijks nieuwe vaccins
- ⇒ Net als nieuwe antibiotica
- ⇒ Gezondheid moet je dus niet aan de markt over laten
- ⇒ En overheid had meer wetenschappelijk onderzoek moeten financieren naar vaccins, en vooral virusremmers. Ipv ontmantelen ned. vaccin instituut.
- ⇒ De onderzoeksvoorstellen hiervoor werden gewoon niet gehonoreerd
- ⇒ NB We hebben ook zo weinig IC-bedden omdat ziekenhuizen moeten concurreren. En (meestal) leegstaande bedden zijn een concurrentie nadeel

Vaccin, nadelen

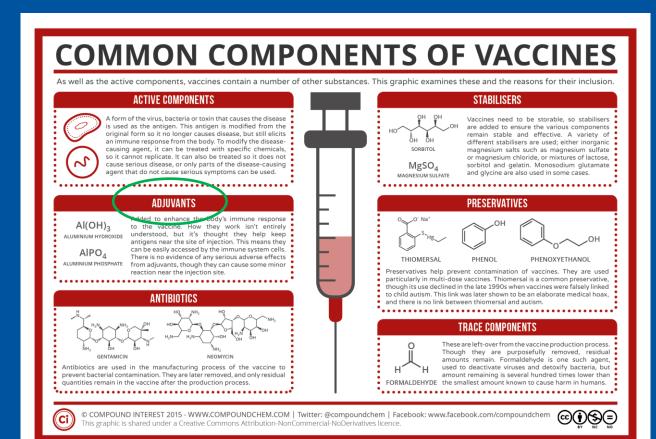


Afweersysteem reageert niet zomaar.

- ⇒ Gevaarsignaal
- ⇒ Veiligheid
- ⇒ Brede werking onder de bevolking nodig
- ⇒ Kost veel tijd
- ⇒ Allergien?
- ⇒ Maatschappelijke weerstand

En vaccins tegen griep/verkoudheidviruss en lopen altijd achter de feiten aan door mutaties (net als bij HIV)

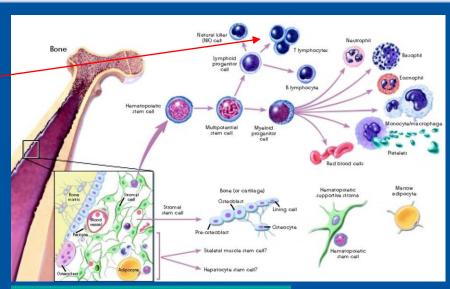
=> Andere oplossingen

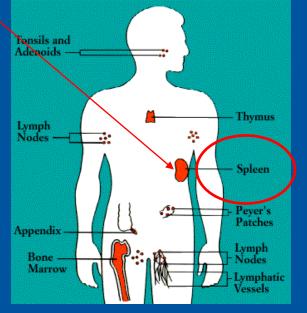


B Cellen B Lymfocyte



- Worden gemaakt in het beenmerg
- Rijpen in het <u>Beenmerg</u>, Lymfeklieren en Milt
- Produceren antilichamen
- ⇒ Humorale (bloed) immuniteit
- ⇒ Serologische test => titer
- ⇒ Te gebruiken voor passieve immunisatie
- ⇒ En onderzoek

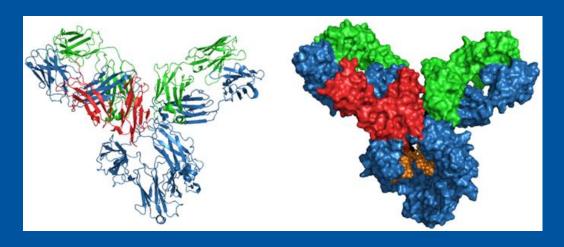


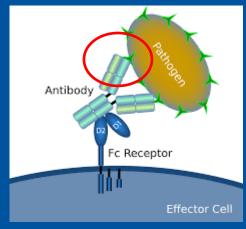


Antilichamen



- Worden gemaakt door plasma cellen (gerijpte B-cellen)
- Zijn gespecialiseerde eiwitten die heel specifiek een antigeen herkennen
- Helpen macrofagen (effector) ziekmaker opruimen (via Fc-receptoren)
- Kunnen overal in het lichaam komen, zelfs in cellen (IgG)





How blood from coronavirus survivors might save lives



- 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

Vaccin v. virus remmer



- Vaccin beschermt nog niet zieke mensen
- ⇒ Wordt gegeven aan gezonde 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
- => Grootste impact gedurende crisis

virus remmers

Een virus volgt een ingewikkeld pad

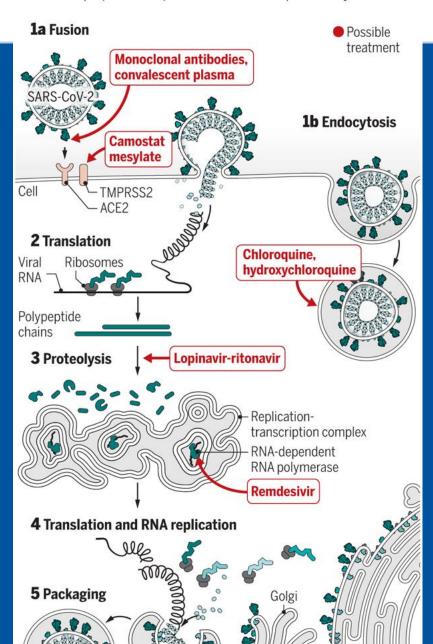
- ⇒ meerdere interventie mogelijkheden
- ⇒ Evt ook recombinant soluble ACE2

Receptor is ACE2

⇒ ACE2 is expressed primarily in alveolar epithelial type II cells, which can serve as a viral reservoir (Zhao et al., 2020). These cells produce surfactant which reduces surface tension, thus preventing alveoli from collapsing, and hence are critical to the gas exchange function of the lung (Dobbs, 1989). Injury to these cells could explain the severe lung injury observed in COVID-19 patients

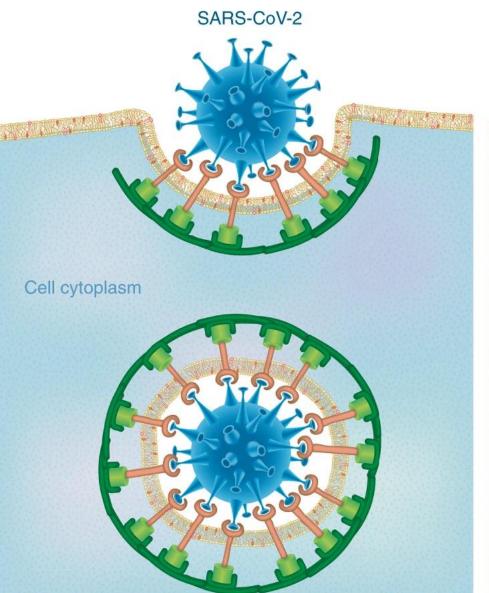
Lines of attack

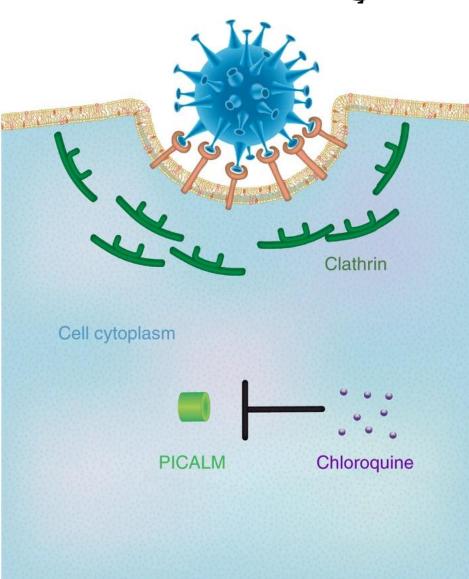
Experimental treatment strategies attempt to interfere with different steps (numbered) in the coronavirus replication cycle.



chloroquine efficacy against COVID-19





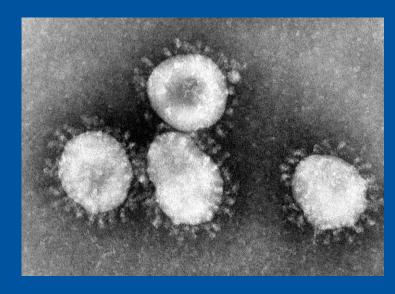


Corona, wat mij opvalt



Each person with the coronavirus appears to infect 2.2 other people, on average (reproduction number).

- => Quarantaine is bedoeld om het reproductienr zo laag mogelijk te krijgen. Dan dooft de epidemie makkelijker uit. Nu op 0,3 na slechts 2 weken quarantaine
- ⇒ Leven met virussen, ipv er tegen vechten, doen we al heel lang
- ⇒ Het is het onbekende (angst), en de media
- ⇒ Het had ook erger kunnen zijn (ebola)
- ⇒ Meer onderzoek naar virus remmers (long-overdue)



https://www.nejm.org/doi/full/10. 1056/NEJMc2001899

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

navirussen

https://www.nytimes.com/2020/0 2/29/health/coronavirus-flu.html

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

protein.html?utm_source=Nature+Briefing&utm_campaign=d04639c3d briefing-dy-20200406&utm_medium=email&utm_term=0_c9dfd39373-

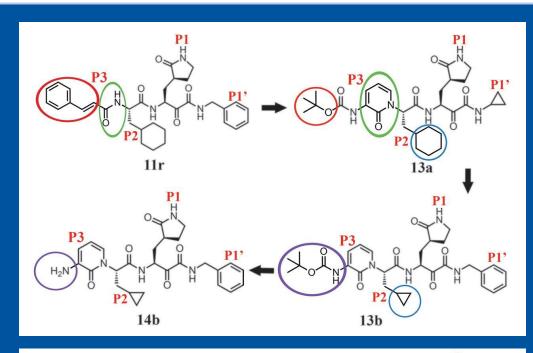
Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved α -ketoamide inhibitors

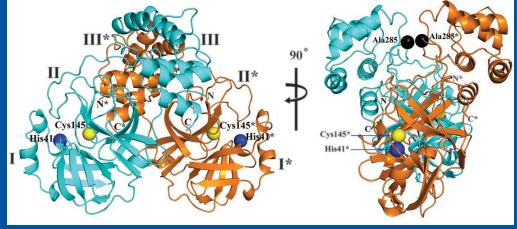


Targeting a key enzyme in SARS-CoV-2

Scientists across the world are working to understand severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Zhang et al. determined the x-ray crystal structure of a key protein in the virus' life cycle: the main protease. This enzyme cuts the polyproteins translated from viral RNA to yield functional viral proteins. The authors also developed a lead compound into a potent inhibitor and obtained a structure with the inhibitor bound, work that may provide a basis for development of anticoronaviral drugs

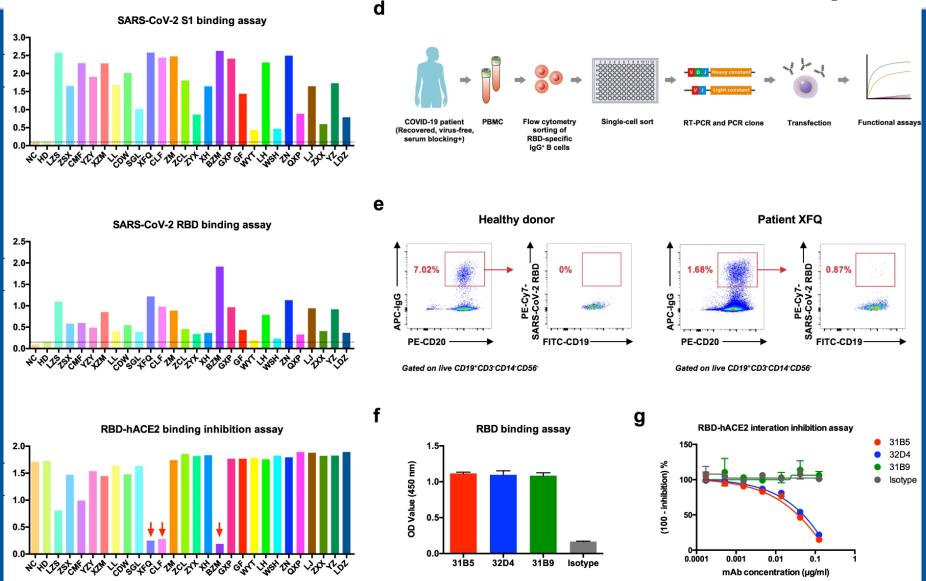
https://science.sciencemag.org/content/368/6489/409





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





Netflix: Coronavirus explained

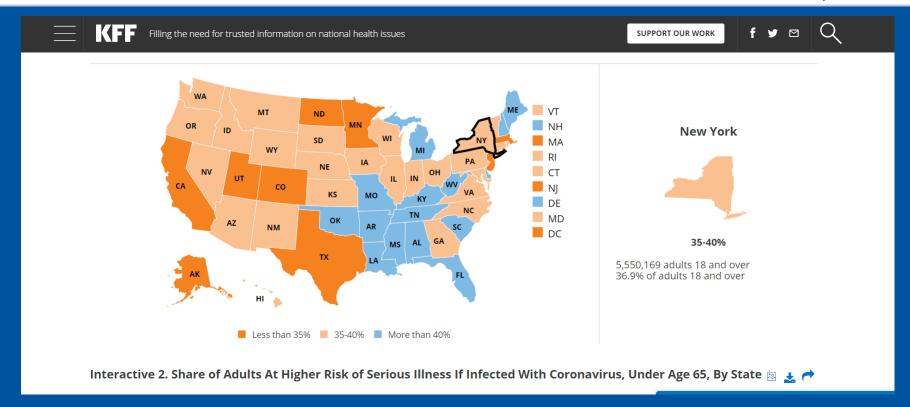




https://www.nature.com/articles/s41467-017-00923-8 https://www.ecohealthalliance.org/publications

40% van de amerikanen heeft hoog risico





Based on the most current information made available by the Centers for Disease Control and Prevention (CDC), older people and younger adults with serious medical conditions, such as heart disease, diabetes, lung disease, asthma and obesity have a greater risk of becoming severely ill if they get infected with coronavirus

Europa doet het niet veel beter



 The proportion of overweight adults in the EU varied in 2014 between 36 % in Italy and 55 % in Malta for women, and between 54 % in the Netherlands and 68 % in Croatia for men.

the complex biology powering the coronavirus pandemic



Bad family

- Of the viruses that attack humans, coronaviruses are big. At 125 nanometres in diameter, they are also relatively large for the viruses that use RNA to replicate, the group that accounts for most newly emerging diseases. But coronaviruses really stand out for their genomes. With 30,000 genetic bases, coronaviruses have the largest genomes of all RNA viruses. Their genomes are more than three times as big as those of HIV and hepatitis C, and more than twice influenza's.
- Coronaviruses are also one of the few RNA viruses with a genomic proofreading mechanism which keeps the virus from accumulating mutations that could weaken it. That ability might be why common antivirals such as ribavirin, which can thwart viruses such as hepatitis C, have failed to subdue SARS-CoV-2. The drugs weaken viruses by inducing mutations. But in the coronaviruses, the proofreader can weed out those changes.

https://www.nature.com/articles/d41586-020-01315-7

The race for coronavirus vaccines

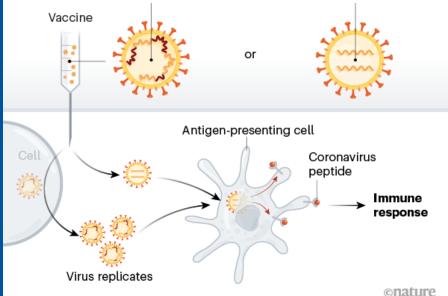
VIRUS VACCINES

Weakened virus

A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. Codagenix in Farmingdale, New York, is working with the Serum Institute of India, a vaccine manufacturer in Pune, to weaken SARS-CoV-2 by altering its genetic code so that viral proteins are produced less efficiently.



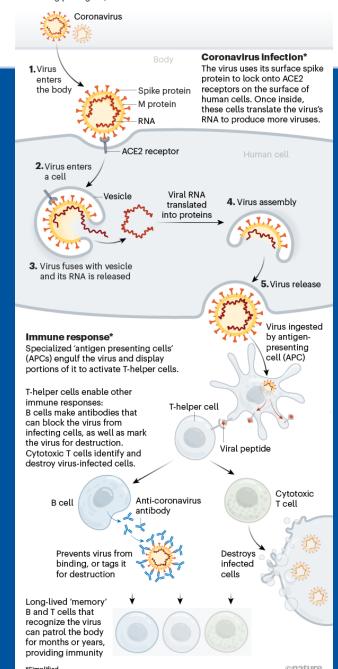
In these vaccines, the virus is rendered uninfectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus.



https://www.nature.com/articles/d415 86-020-01221-y

VACCINE BASICS: HOW WE DEVELOP IMMUNITY

The body's adaptive immune system can learn to recognize new, invading pathogens, such as the coronavirus SARS-CoV-2.



Cytokinestorm en IL-6 blokkade

Cytokine release syndrome in severe COVID-19

Science 01 May 2020

The immediate goal of IL-6 antagonism is to ameliorate severe COVID-19 cases so that requirements for advanced care are minimized.

Obesity has been associated with higher circulating Interleukin 6 => risk factor

https://science.sciencemag.org/cont

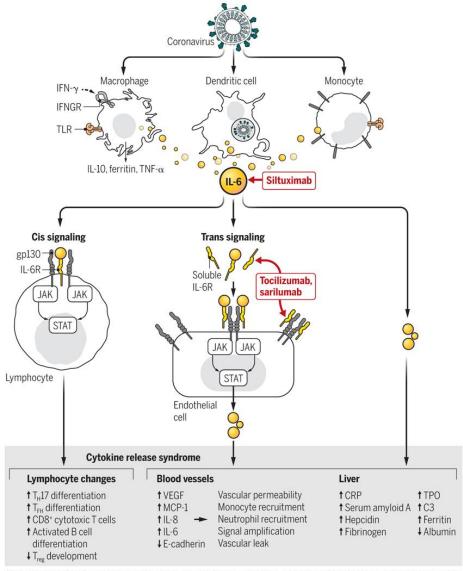
ent/368/6490/473

https://pace-

cme.org/2020/04/30/potential-

Pathways leading to cytokine release syndrome

Coronavirus infection results in monocyte, macrophage, and dendritic cell activation. IL-6 release then instigates an amplification cascade that results in cis signaling with T_H17 differentiation, among other lymphocytic changes, and trans signaling in many cell types, such as endothelial cells. The resulting increased systemic cytokine production contributes to the pathophysiology of severe COVID-19, including hypotension and acute respiratory distress syndrome (ARDS), which might be treated with IL-6 antagonists such as tocilizumab, and siltuximab.



C3, complement 3; CRP, C reactive protein; IFN- γ , interferon- γ ; IFNGR, IFN- γ receptor; IL, interleukin; IL-GR, IL-G receptor; JAK, Janus kinase; MCP-1, monocyte chemoattractant protein-1; STAT3, signal transducer and activator of transcription 3; T_{FR} , Tollicular helper cell; T_{H} 7, Thelper 17 cell; TNF- α , tumor necrosis factor- α ; TLR, Toll-like receptor; TPO, thrombopoietin; T_{Rg} , Tregulatory cell; VEGF, vascular endothelial growth factor.

Totaal in de wereld



- 3,4 miljoen gevallen
- 0,2 miljoen doden
- \Rightarrow CFR = 0,06

NB "The CFR for the Spanish (1918) flu was >2.5%, but about 0.1% for the Asian (1956-58) and Hong Kong (1968-69) flus, and <0.1% for other influenza pandemics (Wikipedia)".

NB 0.2 = 200.000 = veel (and counting)

NB Aantal werkelijke doden is >2x zo groot Maar aantal gevallen waarschijnlijk nog groter.

NB Gevolgen lijken groter omdat Corona ook voorkomt in westerse landen

https://www.worldometers.info/coronavirus/#countries

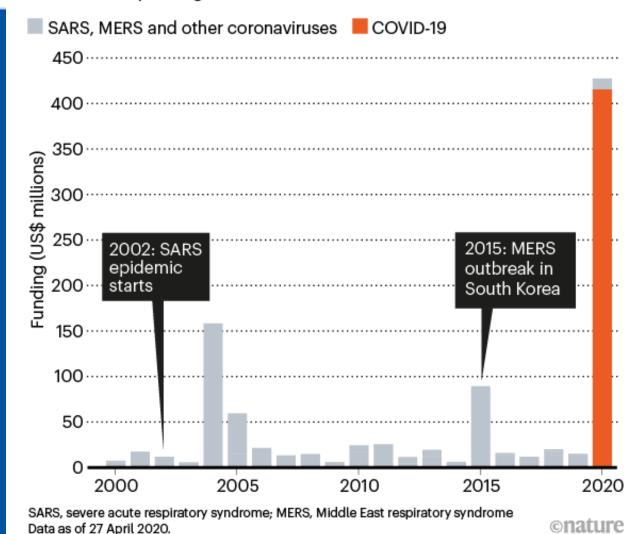
Reactive spending

Spending has generally been reactive — explaining spikes in 2004 and 2015, after outbreaks of the coronaviruses that cause the diseases SARS and MERS, respectively.

⇒ Move to pro-active

CORONAVIRUS CASH

Public and philanthropic organizations have spent US\$985 million on coronavirus research since 2000. But before 2020, this constituted only 0.5% of total spending on infectious-disease research.



the complex biology powering the coronavirus pandemic



- Scientists are learning that the virus has evolved an array of adaptations that make it much more lethal than the other coronaviruses humanity has met so far. Unlike close relatives, SARS-CoV-2 can readily attack human cells at multiple points, with the lungs and the throat being the main targets
- => only throat => non-symptomatic but infectious
- => 60% of new infections by non-symptomatic spreaders (aerosols?
- NB Low viral load
- High viral load => directs spread to the lungs => symptomatic
- Not controlled in the throat and then spread to lungs is also possible

Aerosol-Transmitted Infections



https://link.springer.com/article/10.1007/s40506-015-0057-1

Meeste besmettingen via niet-zieken: asymptomatic spread



a good number – possibly anywhere from around 10% to 40% – of those infected might not experience symptoms.

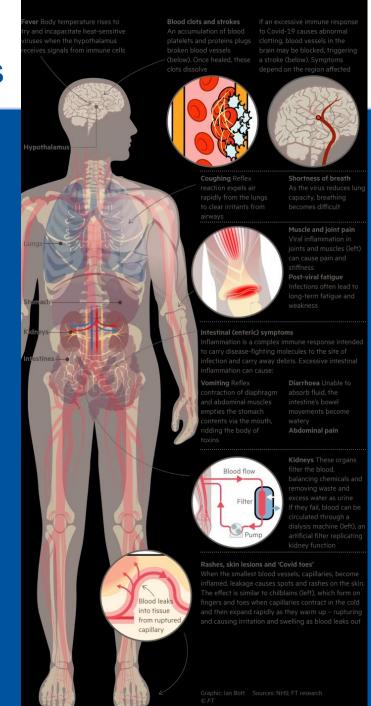
Of concern: The researchers found no difference in how potentially contagious those with and without symptoms were, based on <u>how much of the virus the test found</u> in indiduals' samples.

https://theconversation.com/infected-with-the-coronavirus-but-not-showing-symptoms-a-physician-answers-5-questions-about-asymptomatic-covid-19-137029

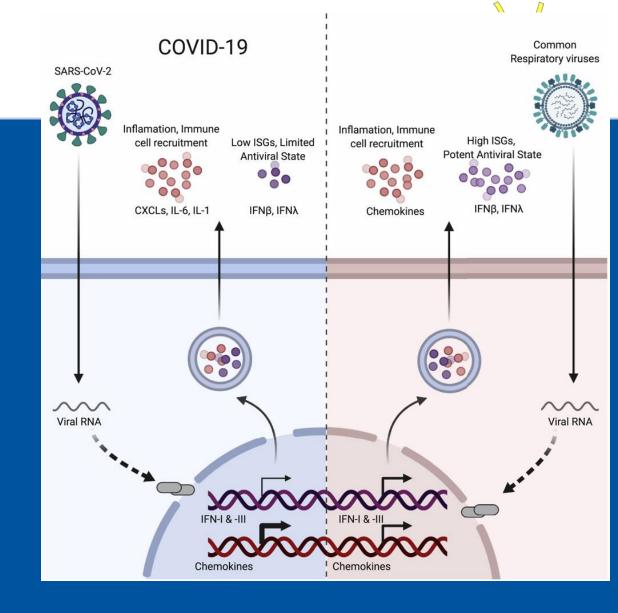
https://www.nature.com/articles/d41586-020-01354-0

From blood clots to 'Covid toe': the medical mysteries of coronavirus

- https://www.ft.com/content/be7e66c0-1243-45dd-829f-8b192c18acff
- https://www.nature.com/articles/d41586
 -020-01403-8



Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19



The IL-6 Blocker Tocilizumab Partially Rescues the Immune Dysregulation Driven by SARS-CoV-2



https://www.cell.com/cell-host-microbe/pdf/S1931-3128(20)30236-5.pdf? returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii% 2FS1931312820302365%3Fshowall%3Dtrue

Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals



An analysis of immune cell responses to SARS-CoV-2 from recovered patients identifies the regions of the virus that is targeted and also reveals cross-reactivity with other common circulating coronaviruses Understanding adaptive immunity to SARS-CoV-2 is important for vaccine development, interpreting coronavirus disease 2019 (COVID-19) pathogenesis, and calibration of pandemic control measures. Using HLA class I and II predicted peptide 'megapools', circulating SARS-CoV-2-specific CD8⁺ and CD4⁺ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively. CD4⁺ T cell responses to spike, the main target of most vaccine efforts, were robust and correlated with the magnitude of the anti-SARS-CoV-2 IgG and IgA titers. The M, spike and N proteins each accounted for 11-27% of the total CD4⁺ response, with additional responses commonly targeting nsp3, nsp4, ORF3a and ORF8, among others. For CD8⁺ T cells, spike and M were recognized, with at least eight SARS-CoV-2 ORFs targeted. Importantly, we detected SARS-CoV-2-reactive CD4⁺ T cells in ~40-60% of unexposed individuals, suggesting cross-reactive T cell recognition between circulating 'common cold' coronaviruses and SARS-CoV-2.

The sprint to solve coronavirus protein structures

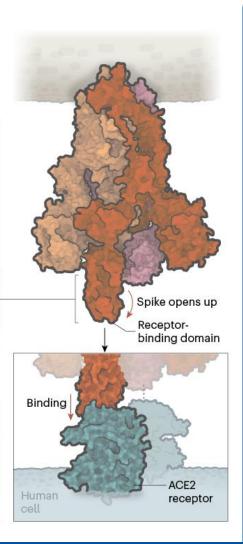
THE SPIKE LOCKS ON

Binding regions on the tip of the spike open out to attach to the human ACE2 receptor, found on lung cells and elsewhere in the body.

Targeting the spike

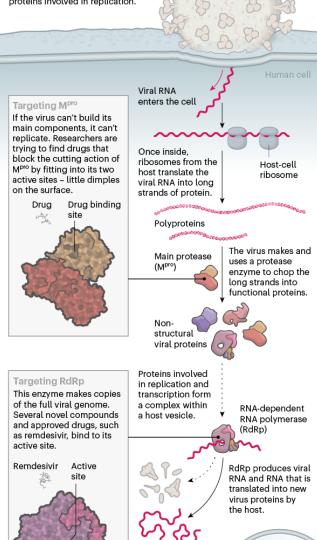
Researchers are finding antibodies — molecules made by the immune system to fight infection — that might interfere with the spike as a way to prevent or treat infection. Antibodies can stick to the top or side of the binding prong.





BREAKING THE CYCLE

Once the virus has fused with a host cell, the virus injects genetic material and uses the host machinery to make copies of itself. Many teams are studying viral proteins involved in replication.



packaged and released

onature

https://www.nature.com/articles/d41586-020-01444-z

Case clustering emerges as key pandemic puzzle



Large numbers of people working close together in a cold environment may make meatpacking plants fertile ground for the novel coronavirus.

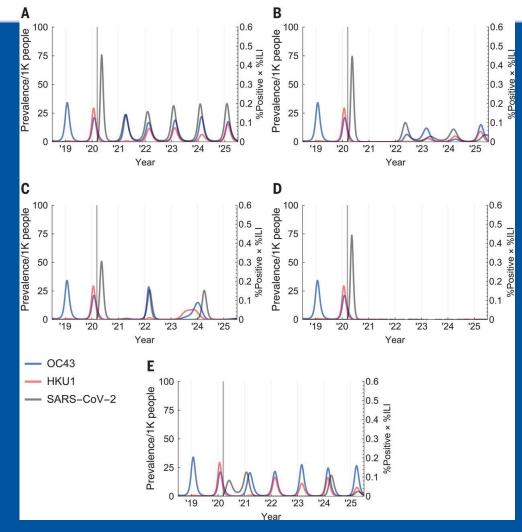


Superspreading usually happens indoors. Researchers in China studying the spread of the coronavirus outside Hubei province—ground zero for the pandemic—identified 318 clusters of three or more cases between 4 January and 11 February, only one of which originated outdoors. A study in Japan found that the risk of infection indoors is almost 19 times higher than outdoors.

https://science.sciencemag.org/content/368/6493/808

Fig. 3 Invasion scenarios for SARS-CoV-2 in temperate regions.



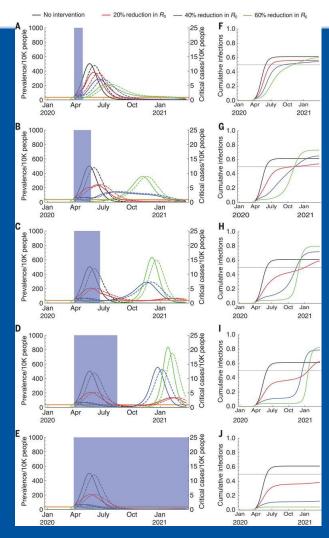


Stephen M. Kissler et al. Science 2020;368:860-868



Fig. 5 One-time social distancing scenarios with seasonal transmission.





Stephen M. Kissler et al. Science 2020;368:860-868



convalescent plasma and COVID-19.



comparing convalescent plasma with standard of care therapy in patients hospitalized for COVID-19 in the Netherlands. Patients were randomized 1:1 and received 300ml of plasma with anti-SARS-CoV-2 neutralizing antibody titers of at least 1:80. The primary endpoint was day-60 mortality and key secondary endpoints were hospital stay and WHO 8-point disease severity scale improvement on day 15. Results The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline. A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40). These observations caused concerns about the potential benefit of convalescent plasma in the study population and after discussion with the data safety monitoring board, the study was discontinued. No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58) was observed between plasma treated patients and patients on standard of care. Conclusion Most COVID-19 patients already have high neutralizing antibody titers at hospital admission. Screening for antibodies and prioritizing convalescent plasmasto riskegroups with recent symptom on set will be key to identify patients that may benefit from convalescent plasma.

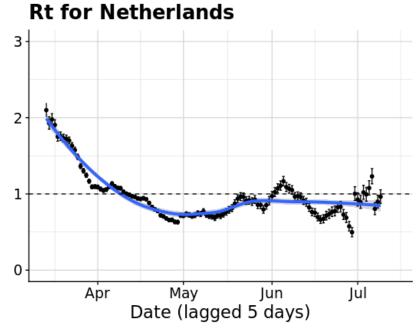
Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients

https://science.sciencemag.org/content/early/2020/07/10/science.abc6027

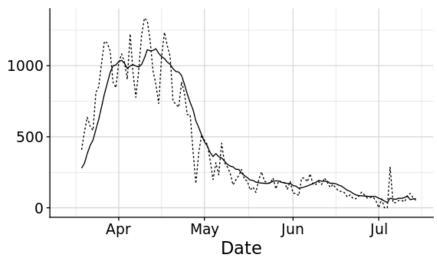


The results suggest that reduction of interferon levels in the blood is a hallmark of severe COVID-19. Treatments that counter inflammation and increase levels of interferons could help people with the disease, the researchers say

http://metrics.covid19-analysis.org/



New Cases for Netherlands



- 7-day average of new cases Daily new cases

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?

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report





We identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system.

The pandemic virus is slowly mutating. But does it matter? https://science.sciencemag.org/content/369/6501/238



Van mens naar fret, naar mens Is Corona al langer onder ons?

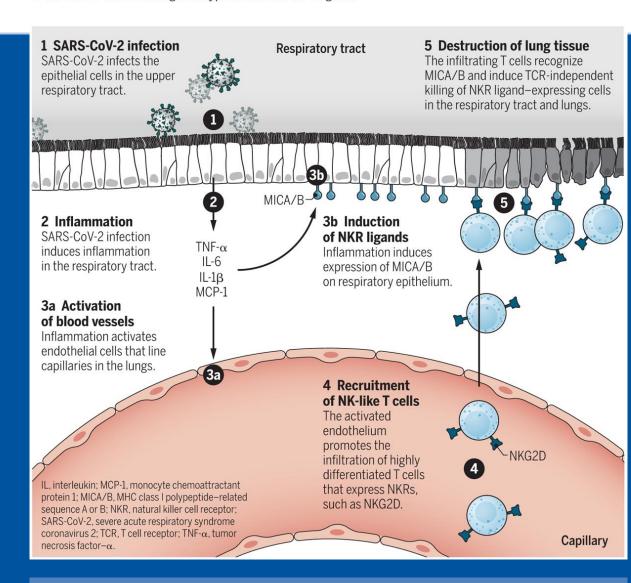


Aging immunity may exacerbate COVID-19

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

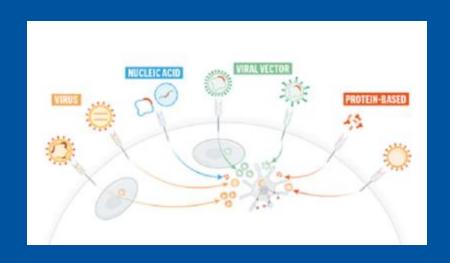
Highly differentiated T cells in older individuals may induce damage in SARS-CoV-2-infected lungs, as hypothesized in the diagram.



https://science.sciencemag.org/content/369/6501/256

The race for coronavirus vaccines: a graphical guide





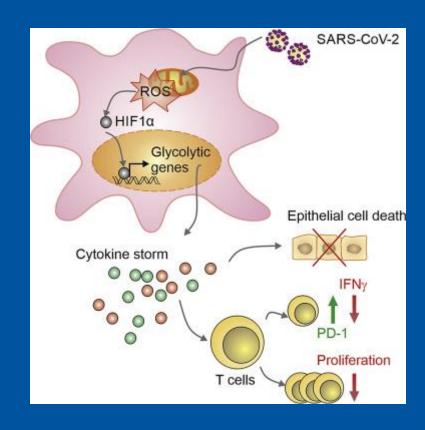
Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(20)30401-



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Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1α/Glycolysis-Dependent Axis https://www.cell.com/cell-metabolism/fulltext/S1550-4131(20)30365-



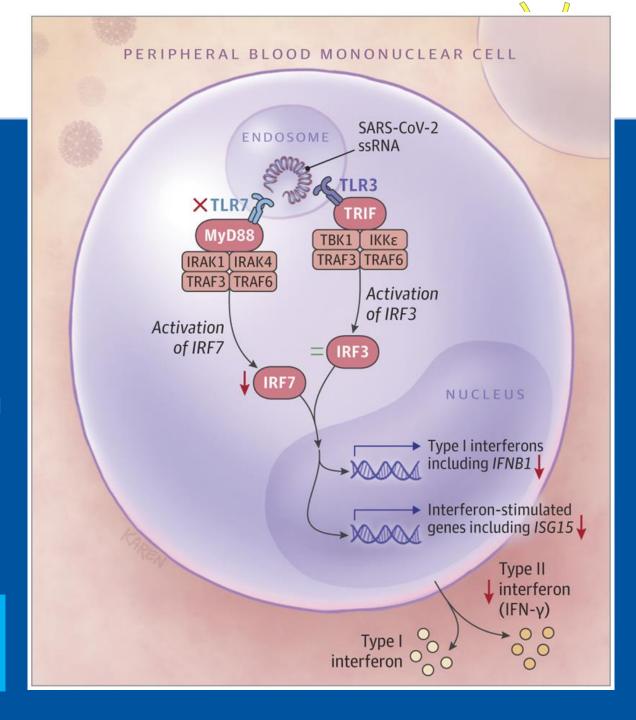


Belang van de aspecifieke afweer

⇒ Interferon geven, vroeg in een infectie?

TLR7 escapes X- inactivation, which could explain the higher basal expression levels of TLR7 and more prominent TLR7-induced type I IFN responses that have been observed in women compared with men. Conversely, the elevated TLR7 expression in women has been linked to an increased susceptibility to develop autoimmune disease.

https://jamanetwork.com/jo urnals/jama/fullarticle/2768 926





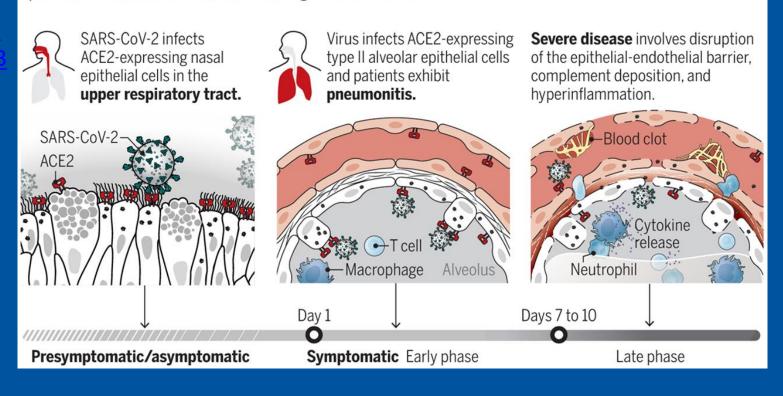
The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice

Pathogenesis and transmission of SARS-CoV-2 in golden hamsters

How does SARS-CoV-2 cause COVID-19?

Key phases of disease progression

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to angiotensin-converting enzyme 2 (ACE2). Initial infection of cells in the upper respiratory tract may be asymptomatic, but these patients can still transmit the virus. For those who develop symptoms, up to 90% will have pneumonitis, caused by infection of cells in the lower respiratory tract. Some of these patients will progress to severe disease, with disruption of the epithelial-endothelial barrier, and multi-organ involvement.



Why are people opposing vaccination:

https://www.nature.com/articles/d41586-020-02192-w



Larson argues that in privileged neoliberal contexts, people see health care as a service rather than a right, and consider all treatment a consumer choice.

Growing Internet use made it possible for people to share experiences across vast distances. A claims lents itself to viral replication. It was, Larson writes, "a simple, repeatable, confirmation of a brewing anxiety". It became a meme that spread like "digital wildfire", leading to resurgences of dangerous diseases.

To defeat the misinformation hydra, Larson calls on scientists to make engagement authentic — public input should begin with the setting of the research agenda and continue through open dialogue as new concerns emerge. All too often, she points out, scientific communication is reduced to marketing and sloganeering, rather than listening and integrating public debate. Vaccine hesitancy is a problem of dignity as much as of the abundance of falsehoods: individuals want to have their choices respected, amid growing distrust in authority.

How the pandemic might play out in 2021 and beyond

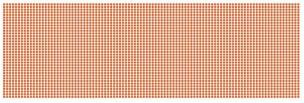
PREDICTING CASES AND DEATHS

Researchers modelled how COVID-19 is unfolding in 86 countries and found that official figures significantly understate infections and deaths so far. The team also projected that by March 2021, these countries will have experienced nearly 300 million infections and more than 2 million deaths.

• = 30,000

Reported infections July 2020: 10,300,000

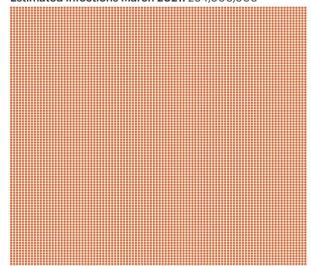
Estimated infections July 2020: 108,000,000



Reported deaths July 2020: 475,000

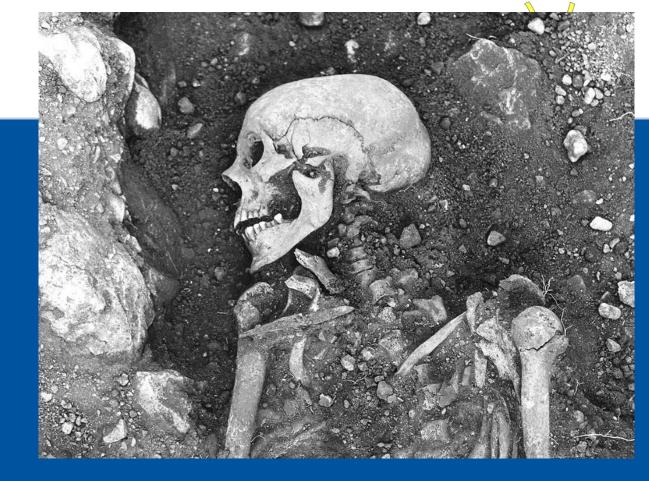
Estimated deaths July 2020: 699,000

Estimated infections March 2021: 294,000,000



Estimated deaths March 2021: 2,010,000

Smallpox and other viruses plagued humans much earlier than suspected



Designer antibodies could battle COVID-19 before vaccines arrive Aug. 4, 2020,



While the world is transfixed by the high-stakes race to develop a COVID-19 vaccine, an equally crucial competition is heating up to produce targeted antibodies that could provide an instant immunity boost against the virus. Clinical trials of these monoclonal antibodies, which could both prevent and treat the disease, are already underway and could produce signs of efficacy in the next few months, perhaps ahead of vaccine trials. "If you were going to put your money down, you would bet that you get the answer with the monoclonal before you get the answer with a vaccine," says Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases (NIAID). "Antibodies have the potential to be an important bridge until the vaccine is available," says Ajay Nirula, a vice president at Eli Lilly, one of several large companies investing in them. Likely to be more effective than the repurposed drugs now available, such as remdesivir and dexamethasone, antibodies could protect the highest risk health care workers from becoming infected while also lessening the severity of COVID-19 disease in hospitalized patients. But making monoclonals involves growing lines of antibodymaking B cells in bioreactors, raising concerns they could be scarce and expensive. On 15 July, Lilly, AbCellera, AstraZeneca, GlaxoSmithKline, Genentech, and Amgen jointly asked the U.S. Department of Justice (DOJ) whether they could share information about manufacturing their monoclonals without violating antitrust laws, "to expand and expedite production."

Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans

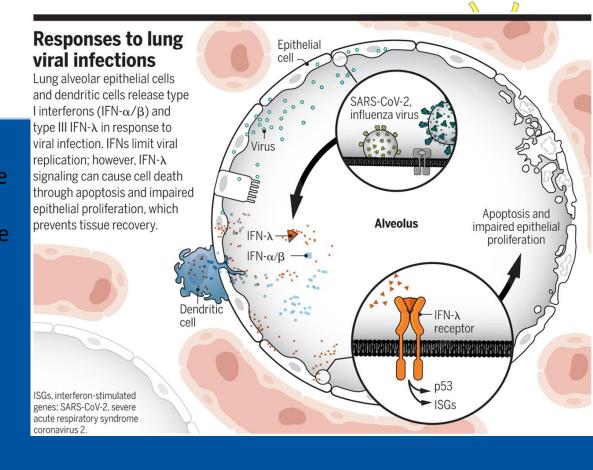


Many unknowns exist about human immune responses to the SARS-CoV-2 virus. SARS-CoV-2 reactive CD4⁺ T cells have been reported in unexposed individuals, suggesting pre-existing crossreactive T cell memory in 20-50% of people. However, the source of those T cells has been speculative. Using human blood samples derived before the SARS-CoV-2 virus was discovered in 2019, we mapped 142 T cell epitopes across the SARS-CoV-2 genome to facilitate precise interrogation of the SARS-CoV-2specific CD4⁺ T cell repertoire. We demonstrate a range of preexisting memory CD4⁺ T cells that are cross-reactive with comparable affinity to SARS-CoV-2 and the common cold coronaviruses HCoV-OC43, HCoV-229E, HCoV-NL63, or HCoV-HKU1. Thus, variegated T cell memory to coronaviruses that cause the common cold may underlie at least some of the extensive heterogeneity observed in COVID-19 disease.

COVID-19 in Africa: Dampening the storm? https://science.sciencemag.org/content/369/6504/624



Given the complexity of IFN responses in SARS-CoV-2 infection, further insight into their impact on the disease is of the utmost importance for continued development of drugs targeting the IFN pathways. Research is needed to establish whether IFN-λ and type I IFNs have similar effects or whether one is more beneficial or detrimental than the other. It should be conclusively established whether type I IFN responses are augmented in lungs of COVID-19 patients in contrast to the suppressed type I IFN responses observed in the blood. Further research will be necessary to determine whether suppression of blood type I IFN in critically ill COVID-19 patients is due to the ability of SARS-CoV-2 proteins to interfere with IFN signaling

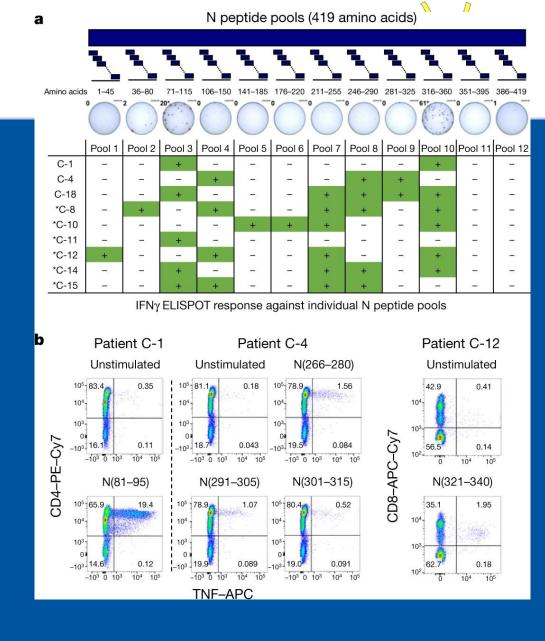


A mathematical model reveals the influence of population heterogeneity on herd immunity to SARS-CoV-2

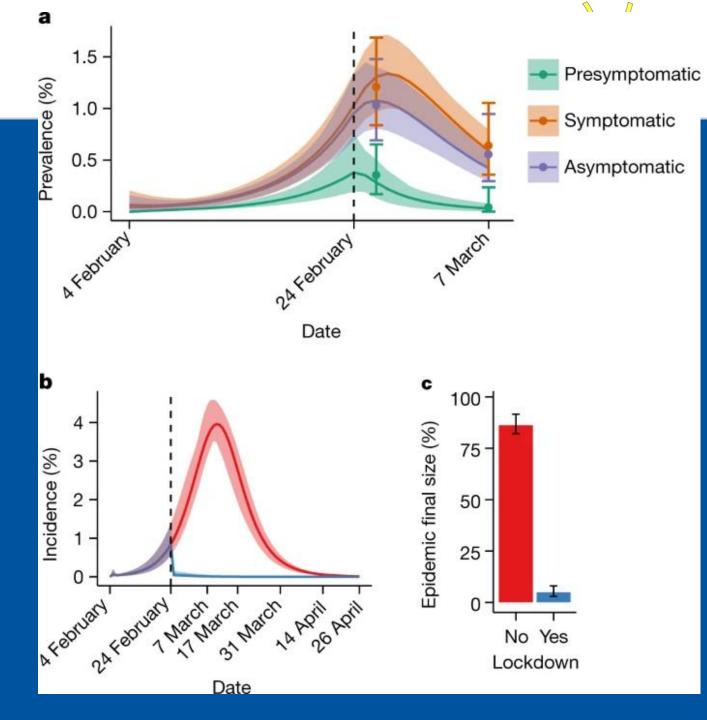


Heterogeneity and herd immunity

into population models for SARS-CoV-2, herd immunity can be achieved at a population-wide infection rate of \sim 40%, considerably lower than previous estimates. This shift is because transmission and SARS-CoV-2-specific <u>T cell immunity</u> in cases of COVID-19 and SARS, and uninfected controls



Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'



Clinical targeting of HIV capsid protein with a long-acting small molecule Nature volume 584, pages614–618(2020)



Six months of coronavirus: the mysteries scientists are still racing to solve https://media.nature.com/original/magazine-assets/d41586-020-01989-z.pdf



Structural basis of a shared antibody response to SARS-CoV-2



A common theme in antibody responses

In the fight against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), antibodies are a key tool, both as potential therapeutics and to guide vaccine development. Yuan *et al.* focused on finding shared antibody responses, in which multiple individuals develop antibodies against the same antigen using the same genetic elements and modes of recognition. The authors identified the immunoglobulin heavy-chain variable region 3-53 gene as the most frequently used among 294 antibodies that target the receptor-binding domain (RBD) of the viral spike protein. These antibodies have few somatic mutations, and crystal structures of two neutralizing antibodies bound to the RBD show that mostly germline-encoded residues are involved in binding. The minimal affinity maturation and high potency of these antibodies is promising for vaccine design.

COVID-19 treatment On the way to HIV-like control?



Association Between Administration of Systemic Corticosteroids and Mortality Among Critically III Patients With COVID-19 https://jamanetwork.com/journals/jama/fullarticle/2770279

Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2

https://www.nature.com/articles/s41586-020-2423-5

Distinct viral reservoirs in individuals with spontaneous control of HIV-1



Sustained, drug-free control of HIV-1 replication is naturally achieved in less than 0.5% of infected individuals (here termed 'elite controllers'),

using next-generation sequencing of near-full-length single HIV-1 genomes and corresponding chromosomal integration sites, we show that the proviral reservoirs of elite controllers frequently consist of oligoclonal to near-monoclonal clusters of intact proviral sequences. In contrast to individuals treated with long-term antiretroviral therapy, intact proviral sequences from elite controllers were integrated at highly distinct sites in the human genome and were preferentially located in centromeric satellite DNA or in Krüppel-associated box domaincontaining zinc finger genes on chromosome 19, both of which are associated with heterochromatin features. Moreover, the integration sites of intact proviral sequences from elite controllers showed an increased distance to transcriptional start sites and accessible chromatin of the host genome and were enriched in repressive chromatin marks => epigenetica

COVID-19 seems to be a normal virus Immunity also seems normal



COVID-19 makes B cells forget, but T cells remember



Understanding which arms of the immune response are responsible for protection against SARS-CoV-2 infection is key to predicting long-term immunity and to inform vaccine design. Two studies in this issue of *Cell* collectively suggest that although SARS-CoV-2 infection may blunt long-lived antibody responses, immune memory might still be achieved through virus-specific memory T cells.

Development and initial psychometric properties of a panic buying scale during COVID-19 pandemic



Fear is a powerful driver of human behavior, even more during times of crisis. Panic buying occurs when fear and panic influence behavior leading people to buy more things than usual. So far, no specific scale on this has been found in the major databases, thus the aim of this exploratory study is to develop a Panic Buying Scale (PBS) during COVID-19 pandemic. 393 Brazilians took part in this study (251 women and 142 men), answering a sociodemographic questionnaire and instruments of these variables: (1)panic buying, (2)impulse buying, (3)temporal focus, (4)optimism, (5)risk perception, (6)need for cognition. Data collection was conducted through an online questionnaire which was shared through social media networks, from April 10th to May 4th, 2020. Factorial exploratory and confirmatory analysis indicated that PBS has a unidimensional solution and showed satisfactory reliability indexes. Results revealed that men buy more by panic than women. PBS also was positively correlated with impulse buying, past and future temporal focus, and risk perception; as well as negatively correlated with optimism and age. Findings suggest that PBS is psychometrically acceptable in the Brazilian context. This new instrument can be useful to understand the psychosocial phenomena associated with consumer behavior. Future investigations could provide more evidences of validity in other contexts.

Emerging Pandemic Diseases: How We Got to COVID-19

https://www.cell.com/cell/pdf/S0092-8674(20)31012-6.pdf



Only a century ago, the 1918 influenza pandemic killed 50 million or more people, apparently the deadliest event in recorded human history (Morens and Taubenberger, 2020). 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).

Since there are four endemic coronaviruses that circulate globally in humans, coronaviruses must have emerged and spread pandemically in the era prior to the recognition of viruses as human pathogens. The severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) emerged from an animal host, likely a civet cat, in 2002–2003, to cause a near-pandemic before disappearing in response to public health control measures. The related Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV) emerged into humans from dromedary camels in 2012, but has since been transmitted inefficiently among humans (Cui et al., 2019). COVID-19, recognized in late 2019, 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 (Morens et al., 2020a ; Morens et al., 2020b). The causes of this new and dangerous situation are multifaceted, complex, and deserving of serious examination

Emerging Pandemic Diseases:

Anthony S. Fauci

https://www.cell.com/cell/pdf/S0092-8674(20)31012-6.pdf



Pandemics such as COVID-19 are not entirely new phenomena. Newly emerging (and reemerging) 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 (Dobson and Carper, 1996; Morens et al., 2020b; Morens et al., 2008a). These beginnings of domestication were the earliest steps in man's systematic, widespread manipulation of nature. Ancient emerging zoonotic diseases (see Box 1) 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.

Do the benefits outweigh the consequences?

=> Hariri

Flawed interferon response spurs severe illness



From the first months of the COVID-19 pandemic, scientists baffled by the disease's ferocity have wondered whether the body's vanguard virus fighter, a molecular messenger called type I interferon, is missing in action in some severe cases. Two papers published online in *Science* this week confirm that suspicion. They reveal that in a significant minority of patients with serious COVID-19, the interferon response has been crippled by genetic flaws or by rogue antibodies that attack interferon itself. "Together these two papers explain nearly 14% of severe COVID-19 cases. That is quite amazing," says Qiang Pan-Hammarström, an immunologist at the Karolinska Institute.

Tadatsugu Taniguchi, a pioneering interferon scientist and emeritus professor at the University of Tokyo, calls the discoveries "remarkable." He says they highlight the "critical" role of type I interferons in SARS-

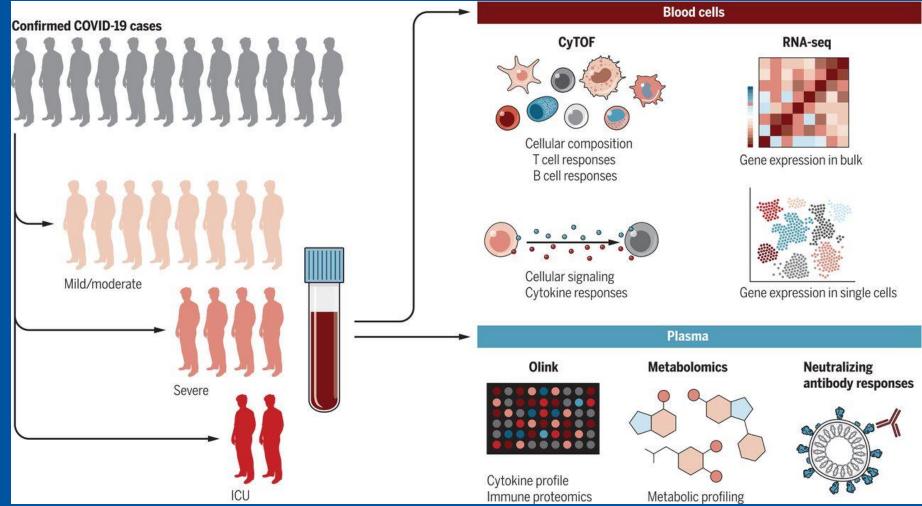
CoV-2 infection and the development of potentially lethal COVID-19.

Co-author Isabelle Meyts, a pediatric immunologist at the University Hospitals Leuven, was struck by one paper's finding that rogue antibodies underlie COVID-19 in 10% of gravely ill patients: "There has never been any infectious disease explained at this level by a factor in the human body. And it's not an isolated cohort of Europeans. Patients are from all over the world, all ethnicities." Another finding, that 94% of the patients with interferon-attacking antibodies were male, also helps explain why men face higher risk of severe disease.

The paired studies have immediate practical implications. Synthetic interferons, long used to treat other diseases, might help some at-risk patients, as might other therapies aimed at removing the damaging antibodies. A common kind of antibody test could be readily developed and return answers in hours. Those found to be at high risk of developing severe COVID-19 could take precautions to avoid exposure or be prioritized for vaccination, says Elina Zuniga, an immunologist who studies interferons at the University of California, San Diego

The science and medicine of human immunology





https://www.sciencemag.org/news/2020/09/provocative-results-boost-hopes-antibody-treatment-covid-19



Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans



Preexisting immune response to SARS-CoV-2

No sign of a health-economy trade-off, quite the opposite

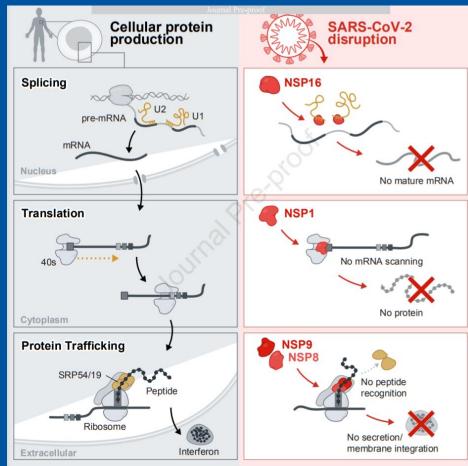
https://ourworldindata.org/covid-health-economy



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



'Near extinction' of influenza in NZ as numbers drop due to lockdown https://www.rnz.co.nz/national/programmes/sunday/audio/2018767
843/near-extinction-of-influenza-in-nz-as-numbers-drop-due-to-



lockdown

Bacteria sting viral invaders



The cGAS–STING signalling pathway, which has a key role in antiviral immune responses in mammals, is found to have originated as an immune-defence system that protects bacteria against viral infection.

Relatives of rubella virus in diverse mammals



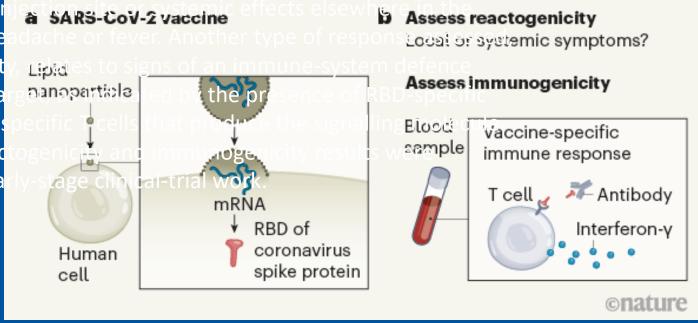
Since 1814, when rubella was first described, the origins of the disease and its causative agent, rubella virus (Matonaviridae: Rubivirus), have remained unclear¹. Here we describe ruhugu virus and rustrela virus in Africa and Europe, respectively, which are, to our knowledge, the first known relatives of rubella virus. Ruhugu virus, which is the closest relative of rubella virus, was found in apparently healthy cyclops leaf-nosed bats (*Hipposideros cyclops*) in Uganda. Rustrela virus, which is an outgroup to the clade that comprises rubella and ruhugu viruses, was found in acutely encephalitic placental and marsupial animals at a zoo in Germany and in wild yellow-necked field mice (Apodemus flavicollis) at and near the zoo. Ruhugu and rustrela viruses share an identical genomic architecture with rubella virus^{2,3}. The amino acid sequences of four putative B cell epitopes in the fusion (E1) protein of the rubella, ruhugu and rustrela viruses and two putative T cell epitopes in the capsid protein of the rubella and ruhugu viruses are moderately to highly conserved 4.5.6. Modelling of E1 homotrimers in the post-fusion state predicts that ruhugu and rubella viruses have a similar capacity for fusion with the hostcell membrane⁵. Together, these findings show that some members of the family *Matonaviridae* can cross substantial barriers between host species and that rubella virus probably has a zoonotic origin. Our findings raise concerns about future zoonotic transmission of rubella-like viruses, but will facilitate comparative studies and animal models of rubella and congenital rubella syndrome.

Assessing a vaccine that targets the SARS-CoV-2 coronavirus.



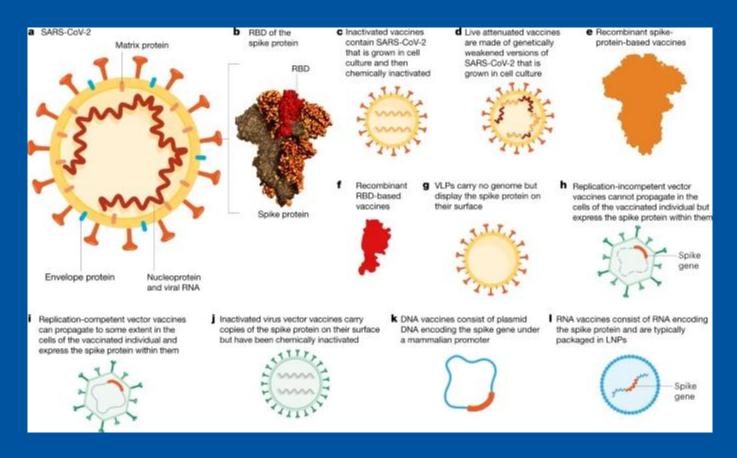
Mulligan et al. $\frac{3}{2}$ and Sahin et al. $\frac{4}{2}$ report vaccine clinical-trial results for a combined phase I and phase II study. **a**, The vaccine contains messenger RNA in a lipid nanoparticle that is taken up by human cells. The mRNA encodes a region of the coronavirus spike protein termed the receptor-binding domain (RBD). **b**, After vaccination, the authors monitored the trial participants' responses. One type of response assessed was 'reactogenicity' — signs of the body's reaction to vaccination, such as

local swelling at the inbody, for example, he called immunogenicit against the vaccine ta antibodies, and RBD-sinterferon-y. The reac acceptable for this ea



SARS-CoV-2 vaccines in development https://www.nature.com/articles/s41586-020-2798-3



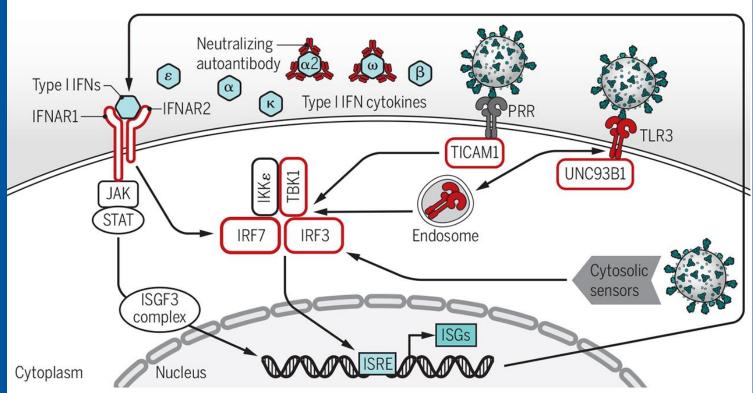


Susceptibility to severe COVID-19



Viral sensing by the type I interferon pathway

Viral particles are sensed by various PRRs, including cytosolic sensors. Type I IFNs are potent antiviral cytokines produced by innate immune cells. They bind a specific cell-surface receptor and signal through the JAK-STAT pathway to induce expression of ISGs that encode other antiviral proteins and various transcription factors. Subsets of patients with severe COVID-19 have loss-of-function genetic variants in several members of the type 1 IFN pathway (red) or neutralizing autoantibodies against type I IFNs, specifically IFN- α 2 and IFN- ω .



COVID-19, coronavirus disease 2019; IFN, interferon; IFNAR, type I IFN receptor; ISG, IFN-stimulated gene; IKKe, inhibitor of nuclear factor kB kinase subunit e; ISRE, IFN-stimulated response element; IRF, IFN-regulatory factor; JAK, Janus kinase; PRR, pattern recognition receptor; STAT, signal transducer and activator of transcription; TBK1, TANK-binding kinase 1; TICAM1, TIR domain—containing adapter molecule 1; TLR, Toll-like receptor.

Supershedder kan coronavirus verspreiden via aerosol



Verspreidt het coronavirus zich nou wel of niet via fijne zweefdruppels? Een groot overzicht laat zien: bij de meeste mensen niet, maar bij sommige *supershedders* wel. 20 oktober 2020 NRC

De kans dat er levend virus in hun aerosol-ademdruppels zit (druppels kleiner dan 5 micrometer, vijf duizendste millimeter, in doorsnede) is bij de meeste geïnfecteerden kleiner dan 0,001 procent, berekenden de onderzoekers.

=> Stoppen met mondkapjes?

The engines of SARS-CoV-2 spread



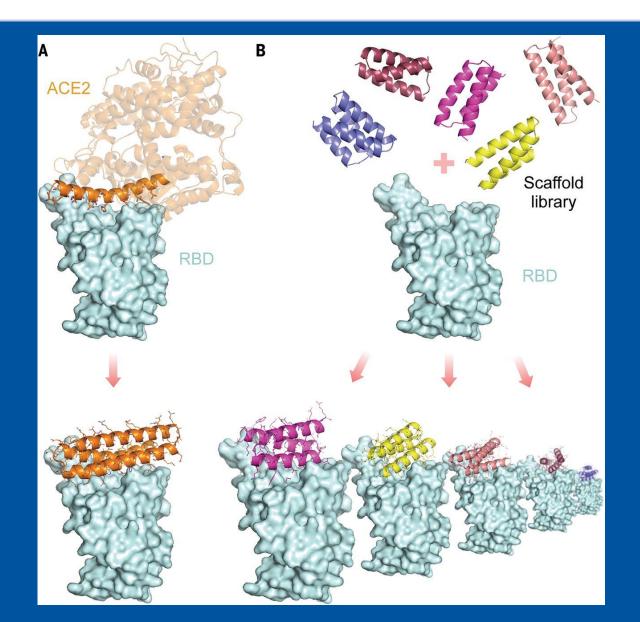
The majority of SARS-CoV-2 infections likely occur within households and other residential settings (such as nursing homes). This is because most individuals live with other people, and household contacts include many forms of close, high-intensity, and long-duration interaction. Both early contact tracing studies and a large study of more than 59,000 case contacts in South Korea found household contacts to be greater than six times more likely to be infected with SARS-CoV-2 than other close contacts (1, 2). Household contacts accounted for 57% of identified secondary infections in the South Korean study, despite exhaustive tracking of community contacts. Globally, the proportion of cases attributable to household transmission will vary because of multiple factors, including household size. Contact studies suggest that 17 to 38% of contacts occur in households, implying that 46 to 66% of transmission is household-based (using the standard formula for attributable fraction) (3). This is consistent with household contact being a key driver of transmission for other respiratory viruses.

Even among close contacts within households, there are considerable heterogeneities in transmission risk. Spouses of index cases are more than twice as likely to be infected as other adult household members, and symptomatic index cases may be more likely to transmit the virus (4). Moreover, older age is associated with increased susceptibility to infection, increased transmissibility, and severe disease (4). Older members may face extra risk in multigenerational households if younger members have unavoidable work or school obligations, although young children may be less susceptible to infection and transmit the virus less readily (4).

=> Vooral niet stoppen met social distancing!

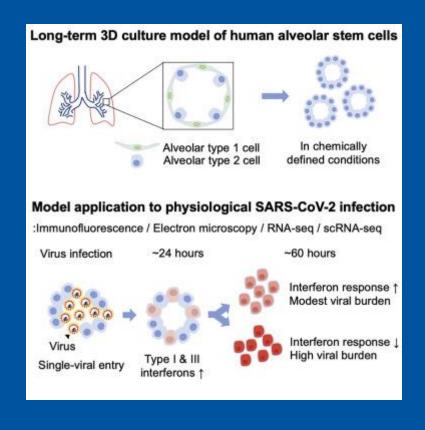
De novo design of picomolar SARS-CoV-2 miniprotein inhibitors





Three-dimensional human alveolar stem cell culture models reveal infection response to SARS-CoV-2





EmergingPandemicDiseases: HowWeGot toCOVID-19 Anthony S. Fauci



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.

Het echte probleem: individualisering



Individuen willen niet meer het (kleine) risico dragen voor de hele groep

Oplossing: Alleen die mensen vaccineren die er direct profijt van hebben.

NB Een kind heeft ook veel profijt van vaccinaties: een zeer kleine kans op bijwerkingen v een grote kans op een ernstige ziekte

Afweer als BOA, politie, leger



Afweer is homeostatisch, en getrapt.

Als er iets mis is moet het dat vroeg detecteren, en gedoseerd reageren Eerst als BOA: wat is hier aan de hand? Dat gaan we dus niet meer doen! Als dat niet werkt als politie: U wordt gearresteerd! En pas als dat niet werkt als leger: we gaan u bombarderen!

NB Corona weet de BOA en soms zelfs de politie om de tuin te leiden. Nee hoor, ik steek helemaal geen vuurwerk af agent..

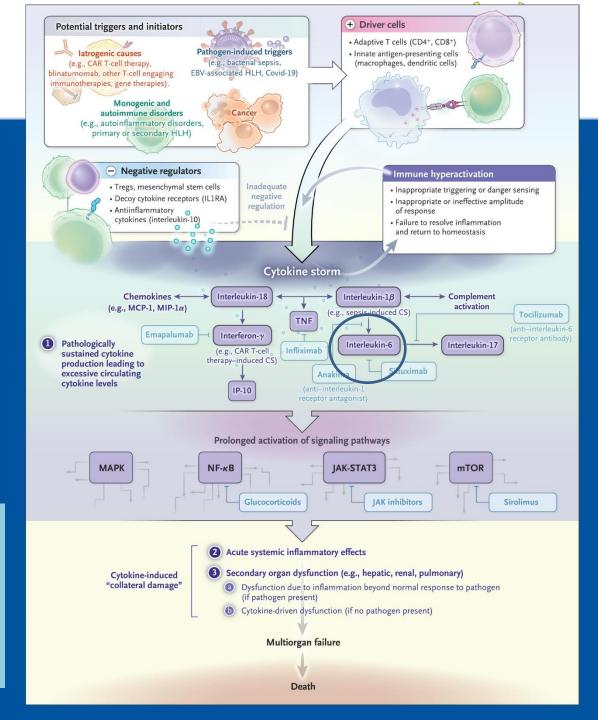
Als dit lang genoeg duurt moet dan uiteindelijk het leger (of de ME) er aan te pas komen => duindorp/Urk

Cytokine Storm and IL-6

However, a-IL-6 (Tocilizumab) was not effective for preventing intubation or death in moderately ill hospitalized patients with Covid-19

https://www.nejm.org/doi/full/10.1056/NEJMra2026131

https://www.nejm.org/doi/full/10.1056/NEJMoa2028836



Adjuvants

https://www.nature.com/articles/s41577-020-0358-6 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7241103/

https://www.tholancot.com/action/showPdf2nii=S0140

6736%2820%2932661-1

https://www.thelancet.com/journals/lancet/article/PIIS0140-

6736(2032466-1/fulltext

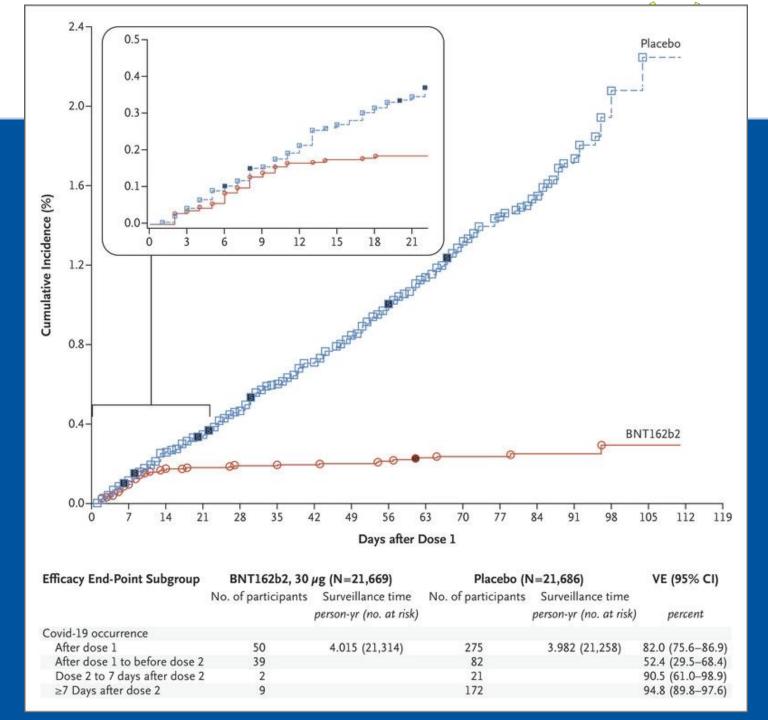
Box 1 US-licensed vaccines containing aluminium

- Anthrax
- Hepatitis A
- Hepatitis B
- Human papillomavirus (HPV)
- Diphtheria—pertussis—tetanus (DPT and TdaP)
- •Haemophilus influenzae type b
- Japanese encephalitis
- Pneumococcal conjugate vaccines



Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

https://www. nejm.org/doi/ full/10.1056/ NEJMoa2034 577





https://www.technologyreview.com/2020/12/09/1013538/what-are-the-ingredients-of-pfizers-covid-19-vaccine/



What's actually on the official ingredient list? This week woman became the first person outside of a trial to get the newly approved vaccine developed by Pfizer and BioNTech, and the US could greenlight the same inoculation as soon as Thursday, December 10. Along with the regulatory actions over the last week have come the most detailed disclosures yet of the new vaccine's makeup. Here, for instance, is what the US Food and Drug Administration says is in Pfizer's vaccine:

Active Ingredient

•nucleoside-modified messenger RNA (modRNA) encoding the viral spike glycoprotein (S) of SARS-CoV-2

Lipids

- (4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis (ALC-3015)
- •(2- hexyldecanoate),2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
- •1,2-distearoyl-snglycero-3-phosphocholine (DPSC)
- cholesterol

Salts

- potassium chloride
- monobasic potassium phosphate
- •sodium chloride
- •basic sodium phosphate dihydrate

Other

sucrose

Reading the ingredient list is like looking at the side of a cereal box, except that you need a degree in organic chemistry to understand it. We got help from various scientists and biotech entrepreneurs to understand what each of the ingredients does and make some educated guesses about others.

The mRNA

Pfizer's vaccine is the first on the market that consists of actual genetic information from a virus in the form of messenger RNA, or mRNA, a type of molecule whose usual job is to transport copies of genetic instructions around a cell to guide the assembly of proteins. Imagine an mRNA as a long ticker tape carrying instructions. It's fairly delicate stuff, and that's why Pfizer's vaccine needs to be kept at around - 100 °F (-73 °C) until it's used.

The new vaccine, delivered as a shot in the arm muscle, contains an RNA sequence taken from the virus itself; it causes cells to manufacture the big "spike" protein of the coronavirus, which the pathogen uses to glom onto a person's cells and gain entry. On its own, without the rest of the virus, the spike is pretty harmless. But your body still reacts to it. This is what leaves you immunized and ready to repel the real virus if it turns up.

The mRNA in the vaccine, to be sure, isn't quite the same as the stuff in your body. That's good, because a cell is full of defenses ready to chop up RNA, especially any that doesn't belong there. To avoid that, what's known as "modified nucleosides" have been substituted for some of the mRNA building blocks.

But Pfizer is holding back a little. The spike gene sequence can be tweaked in small ways for better performance, by means that include swapping letters. We don't think Pfizer has said exactly what sequence it is using, or what modified nucleosides. That means the content of the shot may not be 100% public.

The lipids

The Pfizer vaccine, like one from Moderna, uses lipid nanoparticles to encase the RNA. The nanoparticles are, basically, tiny greasy spheres that protect the mRNA and help it slide inside cells. These particles are probably around 100 nanometers across. Curiously, that's about the same size as the coronavirus itself.

Pfizer says it uses four different lipids in a "defined ratio." The lipid ALC-0315 is the primary ingredient in the formulation. That's because it's ionizable—it can be given a positive charge, and since the RNA has a negative one, they stick together. It's also a component that can cause side-effects or allergic reactions. The other lipids, one of which is the familiar molecule cholesterol, are "helpers" that give structural integrity to the nanoparticles or stop them from clumping. During manufacturing, the RNA and the lipids are stirred into a bubbly mix to form what the FDA describes as a "white to off-white" frozen liquid.

Salts

The Pfizer vaccine contains four salts, one of which is ordinary table salt. Together, these salts are better known as phosphate-buffered saline, or PBS, a very common ingredient that keeps the pH, or acidity, of the vaccine close to that of a person's body. You'll understand how important that is if you've ever squeezed lemon juice on a cut. Substances with the wrong acidity can injure cells or get quickly degraded.

Sugar

The vaccine includes plain old sugar, also called sucrose. It's acting here as a cryoprotectant to safeguard the nanoparticles when they're frozen and stop them from sticking together.

How kids' immune systems can evade COVID

Childrens' untrained immune response seems to be key to eliminating SARS-CoV-2.



https://www.nature.com/articles/d41586-020-03496-7

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.



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

The lightning-fast quest for COVID vaccines — and what it means for other diseases

https://www.nature.com/articles/d41586-020-03626-1

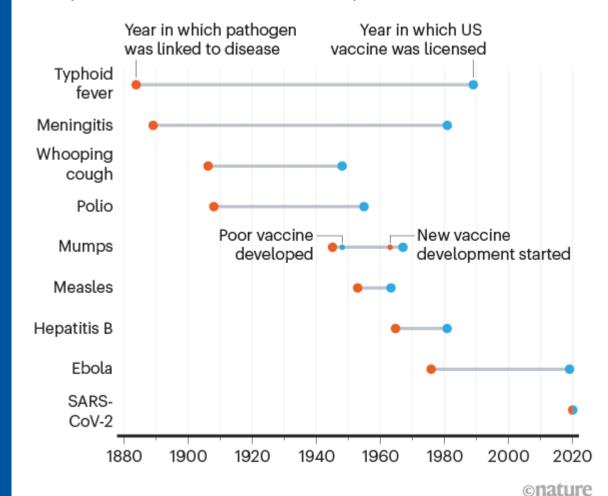


The world was able to develop COVID-19 vaccines so quickly because of years of previous research on related viruses and faster ways to manufacture vaccines, enormous funding that allowed firms to run multiple trials in parallel, and regulators moving more quickly than normal.

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.



Fast-spreading U.K. virus variant raises alarms



Another major question is how the virus accumulated a host of mutations in one go. So far, SARS-CoV-2 typically acquired only one to two mutations per month. Scientists believe the new variant may have gone through a lengthy bout of rapid evolution in a chronically infected patient who then transmitted the virus. "We know this is rare but it can happen," says World Health Organization epidemiologist Maria Van Kerkhove.

The United Kingdom has one of the most elaborate monitoring systems in the world, she says. "My worry is: How much of this is happening globally, where we don't have sequencing capacity?"



Mobility network models of COVID-19 explain inequities and inform reopening => sociale wetenschap



we find that disadvantaged groups have not been able to reduce their mobility as sharply, and that the points of interest that they visit are more crowded and are therefore associated with higher risk. By capturing who is infected at which locations, our model supports detailed analyses that can inform more-effective and equitable policy responses to COVID-19. Certain categories of POIs also contributed far more to infections (for example, full-service restaurants and hotels), although our model predicted time-dependent variation in how much each category contributed. For example, restaurants and fitness centres contributed less to the predicted number of infections over time, probably because of lockdown orders to close these POIs, whereas grocery stores remained steady or even grew in their contribution,

https://www.nrc.nl/nieuws/2020/12/17/ics-ontlast-doordat-oudere-thuis-stierf-a4024379



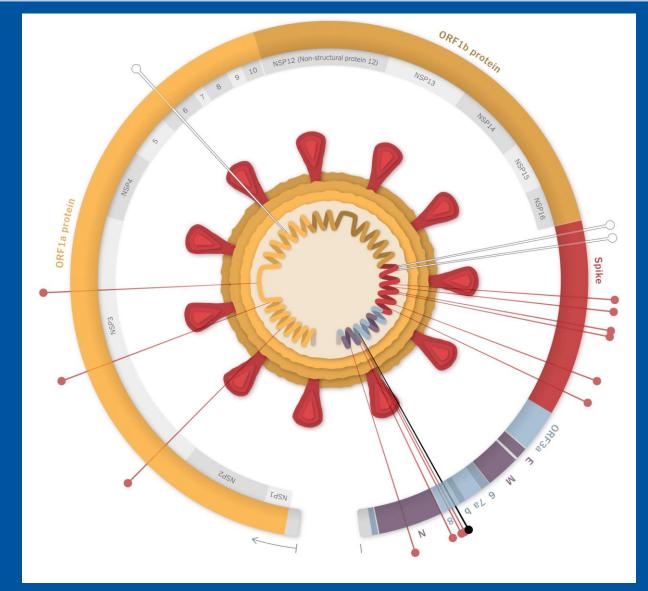
Arthritis drugs could help save lives of Covid patients, research finds Results suggest tocilizumab and sarilumab could cut relative risk of death of those in intensive care by 24%



Both tocilizumab and sarilumab are what are known as IL-6 receptor antagonists, which dampen down the effect of proteins that can cause an overreaction of the immune system. Severe Covid has previously been linked to dangerous levels of inflammation in the body.

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.

Vaccin van de firma Pfizer/BioNTech heet Comirnaty® De werkzame stof (RNA) in dit vaccin heet TOZINAMERAN.



De werkzame stof is in het Comirnaty® vaccin is Tozinameran, een stukje RNA dat codeert voor de spijkereiwitten (de uitsteeksels) van het coronavaccin.

Daarnaast zitten de volgende hulpstoffen in het vaccin:

CHOLESTEROL

DINATRIUMWATERSTOFFOSFAAT 2-WATER (E 339) KALIUMCHLORIDE

KALIUMDIWATERSTOFFOSFAAT 0-WATER (E 340) NATRIUMCHLORIDE

SACCHAROSE WATER VOOR INJECTIE

1,2-DISTEAROYL-SN-GLYCERO-3-PHOSPHOCHOLINE

2-[(POLYETHYLEENGLYCOL)-2000]-N,N-DITETRADECYLACETAMIDE (PEG)

((4-HYDROXYBUTYL)AZAANDIYL)BIS(HEXAAN-6,1-DIYL)BIS(2-HEXYLDECANOAAT)

Vaccins en allergie NTvG 2021

Overgevoeligheidsreacties op basis van preklinisch, fase I/II/III trials en eerdere reacties op vaccincomponenten. De causaliteit is niet in alle gevallen even duidelijk.

Afkortingen: COVID, Coronavirus disease; DSCP, 1,2-distearoyl-sn-glycero-3-fosfocholine; EDTA, disodium edetate dehydrate; PEG, polyethyleenglycol;

Afkortingen vaccins: As, University of Oxford & AstraZeneca; Co, Comirnaty van BioNtech & Pfizer; Cu, Curevac; Mo, Moderna; No, Novavax; Sa, Sanofi & GSK

Alleen adjuvans in reguliere vaccins

Component	Overgevoeligheidsreacties op	Functie	Vaccins
	componenten ¹		
Adjuvantia, zoals MatrixM	Ernstige (anafylactische) reacties zijn niet	Versterking	No / Sa
	bekend, en wel te verwachten.	immuunrespons	
Azijnzuur/acetaat	-	Buffer	Co / Cu
Azijiizuur/acetaat	-	builei	co / cu
EDTA	Urticaria, jeuk, zwelling en roodheid	Anti-oxidant	As
EDIA		Anti oxidant	As
	gezicht, contact dermatitis		
Ethanol		Anti-oxidant	As
			•
		- "	
L-histidine	-	Buffer	As
lonen	-	Regeling ionsterkte	Co / Cu / As
ionen		negering ionsterkte	C0 / Cu / A3
Fosfolipiden (DSCP)	-	Bescherming/ transport	Co / Mo / Cu
		mRNA	
and the idea	A f d ti b ti-	Deceleration/torus	Ca / Naa / Cu
gePEGyleerde lipiden	Anafylactische reactie	Bescherming/ transport	Co / Mo / Cu
		mRNA	
Overige lipiden (oa	-	Bescherming/ transport	Co / Mo / Cu
cholesterol)		mRNA	
undicaterory			
Polysorbaat	Anafylactische reactie	Emulgator	As
Suilvava		Thormostobili	Co / Mo / Cu / A-
Suikers	-	Thermostabilisator	Co / Mo / Cu / As
Tromethamine	Anafylactische reactie	Buffer	Co / Cu

Vaccins en allergie PEG



A **PEGylated** lipid is used as an excipient in both the Moderna and Pfizer-BioNTech vaccines for S Both RNA vaccines consist of Messenger RNA, or mRNA, encased in a bubble of oily molecules called lipids. Proprietary lipid technology is used for each. In both vaccines, the bubbles are coated with a stabilizing molecule of polyethylene glycol.[medical citation needed] As of December 2020 there is some concern that PEG could trigger allergic reaction, and in fact allergic reactions are the driver for both the UK and Canadian regulators to issue an advisory, noting that: two "individuals in the U.K... were treated and have recovered" from anaphylactic shock. [9][10] As of 18 December, the US CDC stated that in their jurisdiction six cases of "severe allergic reaction" had been recorded from more than 250,000 vaccinations, and of those six only one person had a "history of vaccination reactions"

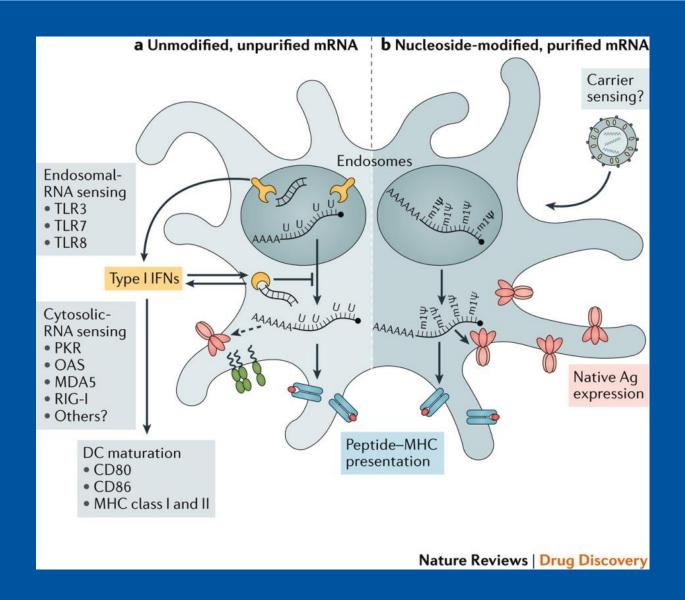
mRNA vaccines — a new era in vaccinology https://www.nature.com/articles/nrd.2017.243



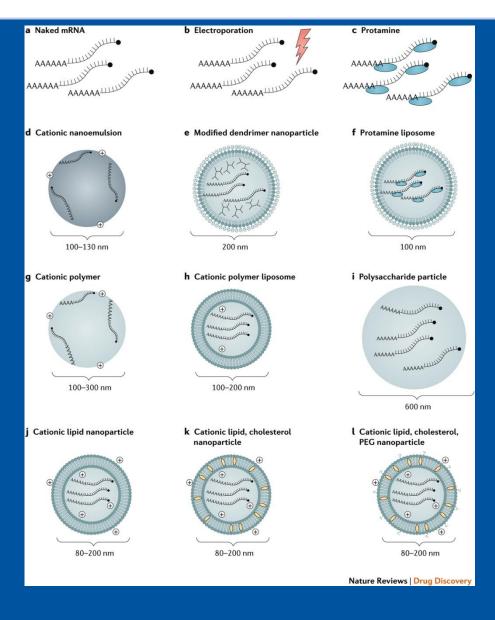
Review published: 12 January 2018, => dus al jaren in ontwikkeling Maar vooral als nieuwe kanker behandeling. Gebruik voor reguliere bescherming tegen virussen is nieuw.

Exogenous mRNA is inherently immunostimulatory, as it is recognized by a variety of cell surface, endosomal and cytosolic innate immune receptors (Fig. 1) (reviewed in Ref. 35). 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 (DC) 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 9,13. 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.

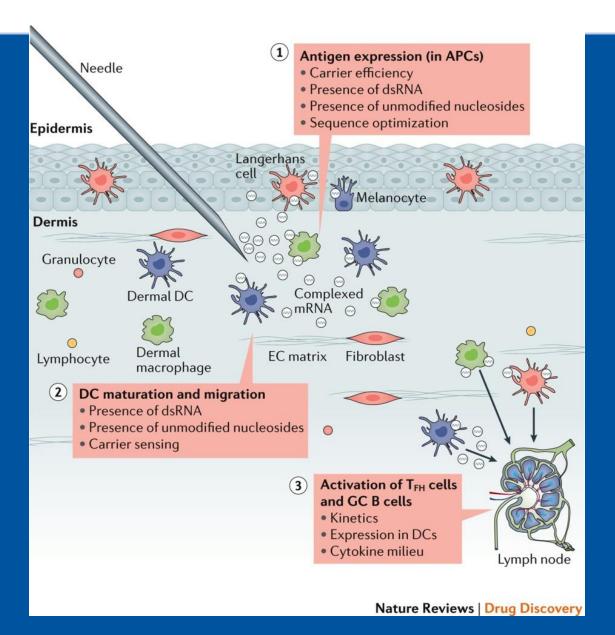










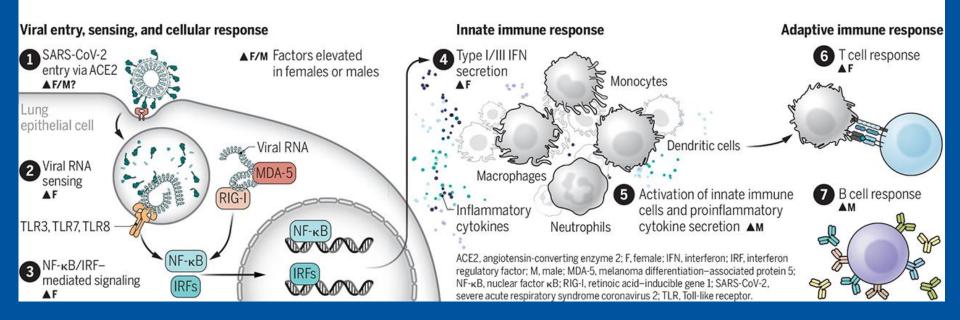


Sex differences in immune responses, including COVID-19



Sex differences in factors that affect infection and immunity in COVID-19

SARS-CoV-2 binds to ACE2 to initiate host cell entry. This activates the viral RNA sensors TLR3/7/8 and RIG-I–MDA-5, which induce secretion of IFNs and other inflammatory cytokines, leading to innate and adaptive immune responses. In each of these steps, sex differences may shape the antiviral immune response.



- Females have better INF responses and overall innate defence
- Males later in the infection overreact, leading to cytokine storms

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

May I Borrow Your Covid Immunity?

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



- 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.
- Our immune systems' ability to churn out a countless variety of antibodies means that sometimes, someone makes a spectacularly successful one an antibody that can be turned into a drug to protect many people. The coronavirus antibodies in the blood of one person from Seattle, Washington, were developed into the promising COVID drug bamlanivimab, made by the pharmaceutical company Eli Lilly. The work builds on efforts to develop an antibody treatment for HIV, based on the uniquely powerful antibodies from a person known as Donor 45. This week scientists announced that they finally had the first evidence that an antibody drug could protect against HIV.



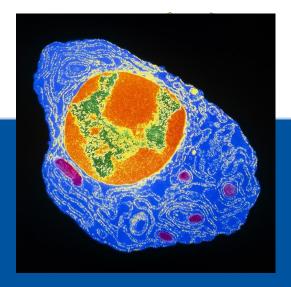
- Article | 27 January 2021
- Ebola virus antibody decay—stimulation in a high proportion of survivors
- In many survivors of Ebola virus infection, antibody responses show longterm patterns of decline followed by restimulation, possibly owing to recrudescence of persisting virus.
- Charlene Adaken
- , Janet T. Scott
- & Georgios Pollakis



- A paradigm shift to combat indoor respiratory infection
- BY LIDIA MORAWSKA,
- Building ventilation systems must get much better

Had COVID? You'll probably make antibodies for life

- A bone-marrow plasma cell (artificially coloured). Such cells, which produce antibodies, linger for months in the bodies of people who have recovered from COVID-19.Credit: Dr Gopal Murti/Science Photo Library
- Many people who have been infected with SARS-CoV-2 will <u>probably make ant</u> <u>ibodies against the virus for most of their lives</u>, suggest researchers who have identified long-lived antibody-producing cells in the bone marrow of people who have recovered from COVID-19.
- A team led by immunologist Ali Ellebedy at Washington University in St. Louis, Missouri, tracked antibody production in 77 people who had recovered from mostly mild cases of COVID-19. As expected, SARS-CoV-2 antibodies plummeted in the four months after infection. But this decline slowed, and up to eleven months after infection, the researchers could still detect antibodies that recognized the SARS-CoV-2 spike protein (J. S. Turner et al. Nature https://doi.org/gj6hmb; 2021).
- In bone-marrow samples collected from a subset of participants, the scientists found ultra-low but detectable populations of bone-marrow plasma cells, the formation of which was triggered by the individuals' coronavirus infections. These cells hide away in bones, trickling out antibodies for decades.
- The study provides evidence that immunity generated by SARS-CoV-2 infection could be extraordinarily long-lasting.



New, fast-spreading coronavirus variants

https://www.nature.com/articles/d41586-021-01390-4



- Reassuringly, no mutation in any of the variant subtypes is associated with increased disease severity.
- Lab studies indicate that vaccines could be less effective against the B.1.617.1 subtype¹. Results from similar experiments with B.1.617.2 have not yet been published, but data released by Public Health England on 23 May suggest that the Pfizer–BioNTech and Oxford–AstraZeneca vaccines are effective against B.1.617.2 after two doses.

How the coronavirus infects cells — and why Delta is so dangerous



- Scientists are unpicking the life cycle of SARS-CoV-2 and how the virus uses tricks to evade detection
- https://www.nature.com/articles/d41586-021-02039-y

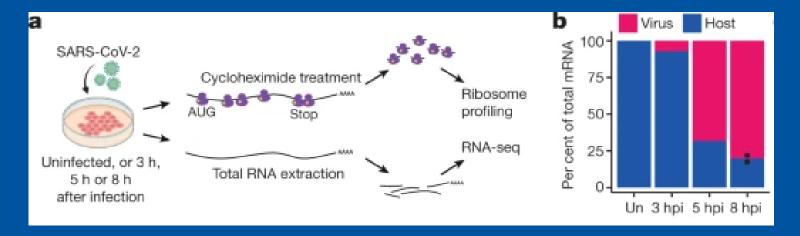
The four most urgent questions about long COVID



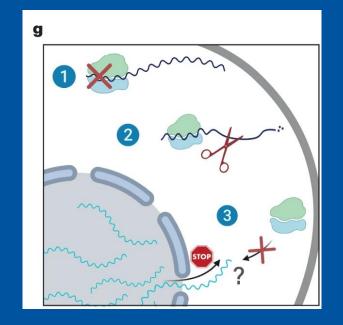
 Scientists are starting to get insights into the lingering disorder that affects some people infected with SARS-CoV-2 — but many mysteries remain unsolved.

SARS-CoV-2 uses a multipronged strategy to impede host protein synthesis





NSP1 acts as a strong inhibitor of translation and at the same time leads to the accelerated degradation of cellular, but not of viral, mRNAs—thus providing the means for viral mRNA to quickly dominate the mRNA pool.



Clonal analysis of immunodominance and cross-reactivity of the CD4 T cell response to SARS-CoV-2

https://science.sciencemag.org/content/372/6548/1336

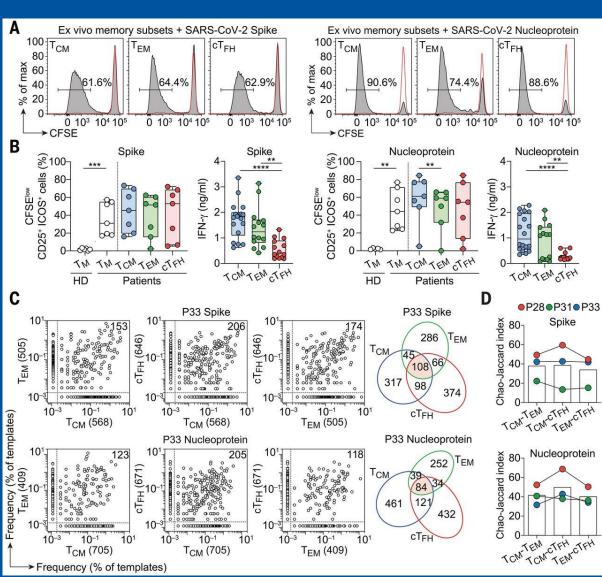


Robust T cell response to SARS-CoV-2 S and N proteins in CD4 $^+$ T_M cell subsets.

Total CD4+ memory T cells from seven COVID-19-recovered patients and six unexposed (pre-COVID-19) healthy donors (HD) or CD4+ T_{CM} , T_{EM} , and cT_{FH} cells from seven COVID-19-recovered patients were labeled with CFSE and cultured with autologous monocytes in the presence or absence of recombinant SARS-CoV-2 S or N protein

(C) The Venn diagrams show the number of unique and shared clonotypes between the T_{CM} , T_{EM} , and cT_{EH} cell subsets.

Cross-reactive T cells can inform vaccination strategies to counteract emerging SARS-CoV-2 variants.



Antibody and B cell responses to SARS-CoV-2 infection and vaccination



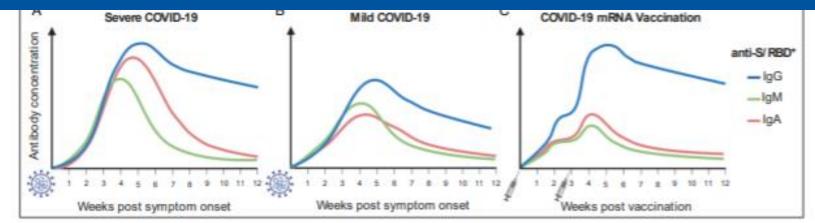
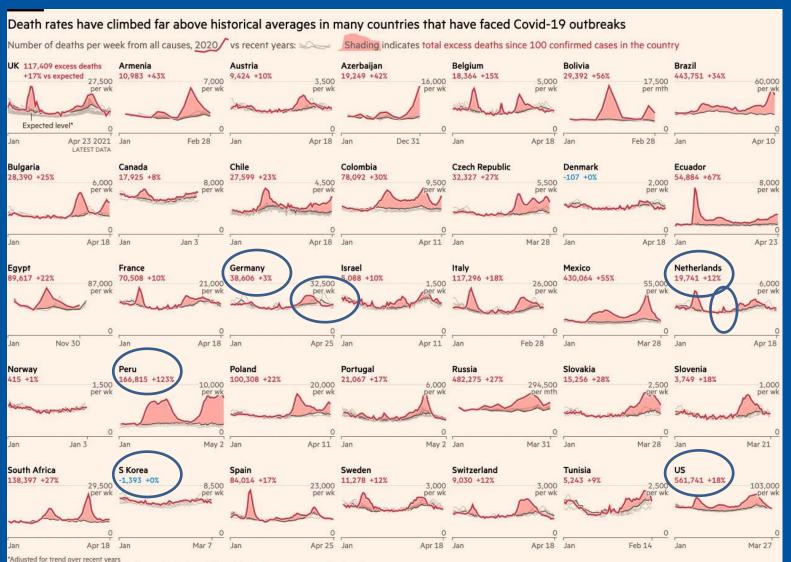


Figure 3. Anti-SARS-CoV-2 antibody responses. SARS-CoV-2 infection elicits robust antibody responses to the S protein. Patients with severe COVID-19 develop significantly higher anti-S IgM, IgG, and IgA titers than do patients with mild manifestations (A, B). Individuals vaccinated with two doses of S protein-encoding mRNA vaccines develop IgG antibody titers comparable to those of severely ill patients, but lower concentrations of IgM and IgA (C). *Anti-RBD antibody responses show similar patterns but are in general lower than those against S and decline more rapidly. Schematic created with biorender.com.

Oversterfte tot Mei 2021





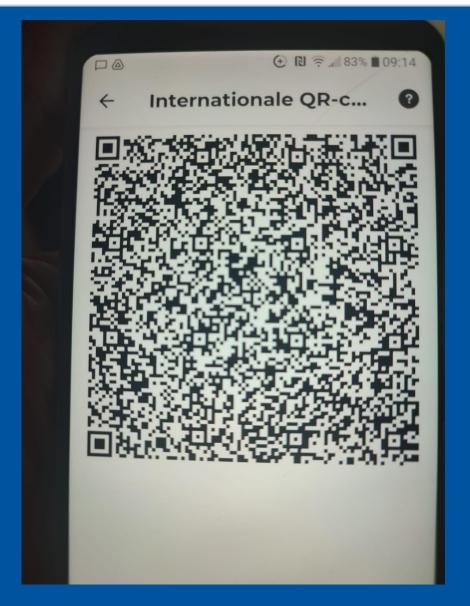
Relatie tussen oversterfte en gebrek aan vertrouwen in de overheid?

Na oversterfte nu ondersterfte?

En oversterfte door hitte! 300 doden in zomer 2020

*Adjusted for trend over recent years
Sources: FT analysis of national mortality data and Karlinsky & Kobak's World Mortality Dataset. Data updated May 5
FT graphic: John Burn-Murdoch / @jburnmurdoch
© FT





Is dit dwang, of vrijwillig?

Assessing the Association Between Social Gatherings and COVID-19 Risk Using Birthdays, June 21, 2021

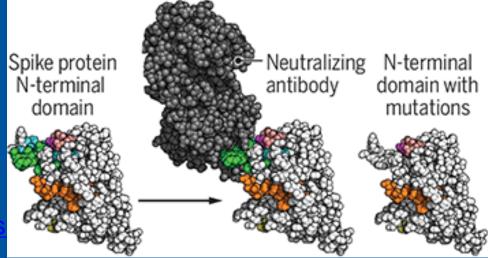


Findings This cross-sectional study used administrative health care data on 2.9 million households from the first 45 weeks of 2020 and found that, among households, those with birthdays had 8.6 more diagnoses per 10 000 individuals compared with households without a birthday, a relative increase of 31% of county-level prevalence, an increase in COVID-19 diagnoses of 15.8 per 10 000 persons after a child birthday, and an increase in COVID-19 diagnoses of 5.8 per 10 000 among households with an adult birthday.



Evasive maneuver

The spike protein's N-terminal domain (left) includes a "supersite" where powerful antibodies latch on to the virus (middle). Mutations there (right) can prevent them from binding.



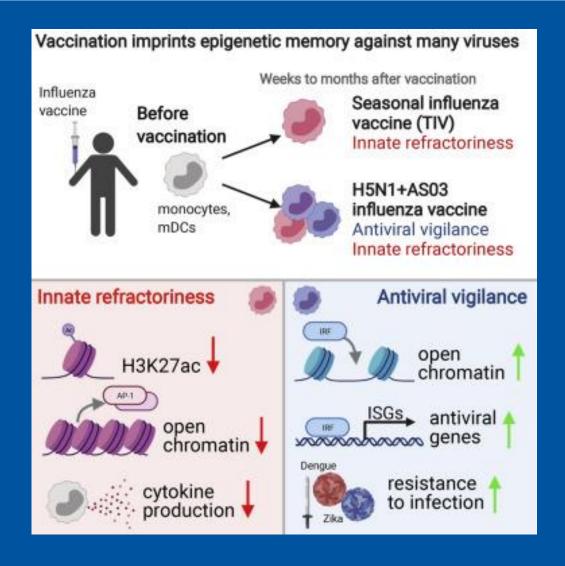
https://s

COVID-19 suppression of human mobility releases mountain lions from a landscape of fear

https://www.cell.com/current-biology/fulltext/S0960-9822(21)00879-4

The single-cell <u>epigenomic</u> and transcriptional landscape of immunity to influenza vaccination

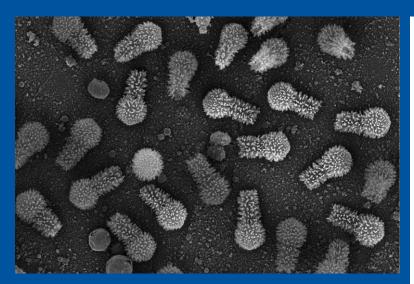




The virosphere: Virus discoveries transforming biology



https://www.nature.com/articles/d41586-021-01749-7

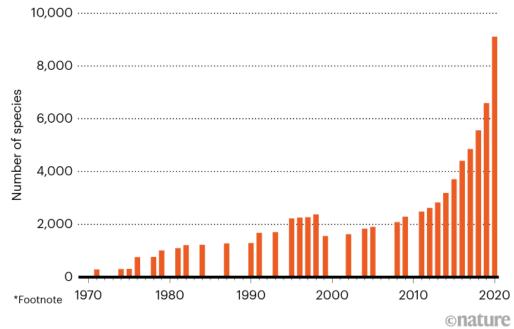


The giant tupanvirus, found in amoebae, is more than 1,000 nanometres long and has the largest set of protein-coding genes of any known virus.

=>Difference between cells and viruses is disappearing

ADDING TO THE FAMILY

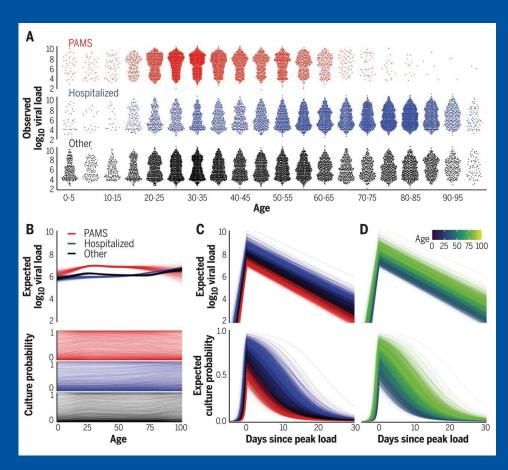
Scientists have found and logged viruses in huge numbers in recent years, thanks to technological advances and a change in the way viruses can be named. Viruses can now be classified on the basis of just their genome, instead of researchers having to culture the virus and its host.



Estimating infectiousness throughout SARS-CoV-2 infection course



- People became infectious
 within 2 days of infection, and
 the time of peak viral load
 occurred 1 to 3 days before the
 onset of symptoms.
- mildly symptomatic (PAMS)
 subjects who test positive at
 walk-in test centers can be
 expected to be approximately
 as infectious as hospitalized
 patients. The level of expected
 infectious viral shedding of
 PAMS people is of high
 importance because they are
 circulating in the community at
 the time of detection of
 infection.



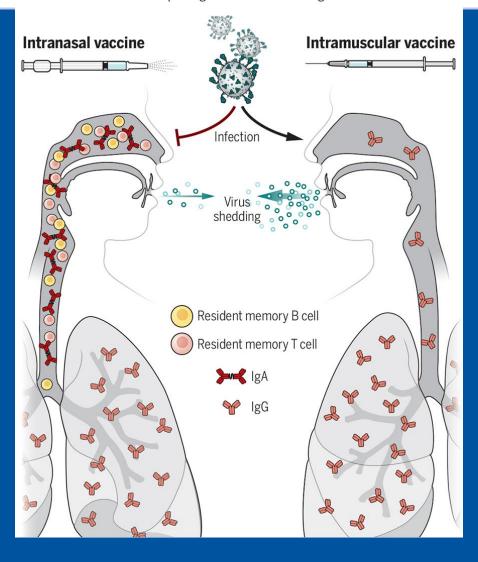
https://science.sciencemag.org/content/373/6551/eabi5273

elicitation of mucosal immunity in the respiratory tract.

The highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects the respiratory tract and is transmitted, in part, by respiratory droplets and aerosols. Consequently, unvaccinated people are encouraged to wear masks in public, self-quarantine if symptomatic, and practice social distancing. Despite these precautions, millions are dying. As the pandemic takes its toll, vaccines are once again headline news, notably for the speed of their development and the success of messenger RNA (mRNA) vaccines. Given the respiratory tropism of the virus, however, it seems surprising that only seven of the nearly 100 SARS-CoV-2 vaccines currently in clinical trials are delivered intranasally. Advantages of intranasal vaccines include needle-free administration. delivery of antigen to the site of infection, and the elicitation of mucosal immunity in the respiratory tract.

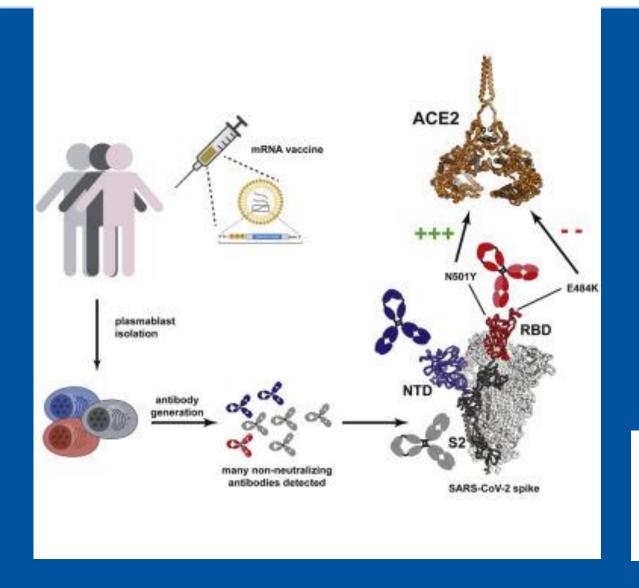
Routes of vaccination

Immunoglobulin A (IgA) and resident memory B and T cells in the nasal passages and upper airways are elicited by intranasal vaccination and prevent infection and reduce virus shedding. Serum IgG elicited by intranuscular vaccination transudates into the lungs and prevents pulmonary infection but allows infection in the nasal passages and virus shedding.



SARS-CoV-2 mRNA vaccination induces functionally diverse antibodies to NTD, RBD, and S2

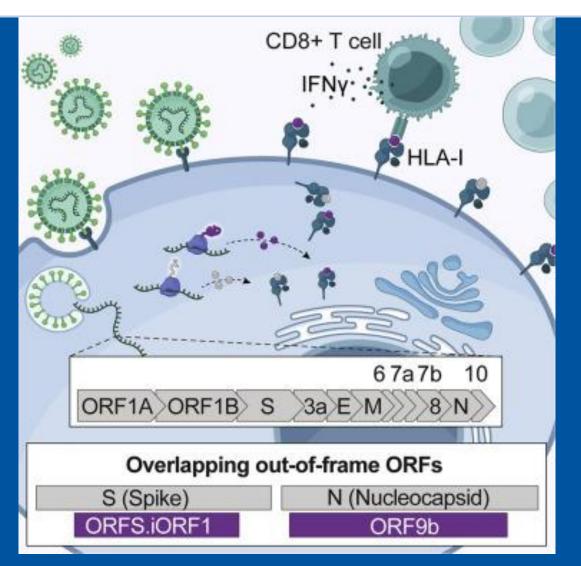




https://www.cell. com/cell/fulltext/ S0092-8674(21)00706-6

Profiling SARS-CoV-2 HLA-I peptidome reveals T cell epitopes from out-of-frame ORFs

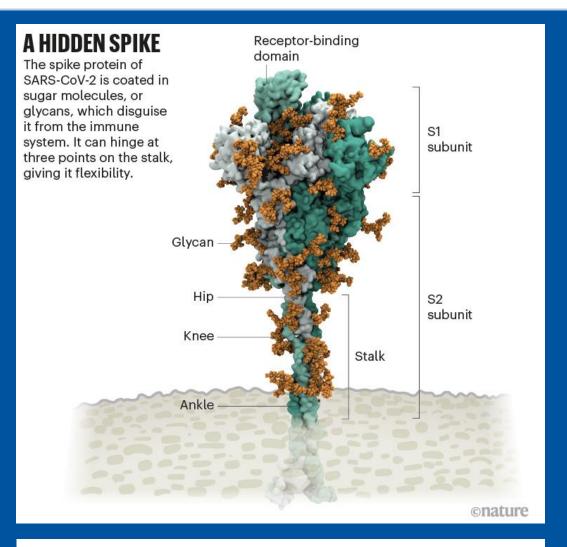


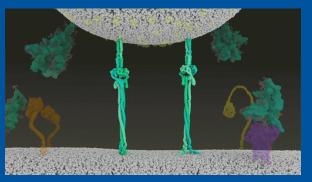


https://www.cell.c om/cell/fulltext/S0 092-8674(21)00701-7

How the coronavirus infects cells, and why Delta is so dangerous







In the Alpha variant, the initial proline amino acid is changed to a histidine (P681H); in the Delta variant, it is changed to an arginine (P681R). This change make the sequence less acidic, and the more basic the string of amino acids, the more effectively furin recognizes and cuts it, says Barclay. "We would hypothesize that this is the virus getting even better at transmitting."

https://www.nature.com/articles/d41586-021-02039-y

Tied in knots:

Zika virus tangles are the most stable RNA known



• A dangerous virus uses a ring-shaped structure to make its RNA resistant to attack.

The road to addressing Long Covid https://science.sciencemag.org/content/373/6554/491

- Around one in three people with symptomatic COVID-19 still experience symptoms 12 weeks after onset.
- Long Covid can be experienced by all age groups and not only those with acute severe disease.
- Long Covid is likely the first illness in history that has been defined by patients through social media platforms such as Twitter and Facebook. People with Long Covid formed a movement that demanded recognition of what was happening to them
- Those whose initial disease was characterized as "mild" commonly experience Long Covid. There is some indication that having more symptoms at the start of the illness is linked to the development of Long Covid and more multisystem involvement later

COVID vaccines slash viral spread – but Delta is an unknown



- Studies show that vaccines reduce the spread of SARS-CoV-2 by more than 80%, but the Delta variant is creating fresh uncertainty.
- https://www.nature.com/articles/d41586-021-02054-z
- Both studies found that two doses of the Pfizer-BioNTech vaccine were 81% effective at preventing infections. Those who did get infected were also less likely to pass the infection to household members than were unvaccinated individuals.
- both papers provide good evidence of a substantial reduction in infectiousness", says Elizabeth Halloran, a biostatistician at the Fred Hutchinson Cancer Research Center in Seattle, Washington.
- So far, there are no published data on how vaccines affect infections and infectiousness with Delta, but a UK study⁵ published on 21 July shows that the Pfizer–BioNTech and Oxford–AstraZeneca vaccines both protect slightly less well against symptomatic disease caused by Delta than against that caused by Alpha. This could also mean a drop in how well they protect against transmission of Delta, but there is still a lot of uncertainty, says Dean.
- Slechts 1% van de gevaccineerden is besmettelijk!?

Pandemic upheaval offers a huge natural experiment,

- The disruption that the coronavirus has caused to daily life has created unique research opportunities for scientists.
- https://www.nature.com/articles/d41586-021-02092-7
- the number of premature births seemed to plummet. Preliminary research in one region of Ireland documented a 73% decrease in verylow-birth-weight babies¹. And scientists in Denmark measured a roughly 90% country-wide drop in extremely premature births compared with the previous five years
- Researchers have long relied on natural experiments to probe subjects that would be difficult — or unethical — to investigate through conventional methods such as randomized controlled trials.
- Industrial shutdowns also provided a rare real-world chemistry
 experiment for atmospheric scientists such as Guy Brasseur at the Max
 Planck Institute for Meteorology in Hamburg, Germany. "We're always
 saying, to clean up the air, we need to shut down the emission sources,"
 he says. "Well, we're doing that."

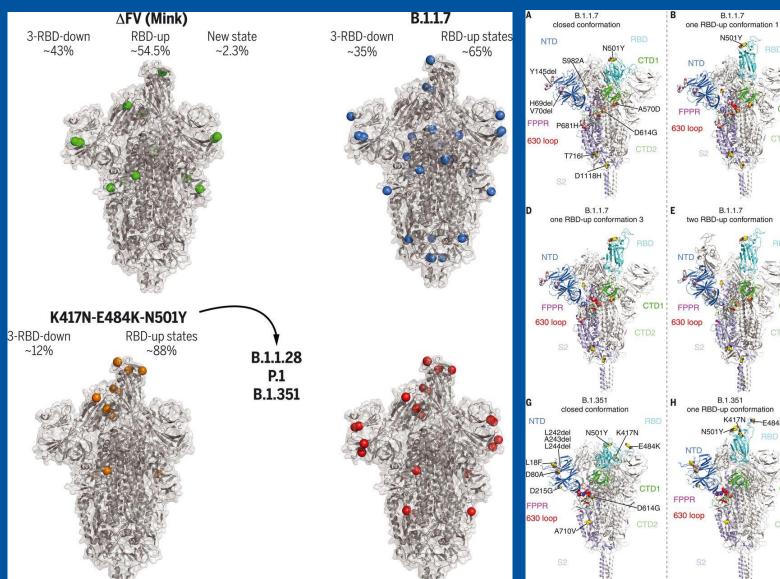
SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses



SARS-CoV-2 mRNA-based vaccines are about 95% effective in preventing COVID-19 The dynamics of antibody-secreting plasmablasts and germinal centre B cells induced by these vaccines in humans remain unclear. Here we examined antigen-specific B cell responses in peripheral blood (n = 41) and draining lymph nodes in 14 individuals who had received 2 doses of BNT162b2, an mRNA-based vaccine that encodes the full-length SARS-CoV-2 spike (S) gene . Circulating IgG- and IgA-secreting plasmablasts that target the S protein peaked one week after the second immunization and then declined, becoming undetectable three weeks later. These plasmablast responses preceded maximal levels of serum anti-S binding and neutralizing antibodies to an early circulating SARS-CoV-2 strain as well as emerging variants, especially in individuals who had previously been infected with SARS-CoV-2 (who produced the most robust serological responses). By examining fine needle aspirates of draining axillary lymph nodes, we identified germinal centre B cells that bound S protein in all participants who were sampled after primary immunization. High frequencies of S-binding germinal centre B cells and plasmablasts were sustained in these draining lymph nodes for at least 12 weeks after the booster immunization. S-binding monoclonal antibodies derived from germinal centre B cells predominantly targeted the receptor-binding domain of the S protein, and fewer clones bound to the N-terminal domain or to epitopes shared with the S proteins of the human betacoronaviruses OC43 and HKU1. These latter cross-reactive B cell clones had higher levels of somatic hypermutation as compared to those that recognized only the SARS-CoV-2 S protein, which suggests a memory B cell origin. Our studies demonstrate that SARS-CoV-2 mRNA-based vaccination of humans induces a persistent germinal centre B cell response, which enables the generation of robust humoral immunity.

Macro Eiwit: Corona Spike varianten 1 bolletje is een aminozuur verandering, die kan leiden tot ander gedrag

=> het best bestuurde eiwit ooit!





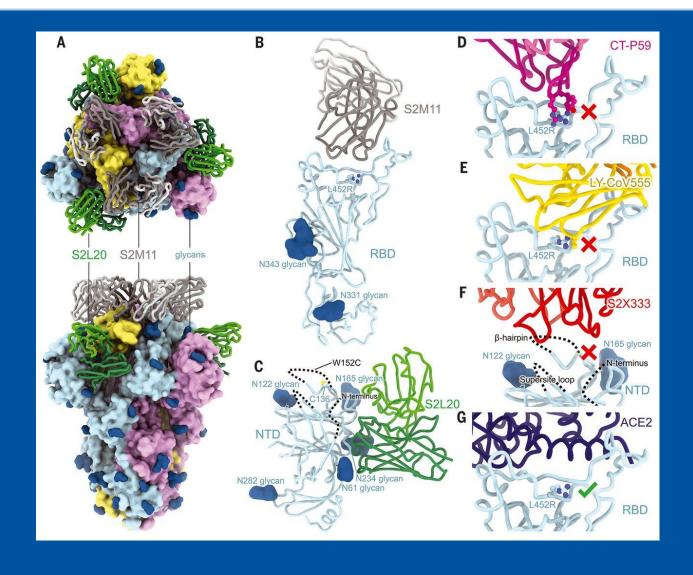
one RBD-up conformation 2

B.1.1.7

one RBD-up conformation

Glycosilatie: suikergroepen => 3D functie





Global cost of coronavirus: \$11.7 trillion (in 2020)



- Out of this global cost, \$9.8 trillion (83%) has been spent by 36 rich nations against just \$42 billion (0.4%) by 59 low-income countries to cope with the fallout from the COVID-19 pandemic, Oxfam said
- The SARS-CoV-2 pandemic is the greatest threat to prosperity and well-being the US has encountered since the Great Depression. This Viewpoint aggregates mortality, morbidity, mental health conditions, and direct economic losses to estimate the total cost of the pandemic in the US on the optimistic assumption that it will be substantially contained by the fall of 2021. These costs far exceed those associated with conventional recessions and the Iraq War, and are similar to those associated with global climate change.
- Estimates of how much money it would take to end global climate change range between \$300 billion and \$50 trillion over the next two decades
- => 2,5 trillion / year
- RL If we spend trillions to save the old from dying, we are obliged to spend at least that amount to give the young a future. => rechtzaken!



- News | 18 August 2021
- Decades-old SARS virus infection triggers potent response to COVID vaccines
- Dramatic antibody production in people infected during the 2002–04 outbreak furthers hopes of a vaccine against many coronaviruses.



- EWS
- 20 August 2021
- The mutation that helps Delta spread like wildfire
- A key amino-acid change might underlie the coronavirus variant's ferocious infectivity.

The animal origin of SARS-CoV-2

http://science.sciencemag.org/content/373/6558/968



One particular ecological event in China that severely disrupted meat trade, and thereby contributed to increased wildlife-human contacts, was the shortage of pork products in 2019. This was a direct consequence of the African swine fever virus (ASFV) pandemic (11), which led to ~150 million pigs being culled in China, resulting in a pork supply reduction of ~11.5 million metric tons in 2019. Although production of other meat, such as poultry, beef, and fish products, moderately increased and China imported more of these products from international markets to mitigate the short-fall, this supply only covered a fraction of the ASFV-associated pork losses. Consequently, pork prices hit a record high in November 2019, with the wholesale price increasing \sim 2.3 times compared with the previous year. Moreover, pig production has been relocating from Southern to Northern China since 2016. This, coupled with tight restrictions on the movement of live pigs and pork products to mitigate the ASFV pandemic, reduced the availability of pork in the Eastern and Southern provinces, resulting in much steeper price increases in these regions. In response, food consumers and producers may have resorted to alternative meats, including farmed or captured wildlife, especially in Southern China where wildlife is traditionally consumed (11). The resulting increased trade of susceptible farmed animals and wildlife could have brought humans into more frequent contact with meat products and animals infected with zoonotic pathogens, including SARSr-CoVs.

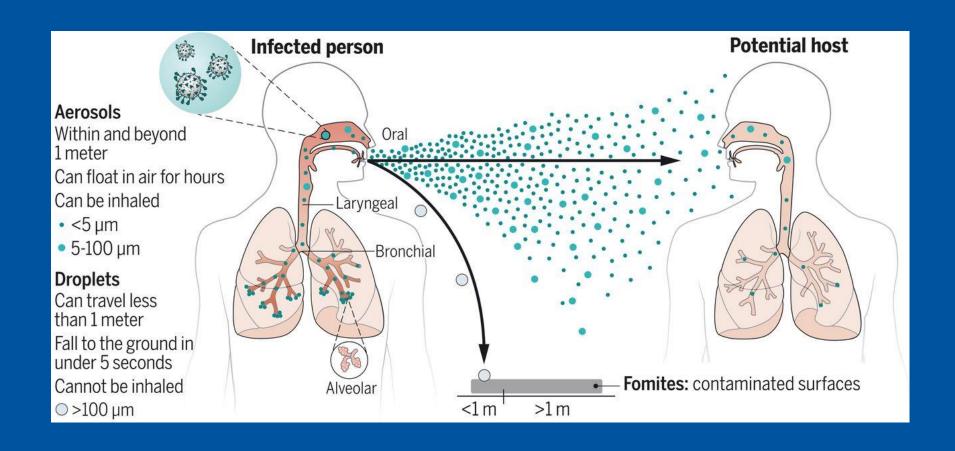
Sarbecoviruses closely related to SARS-CoV-2

Coronaviruses that are evolutionarily closest to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been sampled in China, Cambodia, Japan, and Thailand (5). The phylogenetic tree, inferred from a genomic region minimized for recombination (5), shows sarbecoviruses closely related to SARS-CoV-2. Host species for each virus, horseshoe bat (*Rhinolophus*), human (*Homo sapiens*), and pangolin (*Manis javanica*) and the year of sample collection are shown in the key. Longquan140 is inferred from another genomic region (5) (dashed line). See supplementary table S1 for more details.



Airborne transmission of respiratory viruses





Greece used AI to curb COVID: what other nations can learn



- Governments are hungry to deploy big data in health emergencies.
 Scientists must help to lay the legal, ethical and logistical groundwork.
- Between August and November 2020 with input from Drakopoulos and his colleagues — the authorities launched a system that uses a machine-learning algorithm to determine which travellers entering the country should be tested for COVID-19. The authors found machine learning to be more effective at identifying asymptomatic people than was random testing or testing based on a traveller's country of origin. According to the researchers' analysis, during the peak tourist season, the system detected two to four times more infected travellers than did random testing.

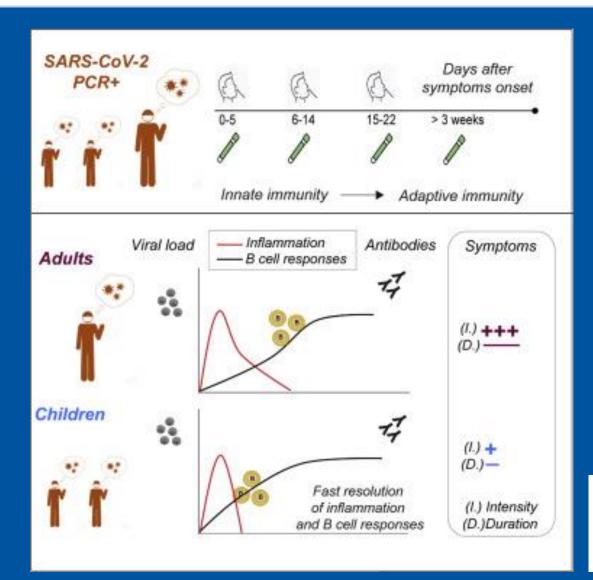
The tangled history of mRNA vaccines



• Hundreds of scientists had worked on mRNA vaccines for decades before the coronavirus pandemic brought a breakthrough

Robust innate responses to SARS-CoV-2 in children resolve faster than in adults without compromising adaptive immunity





Kinderen worden minder ziek van COVID-19. Niet vanwege de hoogte of de sterkte van activatie van hun afweer, maar omdat hun afweer snel weer tot rust komt.

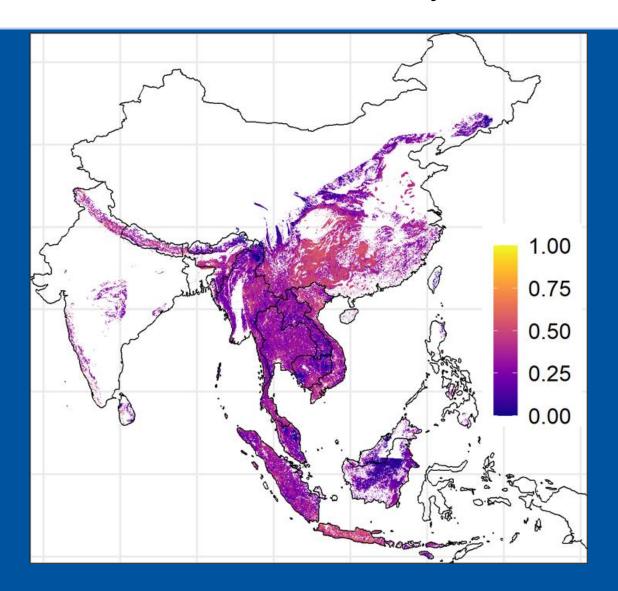
=> (langdurige) afweerreactie is schadelijk.

(Bij COVID-19 gaan
mensen vooral dood aan
hun eigen afweer)

https://www.cell.com/action/ showPdf?pii=S2211-1247%2821%2901227-4

SARS-like viruses may jump from animals to people hundreds of thousands of times a year





Study pinpoints
Asian regions that
could spark the
next coronavirus
pandemic

The emergence, genomic diversity and global spread of SARS-CoV-2



- The global spread of SARS-CoV-2 shows how rapidly geographically disparate countries can be reached by an emerging pathogen
- https://www.nature.com/articles/s41586-021-04188-6

How COVID vaccines shaped 2021 in eight powerful charts



- More than eight billion doses, have now been administered around the world,
- It is estimated that this astonishingly rapid development and deployment has saved at least 750,000 lives in the United States and Europe alone — and likely many more globally,

https://www.nature.com/ articles/d41586-021-03686-x

Omicron:

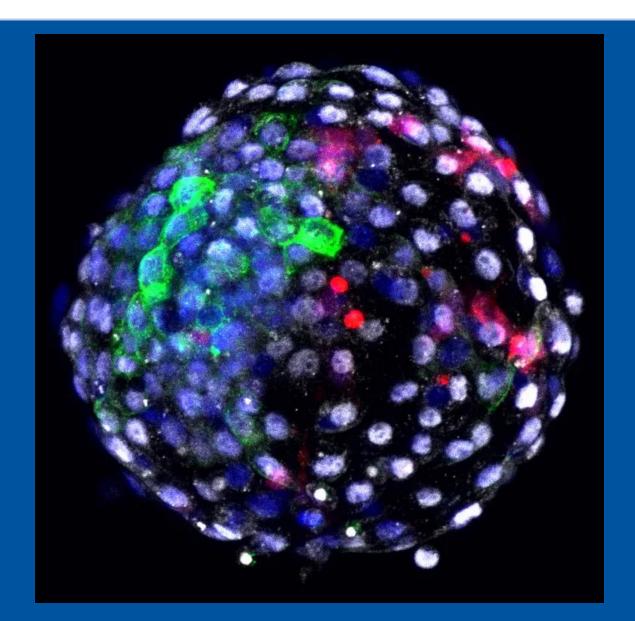
up to 70% less likely to need hospital care



- People catching Omicron are 50% to 70% less likely to need hospital care compared with previous variants, a major analysis says.
- The report comes hot on the heels of data from South Africa, Denmark, England and Scotland which all pointed to reduced severity.
- Omicron wave appears milder, but concern remains
- The latest analysis is based on all cases of Omicron and Delta in the UK since the beginning of November, including 132 people admitted to hospital with the variant. There have also been 14 deaths in people within 28 days of catching Omicron.
- The report shows people catching Omicron are:
- 31% to 45% less likely to go to A&E
- 50% to 70% less likely to be admitted to hospital for treatment

Hybrid embryo. In April, scientists reported successfully growing the <u>first monkey embryos containing human cells</u>.





Exercise plasma boosts memory and dampens brain inflammation via clusterin



Physical exercise is generally beneficial to all aspects of human and animal health, slowing cognitive ageing and neurodegeneration¹. The cognitive benefits of physical exercise are tied to an increased plasticity and reduced inflammation within the hippocampus^{2,3,4}, yet little is known about the factors and mechanisms that mediate these effects. Here we show that 'runner plasma', collected from voluntarily running mice and infused into sedentary mice, reduces baseline neuroinflammatory gene expression and experimentally induced brain inflammation. Plasma proteomic analysis revealed a concerted increase in complement cascade inhibitors including clusterin (CLU). Intravenously injected CLU binds to brain endothelial cells and reduces neuroinflammatory gene expression in a mouse model of acute brain inflammation and a mouse model of Alzheimer's disease. Patients with cognitive impairment who participated in structured exercise for 6 months had higher plasma levels of CLU. These findings demonstrate the existence of anti-inflammatory exercise factors that are transferrable, target the cerebrovasculature and benefit the brain, and are present in humans who engage in exercise.

Oncolytic virotherapy as immunotherapy



SCIENCE • 9 Dec 2021 • Vol 374, Issue 6573 • pp. 1325-1326 **Abstract**

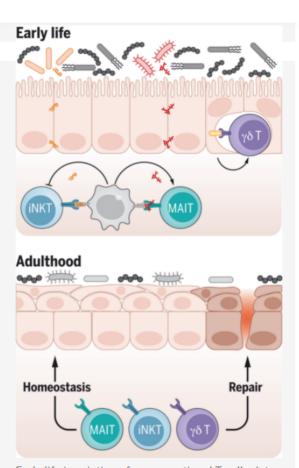
Oncolytic virus (OV) therapy is now something of a misnomer. The initial paradigm was that naturally occurring or genetically engineered viruses would preferentially infect, replicate in, and lyse cancer cells relative to normal cells, leading to selective direct cytotoxicity. The immune system used to be considered detrimental, given its potential to recognize and respond to the virus, prevent its replication, and limit viral spread and tumor cell killing ($\underline{1}$). This view has now been largely replaced by a model in which infection of the tumor by the virus makes it more visible to the immune system for recognition and attack. Tumor cell killing by the virus and/or immune effector cells effectively generates an in situ vaccine, with tumor antigens released into a microenvironment modified by viral infection to reverse tumor-induced immune suppression.

https://www.science.org/doi/ 10.1126/science.abf0095

Abstract

Unconventional T cells—including invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells, and defined subsets of $\gamma \hat{o}$ T cells—are restricted by monomorphic major histocompatibility complex class Ib (MHC-Ib) molecules and seed tissues during development. Early-life instructive signals, including those derived from the microbiota, establish homeostatic set points for unconventional T cells, a phenomenon that has lifelong consequences for the regulation of tissue immunity, inflammation, and repair.

Unconventional T cells compete for niches within tissues, and recent evidence supports the idea that the fundamental role of these cells in tissue physiology may result from their action as a network with overlapping and potentially synergistic functions, rather than as individual subsets.



Early-life imprinting of unconventional T cells determines tissue physiology in adulthood. Unconventional T cells, including invariant natural killer T (iNKT) cells, mucosal-associated invariant T (MAIT) cells, and $\gamma\delta$ T cells, develop in response to microbial and epithelial signals in early life and subsequently promote tissue repair and homeostasis as a coordinated network.

How neutron star collisions flooded Earth with heavy metals required for life

https://www.space.com/neutron-star-collisions-gave-earth-precious-metals



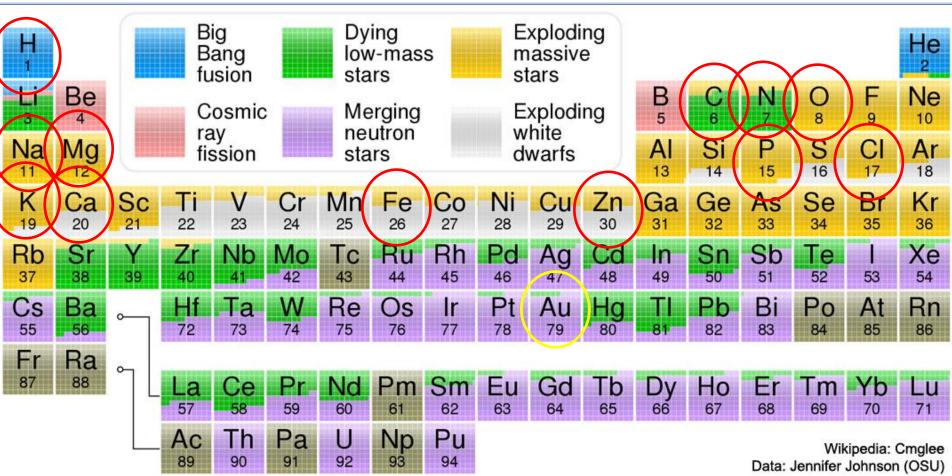
With all the neutrons flying around and combining with each other, and all the energy needed to power the nuclear reactions, kilonovas are responsible for producing enormous amounts of heavy elements, including gold, silver and xenon. Together with their cousins, supernovas, kilonovas fill out the periodic table and generate all the elements necessary to make rocky planets ready to host living organisms.

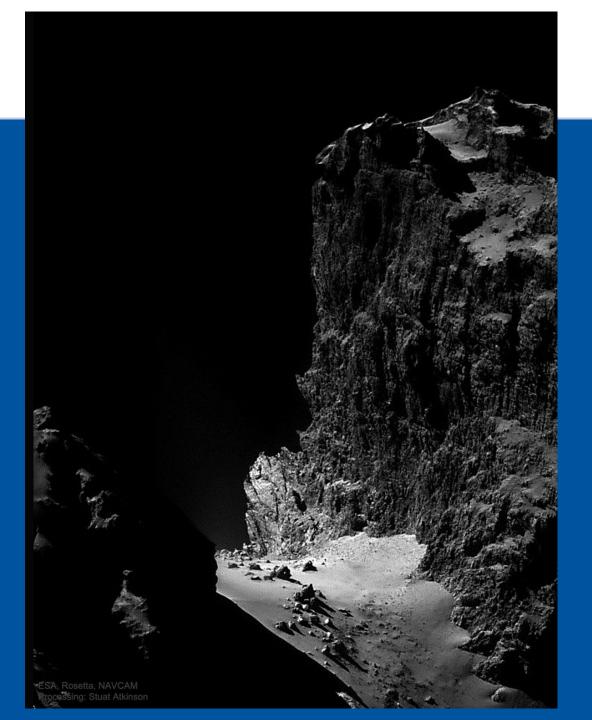
And the addition of gravitational wave signals provided an unprecedented glimpse inside the event itself. Between gravitational waves and traditional electromagnetic observations, astronomers got a complete picture from the moment the merger began.

That kilonova alone produced more than 100 Earths' worth of pure, solid precious metals, confirming that these explosions are fantastic at creating heavy elements.

We are made of star stuff









Ammonium salts found on Rosetta's comet https://www.esa.int/ESA Multimedia/Missions/Rosetta/(resultype)/images

The presence of these salts might hint at a link in the chemical composition between asteroids, comets and possibly the proto-solar nebula, providing a tantalising scenario for the delivery of nitrogen – a key element for the chemistry of life as we know it on Earth – to the inner planets of the Solar System.

Your blood teems with a unique set of stealthy 'anelloviruses'

=> Half of you is not actually you



A single individual harbours tens to hundreds of variants of this DNA-based virus, which can move from one person to another in donated blood.

A deep analysis of a family of viruses found in human blood has revealed the vast variety of these typically harmless 'anelloviruses', and shows that every person hosts their own unique community of resident viruses.

Nathan Yozwiak at Ring Therapeutics, a biotechnology company in Cambridge, Massachusetts, and his colleagues sequenced anelloviruses obtained from blood donors and from people who received transfusions of the donated blood.

The authors analysed viral DNA and showed that anelloviruses have diversified into many more lineages than have eight other viruses and virus families that infect people. The analysis suggests that a person's resident anelloviruses frequently swap DNA, leading to a diverse and individual 'anellome'.

The team also compared the genetic signatures of anelloviruses in people who received a blood transfusion with those in the blood donors. This showed that some lineages from a donor persisted in the recipient.

The authors suggest that anelloviruses could be useful as biomarkers of immune health after organ transplants, or as viral vectors to deliver treatments.

Cell Host Microbe (2021)

Tough recyclable polyacetals



Cyclic acetals such as dioxolane are appealing building blocks for recyclable plastics but have proven to be difficult to polymerize controllably. Abel *et al.* show that optimal pairing of a bromomethyl ether and indium or zinc Lewis acid produces polydioxolane with high tensile strength that may be advantageous for packaging applications. Heating this plastic in strong acid easily breaks it back down to its acetal monomer, which can then be recovered by distillation from mixed plastic waste streams in high yield. *Science*, abh0626, this issue p. <u>783</u>

A fast link between face perception and memory in the temporal pole



What makes familiar faces so special?

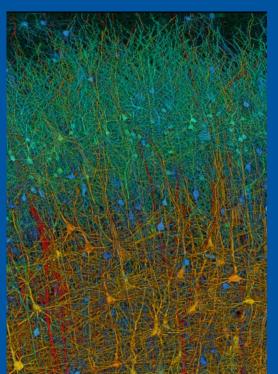
Explicit semantic information in the brain is generated by gradually stripping off the specific context in which the item is embedded. A particularly striking example of such explicit representations are face-specific neurons. Landi et al. report the properties of neurons in a small region of the monkey anterior temporal cortex that respond to the sight of familiar faces. These cells respond to the internal features of familiar faces but not unknown faces. Some of these responses are very highly selective, reliably responding to only one face out of a vast number of other stimuli. These findings will advance our understanding about where and how semantic memories are stored in the brain.

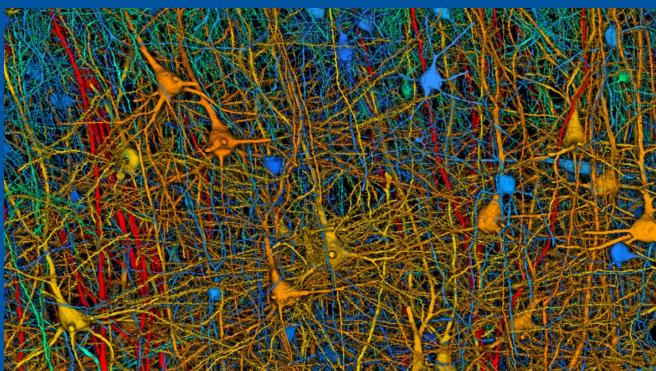
Also place (orientation) neurons found etc.

This exquisitely detailed image <u>charts the connections</u> between thousands of cells in a tiny sliver of human brain.



The sample was taken from the cortex — the part of the brain responsible for complex thought — and cut into thin slices that were imaged using electron microscopes. Scientists then stitched the images back together digitally and analysed them with the help of artificial intelligence programs. Different types of neuron have been artificially colour-coded.









Life beyond earth. Human made Biotech



The Defense Advanced Research Projects Agency in a new program will explore options to conduct biomanufacturing in space, using biological systems like microbes to construct materials for use in orbital operations. The project, led by DARPA's biological technologies office, is called B-SURE, short for biomanufacturing, survival, utility and reliability beyond Earth.

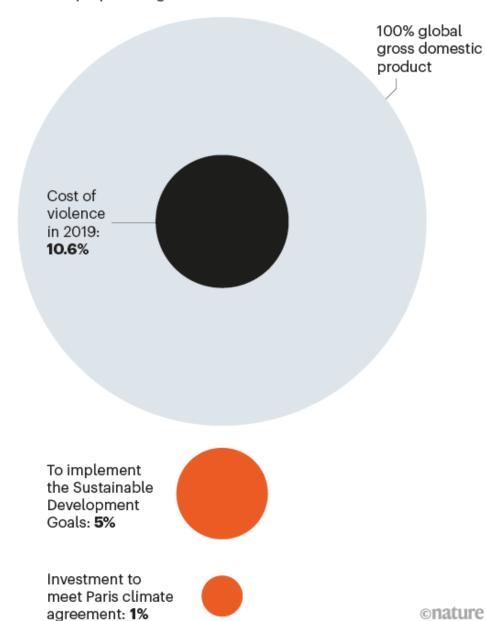
"The B-SURE program is a fundamental study that will explore adapting microbes to space conditions," project manager Anne Cheever said in a news release. "The hope is that eventually this technology will enable inspace production of molecules relevant to space flight."

Biomanufacturing is an emerging sector of the biotechnology industry focused on making products using living systems such as microorganisms, animal cells or plant cells.

https://www.nature.com/article s/d41586-020-02460-9

WRONG PRIORITIES

Protecting the climate and people's well-being costs less than perpetuating violence.



Health is reason enough to axe fossil fuels

The toxic effects of air pollution are so bad that moving from fossil fuels to clean energy would



gains — even if climate change didn't exist. A model presented to the US government by earth scientist Drew Shindell predicts that over 20 years, aggressive decarbonization could save around 1.4 million lives in the United States alone that would otherwise be lost to air pollution. The shocking numbers arise from huge data sets being generated in the United States, China and other countries. "The air-quality scientific community has hypothesized this for at least a decade, but research advances have let us quantify and confirm this notion, over and over," says air-quality researcher Rebecca Saari. "The air quality 'co-benefits' are generally so valuable that they exceed the cost of climate action, often many times over."



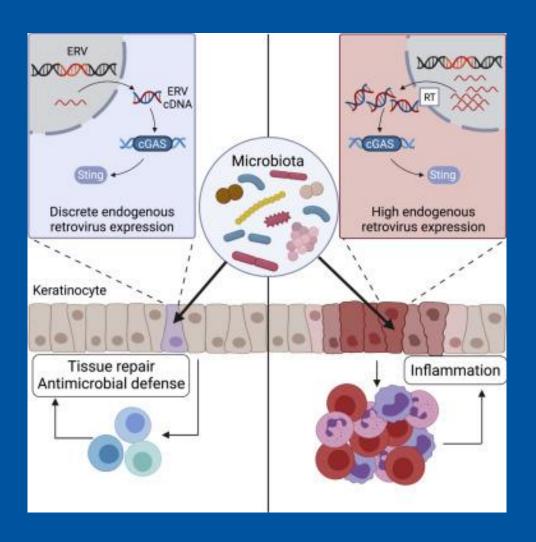
Choreographing water molecules to speed up hydrogen production

A technical feat reveals subtle changes in water structure that can accelerate hydrogen production at an electrode interface. The catalytic process could be developed to help boost supply of this clean fuel.

Electrocatalysis, which accelerates chemical reactions driven by an electric potential at a solid–liquid interface, could be a key contributor to a sustainable global economy because it can convert electrical energy from renewable power sources into green fuels such as hydrogen gas¹. Was and colleagues² describe an important advance in the molecular understanding of how the rate of an electrocatalytic process is rooted in the structure of water at the interface between a solid electrode and an aqueous salt solution (an electrolyte). Their findings could help to improve the reaction selectivity and energy efficiency of electrocatalytic interfaces.

Endogenous retroviruses promote homeostatic and inflammatory responses to the microbiota https://www.cell.com/cell/fulltext/S0092-8674(21)00650-4





Together, our results support the idea that the host may have co-opted its endogenous virome as a means to communicate with the exogenous microbiota, resulting in a multi-kingdom dialog that controls both tissue homeostasis and inflammation.

=> A human is many organisms living together

An aged immune system drives senescence and ageing of solid organs



Ageing of the immune system, or immunosenescence, contributes to the morbidity and mortality of the elderly $\frac{1}{2}$. To define the contribution of immune system ageing to organism ageing, here we selectively deleted *Ercc1*, which encodes a crucial DNA repair protein^{3,4}, in mouse haematopoietic cells to increase the burden of endogenous DNA damage and thereby senescence 5,6,7 in the immune system only. We show that $Vav-iCre^{+/-}$; $Ercc1^{-/fl}$ mice were healthy into adulthood, then displayed premature onset of immunosenescence characterized by attrition and senescence of specific immune cell populations and impaired immune function, similar to changes that occur during ageing in wild-type mice^{8,9,10}. Notably, non-lymphoid organs also showed increased senescence and damage, which suggests that senescent, aged immune cells can promote systemic ageing. The transplantation of splenocytes from Vav*iCre*^{+/-};*Ercc1*^{-/fl} or aged wild-type mice into young mice induced senescence in trans, whereas the transplantation of young immune cells attenuated senescence. The treatment of *Vav-iCre+/-;Ercc1-/fl* mice with rapamycin reduced markers of senescence in immune cells and improved immune function $\frac{11,12}{1}$. These data demonstrate that an aged, senescent immune system has a causal role in driving systemic ageing and therefore represents a key therapeutic target to extend healthy ageing.

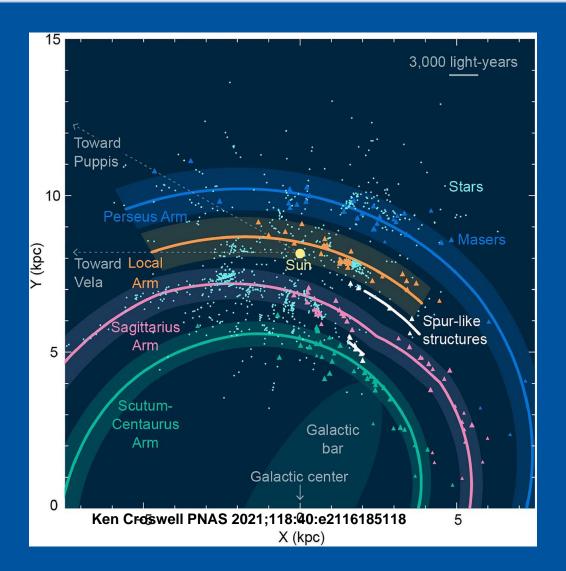


Biology must generate ideas as well as data

Data should be a means to knowledge, not an end in themselves. Paul Nurse

This bird's-eye view of the Milky Way plots O-type stars (small dots) and masers (tria gles) as well as our own Sun (large yellow dot).



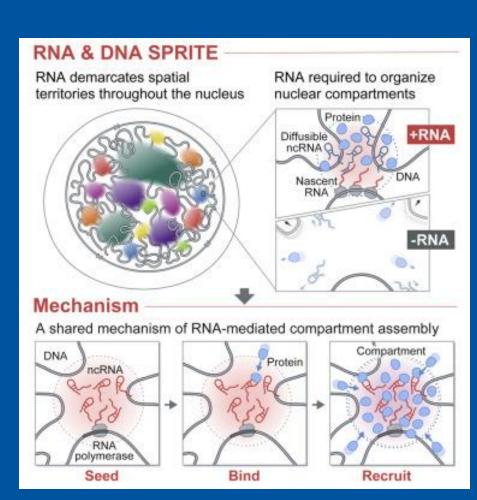


https://www. pnas.org/cont ent/118/40/e 2116185118





- •RNA comprehensively maps the spatial organization of RNA and DNA
- ••Hundreds of ncRNAs form highconcentration territories throughout the nucleus
- ••ncRNAs recruit diffusible RNA and protein regulators into precise 3D structures
- ••ncRNA compartments can shape DNA contacts, heterochromatin, and gene expression
- •https://www.cell.com/cell/fulltext/S00 92-8674(21)01230-7



The widespread IS200/IS605 transposon family encodes diverse programmable RNA-guided endonucleases



Tracing the origin of CRISPR-Cas

CRISPR-Cas systems have transformed genome editing and other biotechnologies; however, the broader origins and diversity of RNA-guided nucleases have largely remained unexplored. Altae-Tran et al. show that three distinct transposon-encoded proteins, IscB, IsrB, and TnpB, are naturally occurring, reprogrammable RNA-guided DNA nucleases (see the Perspective by Rousset and Sorek). In addition to identifying diverse guide-encoding mechanisms, the authors elucidate the evolutionary relationship between IsrB, IscB, and CRISPR-Cas9. Overall, these newly characterized systems, called OMEGA (for obligate mobile element–guided activity) systems, are found in all domains of life and may be harnessed for biotechnology development. — DJ

Literatuur: Nature diagrams

https://youtu.be/iQh63DH9H5w



How Nature creates scientific graphics

Scientific art editors at *Nature* work with authors and editors to create graphics that increase comprehension and provide insight at a glance. Go behind the scenes to see how they use principles of visual communication and design to create a diagram summarizing an entire research article about a magnetic compass in the eyes of the European robin (*Erithacus rubecula*).

From carbon dioxide to starch: no plants required



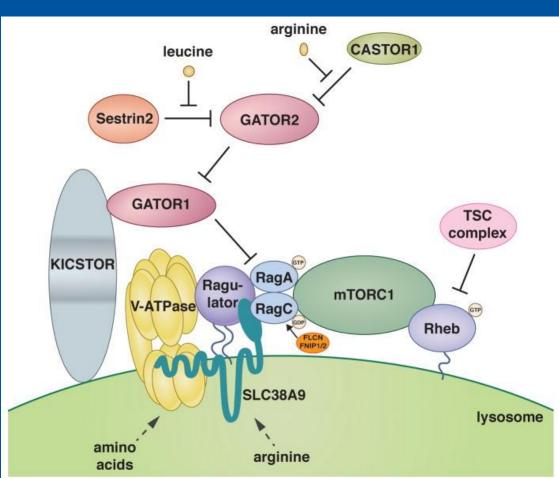
Many plants turn glucose from photosynthesis into polymers that form insoluble starch granules ideal for long-term energy storage in roots and seeds. Cai *et al.* developed a hybrid system in which carbon dioxide is reduced to methanol by an inorganic catalyst and then converted by enzymes first to three and six carbon sugar units and then to polymeric starch. This artificial starch anabolic pathway relies on engineered recombinant enzymes from many different source organisms and can be tuned to produce amylose or amylopectin at excellent rates and efficiencies relative to other synthetic carbon fixation systems—and, depending on the metric used, even to field crops.

Dissecting the biology of mTORC1 beyond rapamycin



The kinase mTOR is a component of two multiprotein complexes, mTORC1 and mTORC2, which have distinct cellular functions. The compound rapamycin does not completely inhibit the kinase activity of mTORC1 and partially inhibits that of mTORC2 in certain cell types. Yang et al. used the rapamycin derivative RapaLink1 to differentiate between those functions mediated by mTORC1 and mTORC2. Because RapaLink1 had improved specificity for mTORC1 compared to rapamycin, the authors showed that cell proliferation and autophagy were regulated by mTORC1, whereas glycolysis was regulated by both complexes, and that starvation resistance in *Drosophila* was mediated by TORC1

The mechanistic target of rapamycin complex 1 (mTORC1) is a master regulator of cell growth that responds to a diverse set of environmental inputs, including amino acids. Over the past ten years, a number of proteins have been identified that help transmit amino acid availability to mTORC1.



https://www.science.org/doi/10.1126/scisignal.abe0161 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5560103/

Reversing aging for heart repair



Partial reprogramming (PR) is an innovative and promising approach for reversing cellular age through short-term induction of pluripotency factors that rejuvenate aged cells to regain functions of young ones. PR takes advantage of the stepwise nature of the reprogramming process (1, 2) by using a controlled short-burst expression of factors that remodel the epigenome and rejuvenate gene expression but do not go as far as erasing cellular identity (3). Applications of PR in age-related diseases and models of premature aging suggest that a controlled regimen can reverse the timeworn molecular signature of aging in a range of cell types (3-5). Unlike many adult tissues, the heart lacks stem cells and is incapable of regeneration. On page 1537 of this issue, Chen et al. (6) show that PR can induce repair of the heart after a myocardial infarction by temporarily reactivating a neonatal developmental program in mature cardiomyocytes in mice.

<u>Human microphysiological systems for drug development</u>

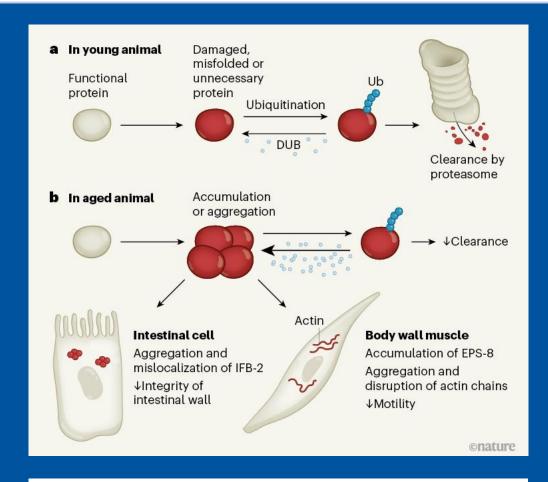
Organs-on-chips could be used to assess drug efficacy and support personalized medicine





Dysfunction of protein clearance in old worms leads to decline of tissue function



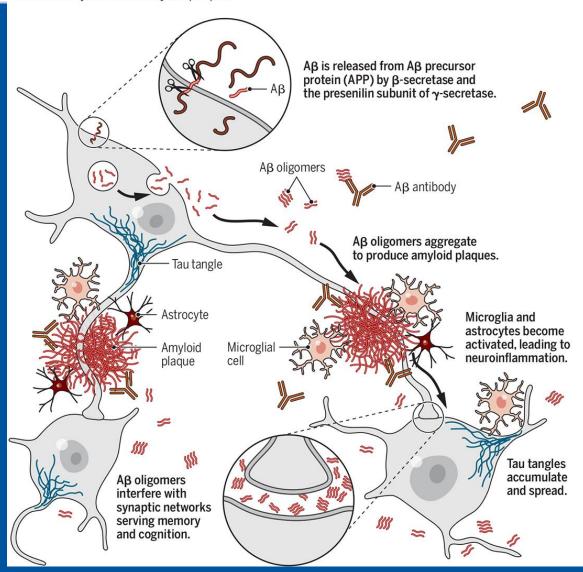


https://www.nature.com/articles/d41586-021-02009-4

Unwanted proteins are reversibly tagged with ubiquitin molecules (Ub), which signal that the protein is ready for clearance by the proteasome, a complex of proteins that breaks down proteins. Ubiquitin molecules are removed by deubiquitinase (DUB) enzymes. **b**, Koyuncu et al.² assessed ubiquitination in Caenorhabditis elegans worms as the worms aged. Ubiquitination of most proteins decreased with age, in part owing to increased activity of DUB enzymes. Some proteins that are normally targets of the proteasome accumulated with age, and the lifespan of C. elegans was extended when expression of these proteins was decreased during adulthood (not shown). Such proteins include IFB-2 and EPS-8. With ageing, IFB-2 aggregation resulted in a loss of intestinal integrity, and reduction of EPS-8 ubiquitination led to disruption of the actin proteins that make up the cell 'skeleton' in the muscles of the body wall and a reduction in the worm's motility.

Drug targets for Alzheimer's disease

Alzheimer's disease neuropathology includes extracellular amyloid plaques containing myriad amyloid- β (A β) oligomers and intraneuronal tangles containing phosphorylated tau. Microglia and astrocytes become activated, leading to neuroinflammation and the spread of neuropathology. Antibodies to A β , administered intravascularly, can clear amyloid plaques.



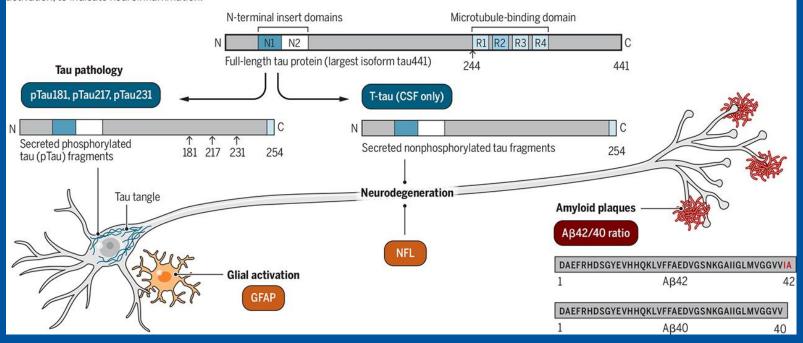


https://science.science mag.org/content/373/ 6555/624



Biomarkers of Alzheimer's disease

Low amyloid-β (Aβ) 42/40 isoform ratio is associated with brain amyloidosis, and several phosphorylated tau (pTau) fragments increase with tau pathology; both are specific blood biomarkers for Alzheimer's disease (AD). Among neurodegeneration biomarkers, neurofilament light (NFL) is modestly increased in AD, and total tau (T-tau) is markedly increased only in cerebrospinal fluid (CSF), and not blood, in AD. Glial fibrillary acidic protein (GFAP) is a candidate blood biomarker for astrocytic activation, to indicate neuroinflammation.



https://science.sciencemag.org/content/373/6555/626

The role of retrotransposable elements in ageing and ageassociated diseases



The genomes of virtually all organisms contain repetitive sequences that are generated by the activity of transposable elements (transposons). Transposons are mobile genetic elements that can move from one genomic location to another; in this process, they amplify and increase their presence in genomes, sometimes to very high copy numbers. In this Review we discuss new evidence and ideas that the activity of retrotransposons, a major subgroup of transposons overall, influences and even promotes the process of ageing and age-related diseases in complex metazoan organisms, including humans. Retrotransposons have been coevolving with their host genomes since the dawn of life. This relationship has been largely competitive, and transposons have earned epithets such as 'junk' DNA' and 'molecular parasites'. Much of our knowledge of the evolution of retrotransposons reflects their activity in the germline and is evident from genome sequence data. Recent research has provided a wealth of information on the activity of retrotransposons in somatic tissues during an individual lifespan, the molecular mechanisms that underlie this activity, and the manner in which these processes intersect with our own physiology, health and well-being.

Vascular rejuvenation is geroprotective



The scientific perception of blood vessels has changed substantially in recent years. They are no longer considered passive conduits of blood that respond to exogenous cues. Now, the vascular endothelium is considered to act as an instructive gatekeeper to actively control organ function (1). Although mechanisms of local regulation by the vasculature have been identified for most organs and many disease states, including cancer, the study of systemic instructive vascular signaling is still in its infancy. On page 533 of this issue, Grunewald et al. (2) report that low-dose systemic increase of vascular endothelial growth factor-A (VEGFA) in the circulation leads to a notable life span extension in mice. The complex multiorgan rejuvenation phenotype of these mice yields insight into the mechanisms of organism aging and highlights the critical role of the vasculature as a gatekeeper of life span and health span.

Losing fat through the skin



Obesity—the excessive accumulation of white adipose tissue (WAT), potentially impairing health—affects millions worldwide and is associated with numerous comorbidities such as type II diabetes and fatty liver disease. The main function of WAT is storage of energy in the form of lipids (fat) and its mobilization as needed. Skin sebaceous glands secrete a lipid-rich product (sebum), which has several functions in maintaining skin integrity, including protection against ultraviolet radiation, elimination of harmful microorganisms (antimicrobial activity), and thermoregulation. Thus, although largely unrelated in structure and function, both WAT and sebaceous glands are stereotyped by intensive lipid metabolism. On page 532 of this issue, Choa et al. (1) show that the cytokine thymic stromal lymphopoietin (TSLP) modulates sebum secretion. Furthermore, they show that if sebum production and release consumes sufficient energy, it can cause significant loss of WAT in mice.

Targeting aging cells improves survival



mortality (1). Whether this is due to preexisting age-related health issue, Camell et al. (2) show that cell senescence, a hallmark of biological aging (3), contributes to mortality in old mice upon

'Inflammation clock' can reveal body's biological age

Using machine learning, researchers created a tool that might help doctors improve people's healthy lifespan.



The researchers who developed iAge hope that, because inflammation is treatable, the tool could help doctors determine who would benefit from intervention — potentially extending the number of years a person lives in good health.

The study "is a further reinforcement of the fact that the immune system is critical, not only for predicting unhealthy ageing, but also as a mechanism driving it",

iAge is based on the idea that as a person ages, their body experiences chronic, systemic inflammation because their cells become damaged and emit inflammation-causing molecules. This ultimately leads to wear and tear on their tissues and organs. People who have a healthy immune system will be able to neutralize this inflammation to some extent, whereas others will age faster.

If caught early, "inflammation is one of the best things we can treat", "We have developed amazing anti-inflammatory tools, so I think it's a biological process that we have a lot of knowledge about and can target easily."

Sayed envisions a future in which anyone can undergo inflammatory-biomarker profiling on a regular basis to keep tabs on their risk of developing age-related disease. "If we can control ageing in a more impactful way," he says, "I think we can have a more graceful ageing process."

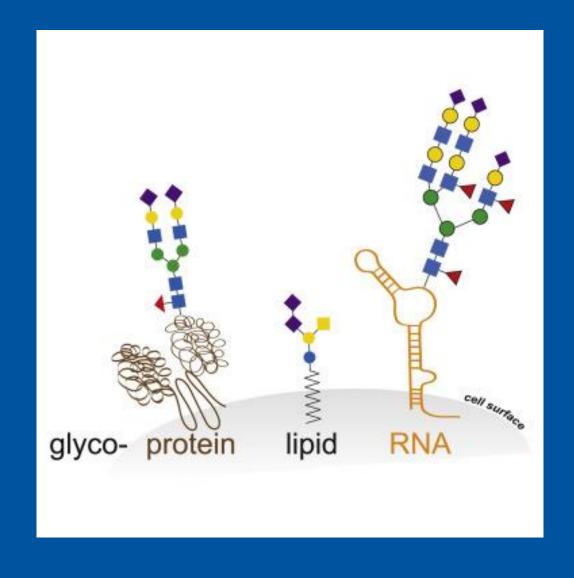
The rise of intelligent matter Nature volume 594, pages345–355 (2021)



Artificial intelligence (AI) is accelerating the development of unconventional computing paradigms inspired by the abilities and energy efficiency of the brain. The human brain excels especially in computationally intensive cognitive tasks, such as pattern recognition and classification. A long-term goal is de-centralized neuromorphic computing, relying on a network of distributed cores to mimic the massive parallelism of the brain, thus rigorously following a nature-inspired approach for information processing. Through the gradual transformation of interconnected computing blocks into continuous computing tissue, the development of advanced forms of matter exhibiting basic features of intelligence can be envisioned, able to learn and process information in a delocalized manner. Such intelligent matter would interact with the environment by receiving and responding to external stimuli, while internally adapting its structure to enable the distribution and storage (as memory) of information. We review progress towards implementations of intelligent matter using molecular systems, soft materials or solid-state materials, with respect to applications in soft robotics, the development of adaptive artificial skins and distributed neuromorphic computing.

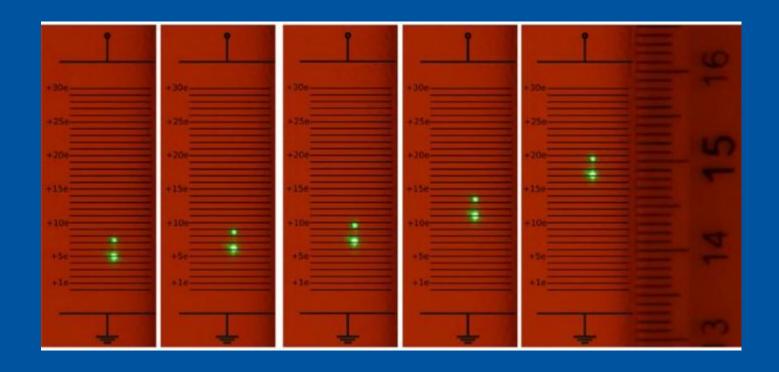
Small RNAs are modified with N-glycans, Just like proteins and lipids: glycosalation





a landmark measurement of the electron's charge goes visual https://www.nature.com/articles/d41586-021-01414-z





An oil droplet levitates as it gains first one electron (second panel from left), and then one, four and six more. A ruler on the right measures the displacement. Credit: J. T. Marmolejo *et al./Sci. Rep.*

Climate change is to blame for an average 37 per cent of heat-related deaths globally in the past three decades, according to researchers who say their finding is a reminder global warming is already having severe impacts.



Every continent saw an increase in deaths from heat linked to climate change over the period, but the percentage of heat deaths linked to climate change varied widely across the world.

The proportion was much higher in Central and South American countries including Guatemala and Colombia, and more than 50 per cent in Kuwait and Iran in the Middle East, and the Philippines in South-East Asia. The percentages were much lower in the US and Canada, and much of Europe.

"The main message is climate change is not something that will come in the future. It's already happening, and we can quantify the negative impacts," says Antonio Gasparrini at the London School of Hygiene & Tropical Medicine, one of the research team.

The team took temperature and mortality data from 43 countries between 1991 and 2018, and modelled a counterfactual world without the 1.1°C of warming the world has seen to date. The difference was used to estimate the number of climate-linked heat deaths.

To account for people in different parts of the world being acclimatised to different heat extremes, the researchers tailored the risk of death from rising temperatures for all 732 locations in the study, so high temperatures in Berlin resulted in a greater increase in deaths than in Johannesburg.

Chloe Brimicombe at the University of Reading, UK, who wasn't involved in the research, says the study is timely given the record-breaking high temperatures in some parts of the world this month. "It also shows how quicker action in the past to limit emissions would have led to fewer heat-related deaths," she says.

Read more: https://www.newscientist.com/article/2278919-climate-change-to-blame-for-37-per-cent-of-worlds-heat-related-deaths/#ixzz6wZO1s1BE

NEWS AND VIEWS 17 FEBRUARY 2021

High-performance plastic made from renewable oils is chemically recyclable by design

Plastics are invaluable materials, but they use up petroleum resources and persist in the environment. A high-performance plastic derived from renewable oils has been designed at the

molecular level to be truly recyclable Mechanical Non-renewable **HDPE** recycling monomers b Break point HDPE-like Renewable polymer monomers Chemical recycling **onature**

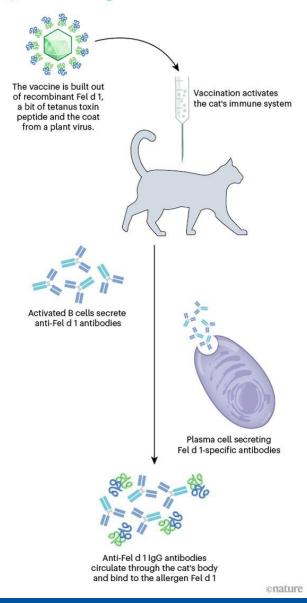
IMMUNIZING CATS AGAINST THEIR OWN ALLERGEN

HypoPet, a spin-off company from the University of Zurich in Switzerland, aims to create hypoallergenic cats by vaccinating them against their own Fel d 1 protein, so that the cat's immunoglobulin G (IgG) antibodies block the protein before it is sniffed up by a human.





Antibody against Fel d 1





Cells in limbo rouse allies before they perish

Dying cells can revive for long enough to trigger their own replacement.



•

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Zombies are a staple of apocalyptic movies, but not all the living dead are evil. In the guts of fruit flies, dying cells revive for a very short time to help other cells to grow.

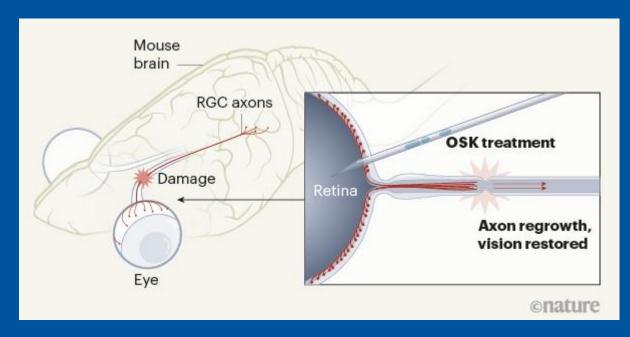
Cell death is part of natural cell turnover, especially for blood, skin and the lining of the gut. Working in fruit flies (*Drosophila melanogaster*), Andreas Bergmann at the University of Massachusetts Medical School in Worcester and his colleagues found that, in the insect's gut, cells that are destined to die can briefly enter an undead-like state that prompts intestinal stem cells to proliferate.

To do so, the dying cells express a protein that binds to the cell's membrane, stimulating the production of potentially harmful molecules called reactive oxygen species. This prompts the insect's immune cells to travel to the tissue and produce molecular messengers that tell 'undead' cells to activate a protein that signals neighbouring stem cells to multiply. Transiently 'undead' cells could be important for tissue renewal in other organisms, including people, the researchers say.

<u> Cell Rep. (2020)</u>

Restoring vision in mice. => epigenetica https://www.nature.com/articles/d41586-020-03119-1



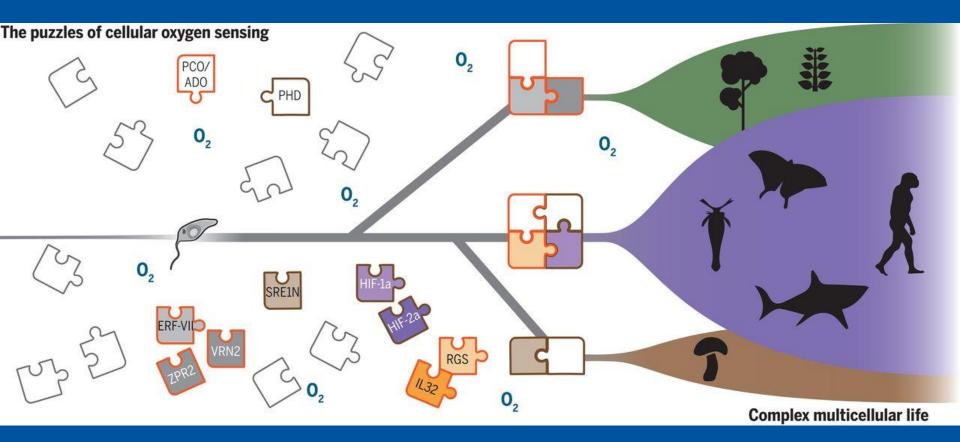




It emerges that treatment with three transcription factors can re-endow neurons in the mature eye with youthful characteristics and the capacity to regenerate.

Oxygen-sensing mechanisms across eukaryotic kingdoms and their roles in complex multicellularity





Creating value from plastic waste

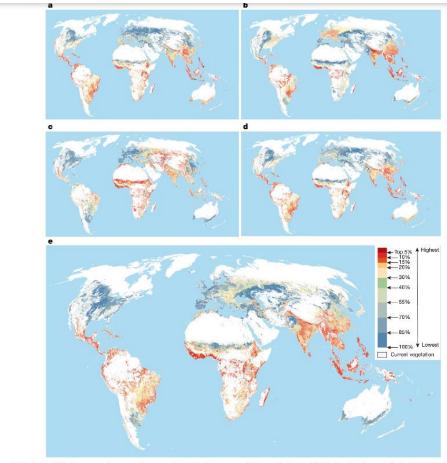


Plastic waste presents a number of environmental problems (1-3). Although only a small fraction of it enters rivers, lakes, and oceans, it can be transformed there into micro- and nanoplastics that are harmful to aquatic organisms. When plastic waste is buried in landfills or incinerated, it generates heat and carbon dioxide. However, plastic waste also offers great opportunities if its economic value can be increased substantially through upcycling processes that convert it into more valuable chemical products. On page 437 of this issue, Zhang et al. (4) report on an upcycling process that converts polyethylene (often used for packaging and grocery bags) into long-chain alkylaromatics that can be sulfonated to make biodegradable surfactants. This process operates at a moderate reaction temperature, does not need any solvent or added hydrogen, and produces only a small amount of light-gas by-products such as methane.

Global priority areas for ecosystem restoration

https://www.nature.com/articles/s41586-020-2784-9





 $\label{eq:Fig.1} \textbf{[Global priorities for restoration according to various criteria.} \\ \textbf{a-e}, \textbf{Priority areas for restoration, focused on biodiversity (a), the mitigation of climate change (b), minimizing costs (c), biodiversity and the mitigation of climate change (d) and all three criteria (e). All converted lands are ranked from$

highest priority (top 5%) (dark red) to lowest priority (85–100%) (blue). The spatial patterns for individual criteria (a–c) vary considerably, which highlights the role of joint optimizations (d, e) in capturing synergies.

Kosten van klimaatverandering



Of de toename van de schade door natuurgeweld ook leidt tot minder economische groei, is nog de vraag. De maatstaf voor groei is het bruto binnenlands product (bbp). In een analyse uit 2017 schreef Moody's dat schade door natuurgeweld vaak amper in bbp-cijfers terechtkomt, omdat het bbp slechts de productie van goederen en diensten meet, niet de waarde van vernietigd vermogen.

in Europa, is het economische klimaateffect onder meer zichtbaar aan de Rijn en zijn uitloper de Waal, die steeds vaker kampen met (extreem) laag water. Het worden, in plaats van 'gemengde' rivieren met smelt- en regenwater, steeds meer <u>pure regenrivieren</u>, omdat de gletsjers in de Alpen krimpen en doordat er minder sneeuw valt. Dat betekent dat het waterpeil sterker fluctueert. Daar komen de toenemend droge zomers in Europa bij. In de zeer droge en hete zomer van 2018 werd de Rijn vrijwel onbevaarbaar, waardoor Duitse industriële giganten als ThyssenKrupp en BASF hun grondstoffen en halffabrikaten niet op tijd kregen. Het effect was aanzienlijk: in het derde kwartaal van 2018 kromp de Duitse economie met 0,2 procent, een daling die volgens economisch onderzoeksinstituut IfW in Kiel volledig toe te schrijven was aan de lage waterstand in de Rijn. In Nederland leed de scheepvaartsector tussen de 65 en 220 miljoen euro schade.

Amygdala inhibitory neurons as loci for translation in emotional memories

To survive in a dynamic environment, animals need to identify and appropriately respond to stimuli that signal danger 1. Survival also depends on suppressing the threat-response during a stimulus that predicts the absence of threat (safety)^{2,3,4,5}. An understanding of the biological substrates of emotional memories during a task in which animals learn to flexibly execute defensive responses to a threat-predictive cue and a safety cue is critical for developing treatments for memory disorders such as post-traumatic stress disorder $\frac{5}{2}$. The centrolateral amygdala is an important node in the neuronal circuit that mediates defensive responses^{6,7,8,9}, and a key brain area for processing and storing threat memories. Here we applied intersectional chemogenetic strategies to inhibitory neurons in the centrolateral amygdala of mice to block cell-type-specific translation programs that are sensitive to depletion of eukaryotic initiation factor 4E (eIF4E) and phosphorylation of eukaryotic initiation factor 2α (p-eIF2 α). We show that de novo translation in somatostatinexpressing inhibitory neurons in the centrolateral amygdala is necessary for the long-term storage of conditioned-threat responses, whereas de novo translation in protein kinase $C\delta$ -expressing inhibitory neurons in the centrolateral amygdala is necessary for the inhibition of a conditioned response to a safety cue. Our results provide insight into the role of de novo protein synthesis in distinct inhibitory neuron populations in the centrolateral amygdala during the consolidation of long-term memories.

Negative feedback control of neuronal activity by microglia



Microglia, the brain's resident macrophages, help to regulate brain function by removing dying neurons, pruning non-functional synapses, and producing ligands that support neuronal survival¹. Here we show that microglia are also critical modulators of neuronal activity and associated behavioural responses in mice. Microglia respond to neuronal activation by suppressing neuronal activity, and ablation of microglia amplifies and synchronizes the activity of neurons, leading to seizures. Suppression of neuronal activation by microglia occurs in a highly region-specific fashion and depends on the ability of microglia to sense and catabolize extracellular ATP, which is released upon neuronal activation by neurons and astrocytes. ATP triggers the recruitment of microglial protrusions and is converted by the microglial ATP/ADP hydrolysing ectoenzyme CD39 into AMP; AMP is then converted into adenosine by CD73, which is expressed on microglia as well as other brain cells. Microglial sensing of ATP, the ensuing microglia-dependent production of adenosine, and the adenosine-mediated suppression of neuronal responses via the adenosine receptor A₁R are essential for the regulation of neuronal activity and animal behaviour. Our findings suggest that this microglia-driven negative feedback mechanism operates similarly to inhibitory neurons and is essential for protecting the brain from excessive activation in health and disease.

C. elegans interprets bacterial non-coding RNAs to learn pathogenic avoidance



Caenorhabditis elegans must distinguish pathogens from nutritious food sources among the many bacteria to which it is exposed in its environment¹. Here we show that a single exposure to purified small RNAs isolated from pathogenic *Pseudomonas aeruginosa* (PA14) is sufficient to induce pathogen avoidance in the treated worms and in four subsequent generations of progeny. The RNA interference (RNAi) and PIWI-interacting RNA (piRNA) pathways, the germline and the ASI neuron are all required for avoidance behaviour induced by bacterial small RNAs, and for the transgenerational inheritance of this behaviour. A single *P. aeruginosa* non-coding RNA, P11, is both necessary and sufficient to convey learned avoidance of PA14, and its *C. elegans* target, *maco-1*, is required for avoidance. Our results suggest that this non-coding-RNA-dependent mechanism evolved to survey the microbial environment of the worm, use this information to make appropriate behavioural decisions and pass this information on to its progeny.

Brain-inspired computing boosted by new concept of completeness https://www.nature.com/articles/d41586-020-02829-w



A system hierarchy for brain-inspired computing



Neuromorphic computing draws inspiration from the brain to provide computing technology and architecture with the potential to drive the next wave of computer engineering 1,2,3,4,5,6,7,8,9,10,11,12,13. Such brain-inspired computing also provides a promising platform for the development of artificial general intelligence 14,15. However, unlike conventional computing systems, which have a well established computer hierarchy built around the concept of Turing completeness and the von Neumann architecture 16,17,18, there is currently no generalized system hierarchy or understanding of completeness for braininspired computing. This affects the compatibility between software and hardware, impairing the programming flexibility and development productivity of brain-inspired computing. Here we propose 'neuromorphic completeness', which relaxes the requirement for hardware completeness, and a corresponding system hierarchy, which consists of a Turing-complete software-abstraction model and a versatile abstract neuromorphic architecture. Using this hierarchy, various programs can be described as uniform representations and transformed into the equivalent executable on any neuromorphic complete hardware—that is, it ensures programming-language portability, hardware completeness and compilation feasibility. We implement toolchain software to support the execution of different types of program on various typical hardware platforms, demonstrating the advantage of our system hierarchy, including a new systemdesign dimension introduced by the neuromorphic completeness. We expect that our study will enable efficient and compatible progress in all aspects of brain-inspired computing systems, facilitating the development of various applications, including artificial general intelligence.

https://www.newscientist.com/article/2256822-microwaving-plastic-waste-can-generate-clean-hydrogen/



A plausible metal-free ancestral analogue of the Krebs cycle composed entirely of α -ketoacids



https://www.nature.com/articles/s41557-020-00560-

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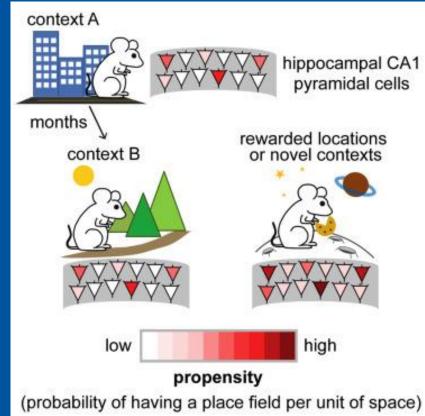
<u>vbFpHhl1DXylNpFVm8RB3rdp4h3dxifEhRxmKPY12Q%3D</u>

The Statistical Structure of the Hippocampal Code for Space as a Function of Time, Context, and Value



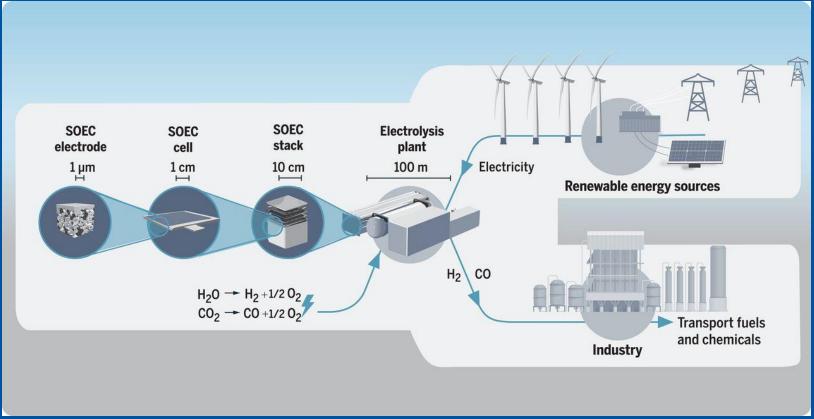
Hippocampal activity represents many behaviorally important variables, including context, an animal's location within a given environmental context, time, and reward. Using longitudinal calcium imaging in mice, multiple large virtual environments. and differing reward contingencies, we derived a unified probabilistic model of CA1 representations centered on a single feature—the field propensity. Each cell's propensity governs how many place fields it has per unit space, predicts its reward-related activity, and is preserved across distinct environments and over months. Propensity is broadly distributed—with many low, and some very high, propensity cells—and thus strongly shapes hippocampal representations. This results in a range of spatial codes, from sparse to dense. Propensity varied ~10-fold between adjacent cells in salt-andpepper fashion, indicating substantial functional differences within a presumed cell type. Intracellular recordings linked propensity to cell excitability. The stability of each cell's propensity across conditions suggests this fundamental property has anatomical, transcriptional, and/or developmental origins.

Propensity is a natural tendency to behave in a particular way



Solid oxide electrolyzers: From nanoscale to macroscale.





The splitting of H₂O or CO₂ occurs at solid oxide electrolysis cell (SOEC) electrodes. Multiple cells are combined into SOEC stacks, which are in turn combined into SOEC plants. When renewable electricity is used, the production of transport fuels and chemicals can be decoupled from fossil resources. SOECs operate at elevated temperatures, resulting in electrolysis efficiencies unattainable by other electrolysis technologies. SOECs offer an opportunity to decrease the costs of future renewable energy systems through more efficient conversion and enable further integration of renewables into the energy mix

Na⁺ controls hypoxic signalling by the mitochondrial respiratory chain



https://www.sciencemag.org/news/2020/10/europebuilding-digital-twin-earth-revolutionize-climate-forecasts





WHY / SETTLE SPACE? THE REAL QUESTION IS:

> WHY HAVENT WE?

IT'S OUR FUTURE

BUT WE NEED TO SETTLE IT DIFFERENTLY THAN WE DID HERE

WE CAN BUILD AN EXCITING FUTURE PROTECT & EXPAND LIFE

HUMAN CIVILIZATION

EXPERIENCE THE

THE ENGINE & INNOVATION
TO WORK THERE MUST BE

TUEL OIL direction

SCIENCE + TECHNOLOGY

EVENTS LIKE THESE! PEOPLE COLLABORATING

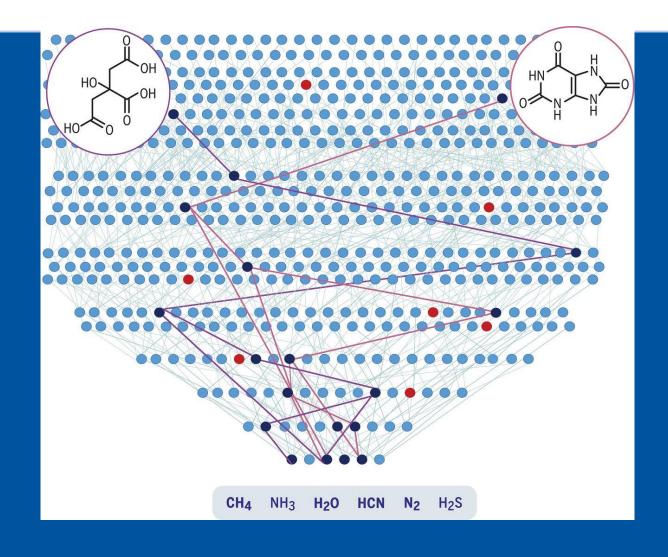
THERE IS CUPPENTLY A LOT OF PRIVATE INVESTMENT IN SPACE

SO COMMERCE MUST REMAIN OPEN

SPACE

Synthetic connectivity, emergence, and self-regeneration in the network of prebiotic chemistry





A neural correlate of sensory consciousness in a corvid bird https://science.sciencemag.org/content/369/65



Subjective experiences that can be consciously accessed and reported are associated with the cerebral cortex. Whether sensory consciousness can also arise from differently organized brains that lack a layered cerebral cortex, such as the bird brain, remains unknown. We show that single-neuron responses in the pallial endbrain of crows performing a visual detection task correlate with the birds' perception about stimulus presence or absence and argue that this is an empirical marker of avian consciousness. Neuronal activity follows a temporal two-stage process in which the first activity component mainly reflects physical stimulus intensity, whereas the later component predicts the crows' perceptual reports. These results suggest that the neural foundations that allow sensory consciousness arose either before the emergence of mammals or independently in at least the avian lineage and do not necessarily require a cerebral cortex.

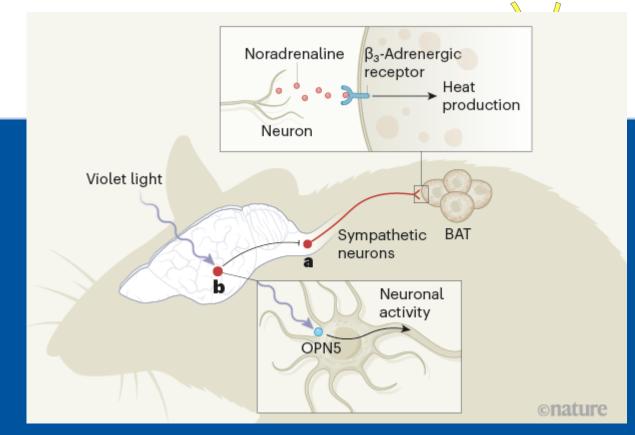
Adaptable haemodynamic endothelial cells for organogenesis and tumorigenesis



Endothelial cells adopt tissue-specific characteristics to instruct organ development and regeneration $\frac{1}{2}$. This adaptability is lost in cultured adult endothelial cells, which do not vascularize tissues in an organotypic manner. Here, we show that transient reactivation of the embryonic-restricted ETS variant transcription factor 2 (ETV2)³ in mature human endothelial cells cultured in a serum-free three-dimensional matrix composed of a mixture of laminin, entactin and type-IV collagen (LEC matrix) 'resets' these endothelial cells to adaptable, vasculogenic cells, which form perfusable and plastic vascular plexi. Through chromatin remodelling, ETV2 induces tubulogenic pathways, including the activation of RAP1, which promotes the formation of durable lumens 4.5. In three-dimensional matrices—which do not have the constraints of bioprinted scaffolds—the 'reset' vascular endothelial cells (R-VECs) self-assemble into stable, multilayered and branching vascular networks within scalable microfluidic chambers, which are capable of transporting human blood. In vivo, R-VECs implanted subcutaneously in mice self-organize into durable pericyte-coated vessels that functionally anastomose to the host circulation and exhibit long-lasting patterning, with no evidence of malformations or angiomas. R-VECs directly interact with cells within three-dimensional co-cultured organoids, removing the need for the restrictive synthetic semipermeable membranes that are required for organ-on-chip systems, therefore providing a physiological platform for vascularization, which we call 'Organ-On-VascularNet'. R-VECs enable perfusion of glucose-responsive insulin-secreting human pancreatic islets, vascularize decellularized rat intestines and arborize healthy or cancerous human colon organoids. Using single-cell RNA sequencing and epigenetic profiling, we demonstrate that R-VECs establish an adaptive vascular niche that differentially adjusts and conforms to organoids and tumoroids in a tissue-specific manner. Our Organ-On-VascularNet model will permit metabolic, immunological and physiochemical studies and screens to decipher the crosstalk between organotypic endothelial cells and parenchymal cells for identification of determinants of endothelial cell heterogeneity, and could lead to advances in therapeutic organ repair and tumour targeting.

Shining a light on heat production in mice.

Neurons of the sympathetic nervous system project from the brain to the cells of brown adipose tissue (BAT). These neurons release the neurotransmitter molecule noradrenaline, which binds to β_3 -adrenergic-receptor proteins on the BAT cells, triggering the cells to break down glucose and so produce heat. **b**, Zhang et al.³ report that violet light activates a light-sensitive protein called opsin 5 (OPN5) on neurons in the preoptic area of mouse brains. When activated, these neurons inhibit the pathway outlined above, and so prevent heat production.



Innovation in trial operations

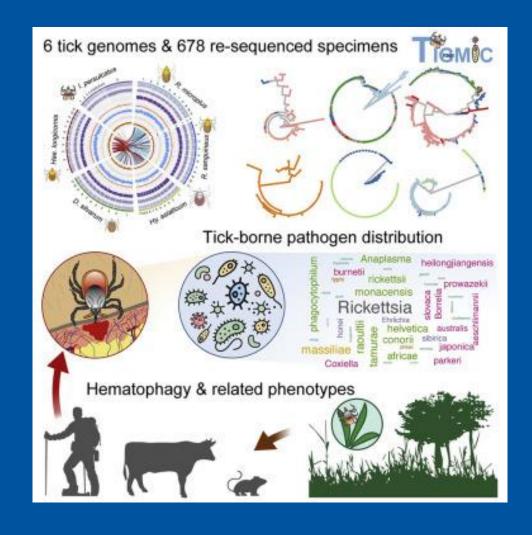


COVID-19 altered the conduct of ongoing trials, with investigators reporting 57% of patient interactions and 79% of interactions between sponsors and contract research organizations (CROs) taking place remotely.

COVID-19 has demonstrated that sponsors and investigators can achieve in weeks what was previously thought to require months or years, and highlighted the humanitarian importance of efficient, robust and definitive clinical research. The industry's actions over the next 1–2 years may determine fundamental pivots for how medicines are developed, giving each stakeholder an opportunity not only to adapt but to shape the future clinical trial paradigm.

<u>Large-Scale Comparative Analyses of Tick Genomes</u> <u>Elucidate Their Genetic Diversity and Vector Capacities</u>





Why some animals have the power of regeneration

Newly identified genetic elements help to replace missing tails and other body parts.



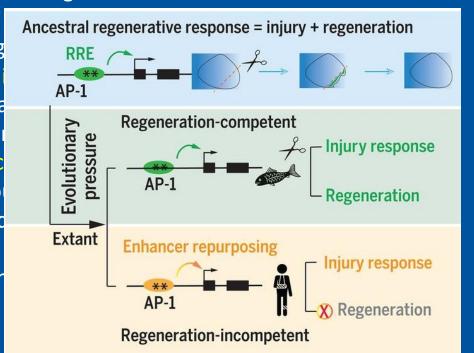
Scientists have pinpointed gene-activating stretches of DNA that help animals to regenerate limbs, fins and other tissues.

Some vertebrates can regenerate tissues after injury, but many cannot — suggesting that this trait has been lost and gained across the vertebrate family tree. Alejandro Sánchez Alvarado at the Stowers Institute for Medical Research in Kansas City, Missouri, and his colleagues studied zebrafish (*Danio rerio*) and African killifish (*Nothobranchius furzeri*), which can regenerate their tail fins, and identified genes that were active in the

regenerating tissue.

There was little overlap in the active g that did overlap, including one called during regeneration of ear tissue in Cabut not after ear injury in non-regener A type of non-coding DNA sequence cactivity of inhibin beta A. The team for replacing it with a human version hinckillifish. The researchers propose that sequences are responsible for different their tissues.

<u> Science (2020)</u>



Origin and elaboration of a major evolutionary transition in individuality



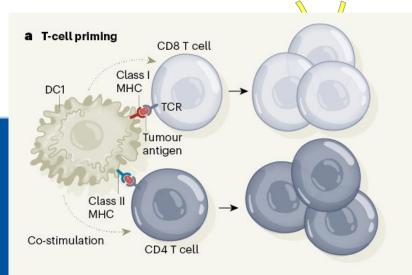
Obligate endosymbiosis, in which distantly related species integrate to form a single replicating individual, represents a major evolutionary transition in individuality^{1,2,2}. Although such transitions are thought to increase biological complexity 52.4.5.6, the evolutionary and developmental steps that lead to integration remain poorly understood. Here we show that obligate endosymbiosis between the bacteria *Blochmannia* and the hyperdiverse ant tribe Camponotini^{7,8,9,10,11} originated and also elaborated through radical alterations in embryonic development, as compared to other insects. The Hox genes Abdominal A (abdA) and Ultrabithorax (Ubx) which, in arthropods, normally function to differentiate abdominal and thoracic segments after they form—were rewired to also regulate germline genes early in development. Consequently, the mRNAs and proteins of these Hox genes are expressed maternally and colocalize at a subcellular level with those of germline genes in the germplasm and three novel locations in the freshly laid egg. *Blochmannia* bacteria then selectively regulate these mRNAs and proteins to make each of these four locations functionally distinct, creating a system of coordinates in the embryo in which each location performs a different function to integrate *Blochmannia* into the Camponotini. Finally, we show that the capacity to localize mRNAs and proteins to new locations in the embryo

CRISPR-engineered human brown-like adipocytes prevent diet-induced obesity and ameliorate metabolic syndrome in mice https://stm.sciencemag.org/content/12/558/eaaz8664

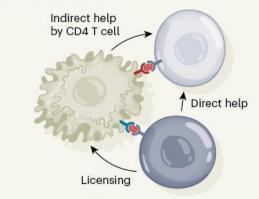


How a dendritic cell helps T cells to target tumours.

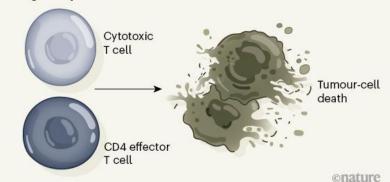
a, An immune cell called a conventional type 1 dendritic cell (DC1) ingests pieces of tumour cells and processes them to generate peptide fragments called antigens. These then bind proteins called major histocompatibility complex (MHC) molecules. Class I MHC molecules present antigens to a type of immune cell called a CD8 T cell, whereas class II MHC molecules present antigens to a CD4 T cell. If a T-cell receptor (TCR) on a T cell recognizes an antigen, the cell is activated and it divides. Until now, it has mainly been thought that DC1s provide such priming signals only to CD8 T cells. However, Ferris et al. 1 show in mice that DC1s also stimulate CD4 T cells. **b**, Activated T cells then interact with a DC1, which acts as a 'platform' for a CD4 T cell to directly interact with a CD8 T cell and boost its activation. The CD4 T cell also indirectly helps in readying the CD8 T cell by 'licensing' the DC1-mediated activation of the CD8 Tcell. **c**, CD8 and CD4 T cells that are capable of launching immune responses (termed cytotoxic and effector cells, respectively) drive tumour rejection and provide a memory capacity that offers long-term protection against tumour regrowth



b Help for the CD8 T cell



C Tumour rejection and long-term protection



Honderden hittedoden door heetste week ooit, eerste sterftepiek sinds corona

=> Klimaat zien als corona



Here's what Exxon's removal from the Dow says about the energy sector

'Sign of the times' as energy heavyweight replaced by Salesforce



Species that can make us ill thrive in human habitats

https://www.nature.com/articles/d41586-020-02189-5



The importins of pain



Neuropathic pain, which is pain that arises from injury or disease affecting the somatosensory nervous system, affects millions of people with devastating consequences to their well-being. Available therapeutics have limited efficacy, and the underlying mechanisms governing the persistence of this disorder are mysterious. On page 842 of this issue, Marvaldi et al. (1) reveal that the nuclear import protein, importin α3, plays a crucial role in maintaining neuropathic pain months after a peripheral nerve injury in mice. Their findings demonstrate that activator protein 1 (AP1) family transcription factors require this nuclear transport complex for entrance to the sensory neuronal nucleus, pointing to a defined set of drug targets for the potential disruption of persistent neuropathic pain. An implication of the findings is that even very long-lasting neuropathic pain can be disrupted with disease-modifying therapeutics.

The Atlantic: Why the Coronavirus Has Been So Successful Immunology Is Where Intuition Goes to Die

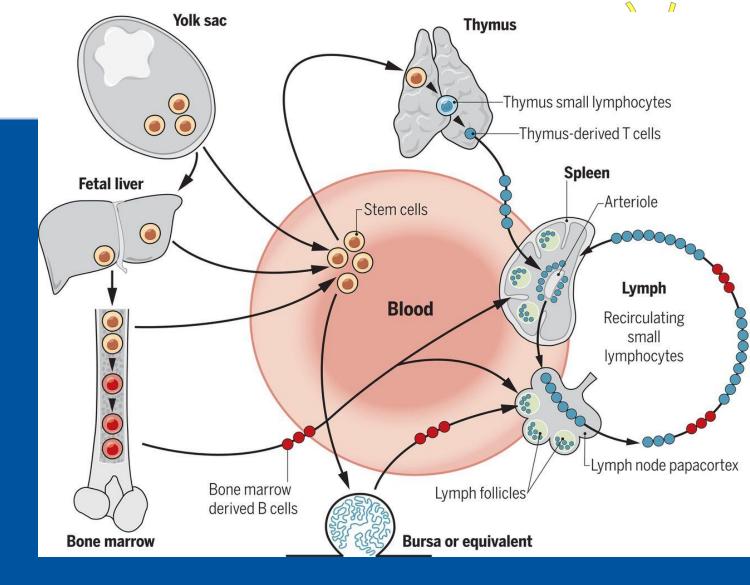


For example, most respiratory viruses tend to infect either the upper or lower airways. In general, an upper-respiratory infection spreads more easily, but tends to be milder, while a lower-respiratory infection is harder to transmit, but is more severe. SARS-CoV-2 seems to infect both upper and lower airways, perhaps because it can exploit the ubiquitous furin. This double whammy could also conceivably explain why the virus can spread between people before symptoms show up—a trait that has made it so difficult to control. Perhaps it transmits while still confined to the upper airways, before making its way deeper and causing severe symptoms. All of this is plausible but totally hypothetical; the virus was only discovered in January, and most of its biology is still a mystery.

The function of the thymus

and its impact on modern medicine

https://science.s ciencemag.org/c ontent/369/6503 /eaba2429



Human consciousness is supported by dynamic complex patterns of brain signal coordination



Adopting the framework of brain dynamics as a cornerstone of human consciousness, we determined whether dynamic signal coordination provides specific and generalizable patterns pertaining to conscious and unconscious states after brain damage. A dynamic pattern of coordinated and anticoordinated functional magnetic resonance imaging signals characterized healthy individuals and minimally conscious patients. The brains of unresponsive patients showed primarily a pattern of low interareal phase coherence mainly mediated by structural connectivity, and had smaller chances to transition between patterns. The complex pattern was further corroborated in patients with covert cognition, who could perform neuroimaging mental imagery tasks, validating this pattern's implication in consciousness. Anesthesia increased the probability of the less complex pattern to equal levels, validating its implication in unconsciousness. Our results establish that consciousness rests on the brain's ability to sustain rich brain dynamics and pave the way for determining specific and generalizable fingerprints of conscious and unconscious states.

Default-mode network streams for coupling to language and control systems

https://www.pnas.org/content/117/29/17308



Expanded encyclopaedias of DNA elements in the human and mouse genomes

https://www.nature.com/articles/s41586-020-2449-8



A leptin-BDNF pathway regulating sympathetic innervation of adipose tissue

https://www.nature.com/articles/s41586-020-2527-y



Ageing hallmarks exhibit organ-specific temporal signatures

Ageing is the single greatest cause of disease and death worldwide,

Here we performed bulk RNA sequencing of 17 organs and plasma proteomics at 10 ages across the lifespan of Mus musculus, and integrated these findings with data from the accompanying *Tabula Muris Senis*²—or 'Mouse Ageing Cell Atlas'—which follows on from the original *Tabula Muris*². We reveal linear and nonlinear shifts in gene expression during ageing, with the associated genes clustered in consistent trajectory groups with coherent biological functions—including extracellular matrix regulation, unfolded protein binding, mitochondrial function, and inflammatory and immune response. Notably, these gene sets show similar expression across tissues, differing only in the amplitude and the age of onset of expression. Widespread activation of immune cells is especially pronounced, and is first detectable in white adipose depots during middle age. Single-cell RNA sequencing confirms the accumulation of T cells and B cells in adipose tissue—including plasma cells that express immunoglobulin J—which also accrue concurrently across diverse organs. Finally, we show how gene expression shifts in distinct tissues are highly correlated with corresponding protein levels in plasma, thus potentially contributing to the ageing of the systemic circulation. Together, these data demonstrate a similar yet asynchronous inter- and intra-organ progression of ageing, providing a foundation from which to track systemic sources of declining health at old age.

https://www.nature.com/articles/s41586-020-2499-y https://www.nature.com/articles/s41586-020-2496-1

Microbiota modulate sympathetic neurons via a gut-brain circuit



A combination of gnotobiotic mouse models, transcriptomics, circuit tracing and chemogenetic manipulations identifies neuronal circuits that integrate microbial signals in the gut with regulation of the sympathetic nervous system.

A neurotransmitter produced by gut bacteria modulates host sensory behaviour

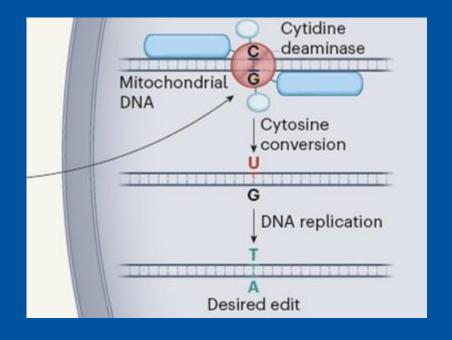
A neuromodulator produced by commensal *Providencia* bacteria that colonize the gut of *Caenorhabditis elegans* mimics the functions of the cognate host molecule to manipulate a sensory decision of the host.

Mitochondrial genome editing: another win for curiosity-driven research

A promising biomedical tool began life as part of efforts to answer a different question. https://www.nature.com/articles/d41586-020-02094-x

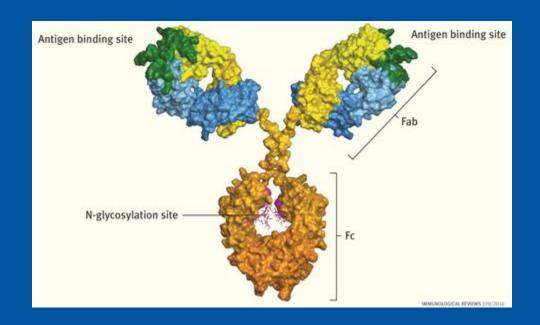


Microbiologist Joseph Mougous has plenty of reasons to study microscopic warfare. Understanding inter-bacterial conflict, for example, can help researchers to learn why some microbes make animals and humans ill. But, as so often in research, his attempts to understand one set of problems have led to a tool for something different.



Antibodies as leading tools to unlock the therapeutic potential in human disease Immunological reviews



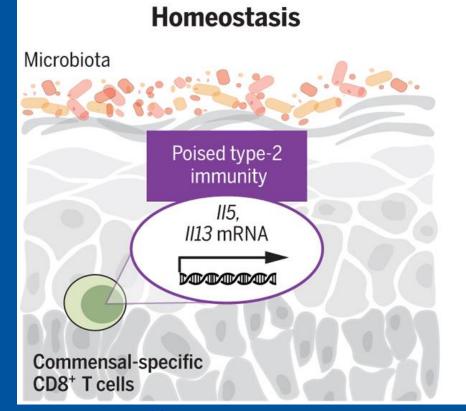


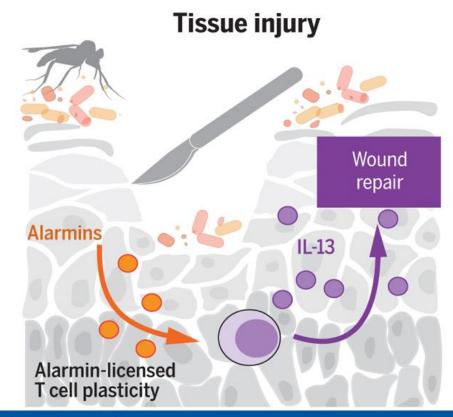
Nonclassical Immunity to Commensal Microbes



Commensal-specific CD8⁺ T cells harbor a poised type-2 transcriptome during homeostasis

Tissue injury licenses poised type-2 immunity, including translation of interleukin-13 (IL-13) protein by commensal-specific CD8+ T cells, thereby promoting tissue repair.







Plasma transfers exercise benefit in mice

Exercise has a broad range of beneficial healthful effects. Horowitz *et al.* tested whether the beneficial effects of exercise on neurogenesis in the brain and improved cognition in aged mice could be transferred in plasma (blood without its cellular components) from one mouse to another (see the Perspective by Ansere and Freeman). Indeed, aged mice that received plasma from young or old mice that had exercised showed beneficial effects in their brains without hitting the treadmill. The authors identified glycosylphosphatidylinositol-specific phospholipase D1 as a factor in plasma that might, in part, mediate this favorable effect.

https://science.sciencemag.org/content/369/6500/167

Biological functions of lymphatic vessels



https://science.sciencemag.org/content/369/6500/eaax4063

All who wander are not lost

At least three species of *Homo* coexisted in Africa starting about 2 million years ago

https://science.sciencemag.org/content/368/6486/34

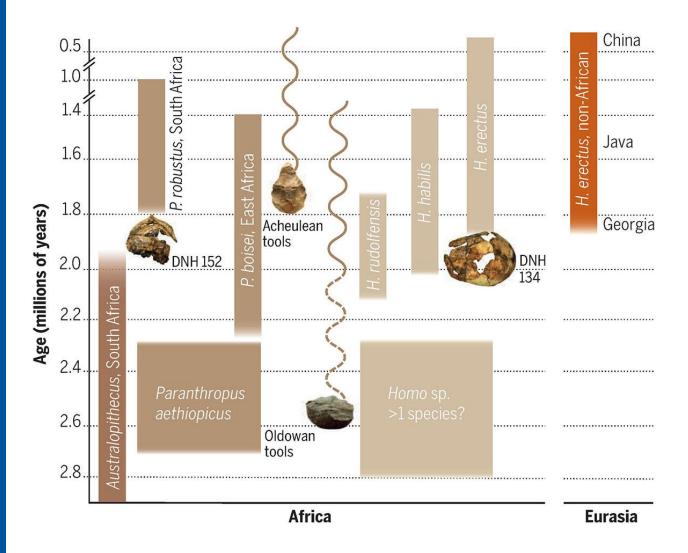
=> Anthropocentrisme

almost as soon as they arose, *H.erectus* appeared outside of Africa at the site of Dmanisi in the Republic of Georgia. Over the next nearly 2 million years, *H.erectus* occupied a variety of different habitats and contexts before going extinct well after 0.5 million years ago on presentday Java

=> H.erectus already was a traveler, and adaptive

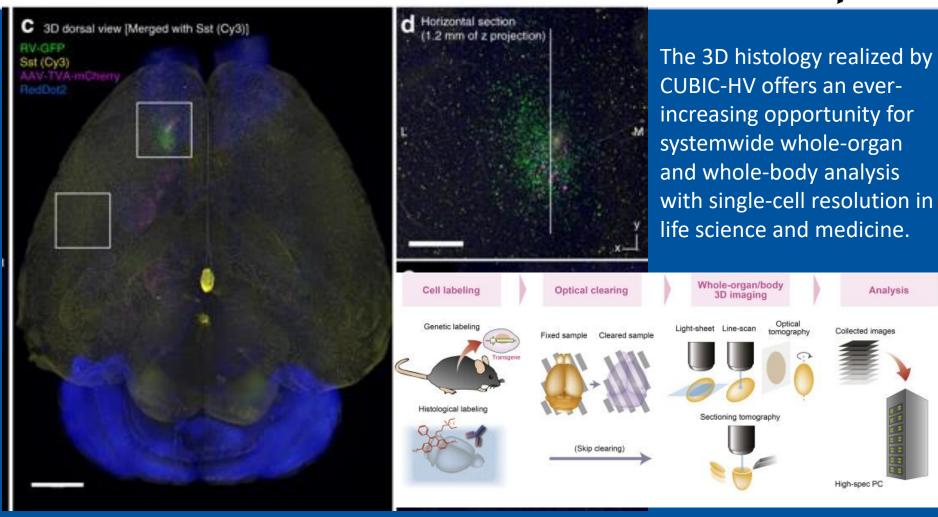
Temporal existence of archaic human species

Shown are the ages of fossils DNH 134 and DNH 152. Stone-tool time ranges are shown with wavy lines. The dashed part of the wavy line indicates lesser frequency of find sites.



Versatile whole-organ/body staining and imaging based on electrolyte-gel properties of biological tissues





https://www.nature.com/articles/s41467-020-15906-5

https://www.cell.com/cell-chemical-biology/fulltext/S2451-9456(15)00468-7

Cells edited with CRISPR prove safe in humans

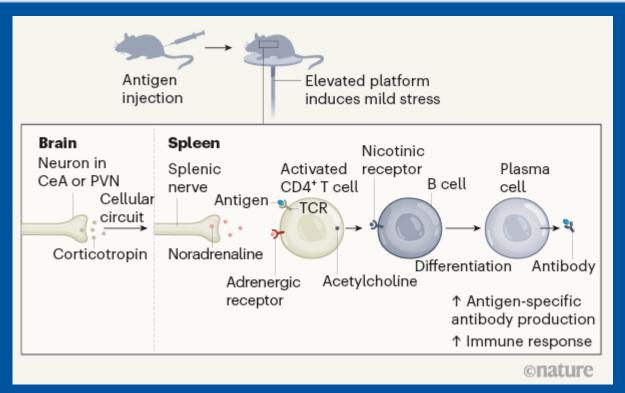


https://www.nature.com/articles/d41586-020-01262-3

Brain-spleen connection => stress improves immunity



The authors injected animals with an antigen. Placing the animal on a high platform activated neurons that produce the molecule corticotropin. These neurons are located in brain regions that respond to stress. A cellular circuit connects these activated neurons to the splenic nerve and drives it to release the molecule noradrenaline. When CD4+ T cell encounters noradrenaline released in the spleen, this leads the T cell to secrete the molecule acetylcholine. This molecule binds to a nicotinic receptor on an immune cell called a B cell, causing it to differentiate into a plasma cell.



https://www.nature.com/articles/d41586-020-01168-0

Construction of a human cell landscape a single-cell level



Single-cell analysis is a valuable tool for dissecting cellular heterogeneity in complex systems. However, a comprehensive single-cell atlas has not been achieved for humans. Here we use single-cell mRNA sequencing to determine the cell-type composition of all major human organs and construct a scheme for the human cell landscape (HCL). We have uncovered a single-cell hierarchy for many tissues that have not been well characterized. We established a 'single-cell HCL analysis' pipeline that helps to define human cell identity. Finally, we performed a single-cell comparative analysis of landscapes from human and mouse to identify conserved genetic networks. We found that stem and progenitor cells exhibit strong transcriptomic stochasticity, whereas differentiated cells are more distinct. Our results provide a useful resource for the study of human biology.

Artificial eye boosted by hemispherical retina

An artificial visual system that mimics the human eye. A lens is fixed over an aperture in an 'eyeball', which consists of a metal shell at the front, an artificial retina at the back and an ionic liquid in the middle. The key advance is the hemispherical retina: a dense array of light-sensitive nanowires held in the pores of an aluminium oxide membrane. The nanowires mimic the photoreceptor cells in biological retinas. A polymeric socket holds the retina, ensuring electrical contact between the nanowires and liquid-metal wires at the back. The liquid-metal wires mimic the nerve fibres by transmitting signals from the nanowires to external circuitry for signal processing.

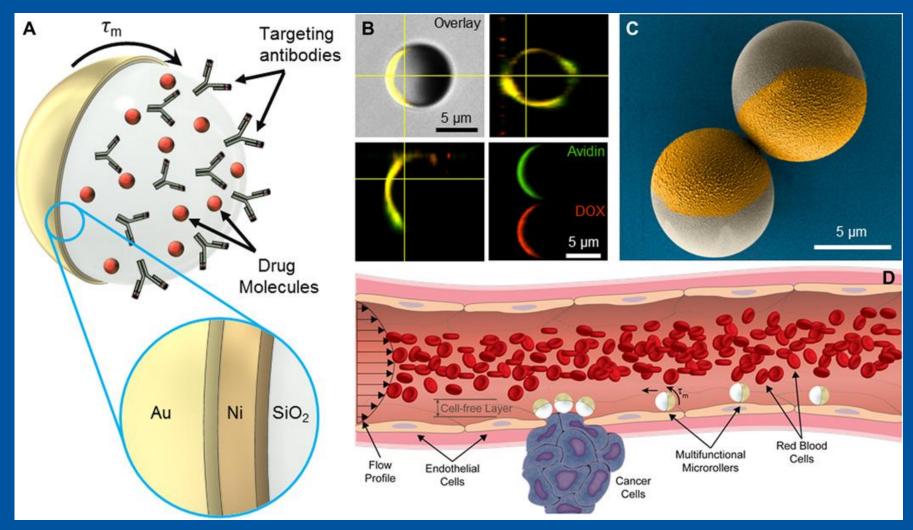
Retina Socket Liquid-metal wire Aluminium Ionic shell liquid Lens Nanowire

https://www.nature.com/articles/d4

onature

Kunstmatige T-cel

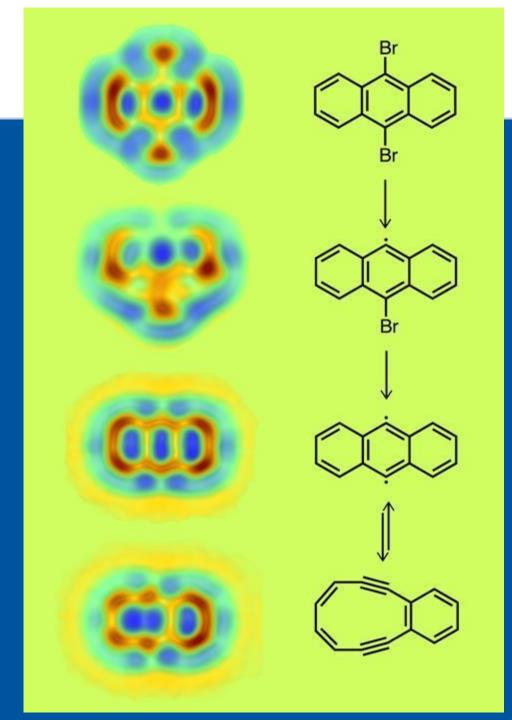




Science Robotics 20 May 2020: Vol. 5, Issue 42

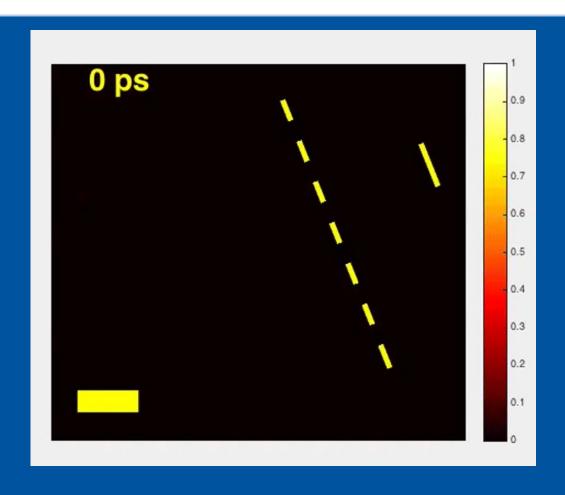
Chemistry in action: very small detail and very short time scale

- The reversible Bergman cyclization (right) has been examined by AFM (left), which clearly shows the bonds being made and broken
- https://www.chemistryworld.
 com/features/watching molecular movies/3008480.article
- Source: © IBM
 Research/Science Photo
 Library



Video at <u>four trillion</u> (10¹²) <u>frames per second</u> pictures light in a flash

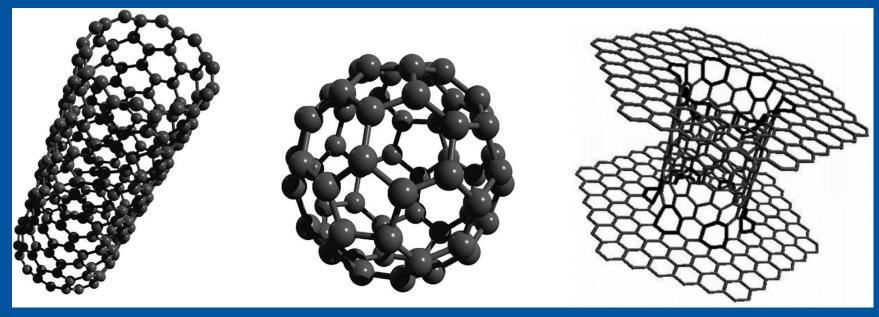




https://www.nature.com/articles/d41586-019-01625-5

Atomically precise, custom-design origami graphene nanostructures Niet alleen meten, maar ook bouwen op nano-niveau



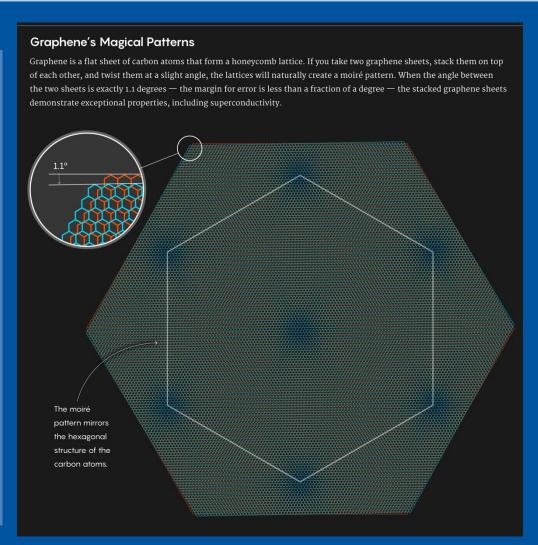


- The present atomically precise graphene origami provides a platform for constructing carbon nanostructures with engineered quantum properties and, ultimately, quantum machines.
- NB Bouwen met plakband (en geavanceerde chemie)

Twisted bilayer graphene Low-Tech!

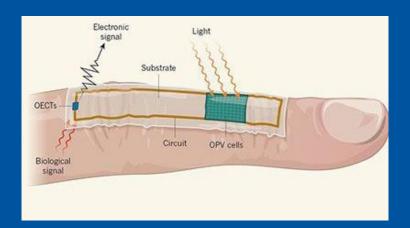


- intriguing similarity
 between <u>magic-angle</u>
 twisted bilayer graphene
 and high-temperature
 superconductors.
- https://www.quantamaga zine.org/how-twistedgraphene-became-thebig-thing-in-physics-20190430/

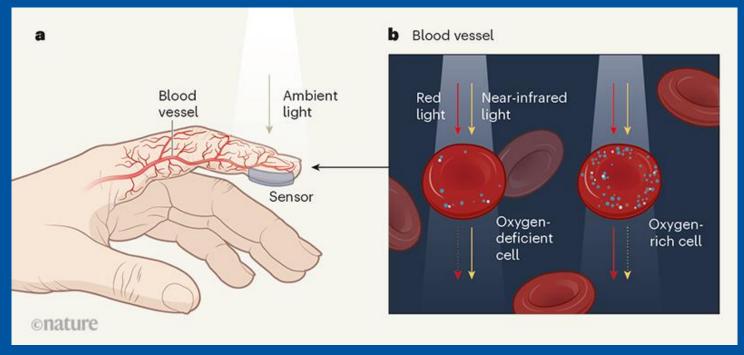


Wearable graphene sensors use ambient light to monitor health





Ambient light passes easily through human skin and tissue, but is absorbed by the haemoglobin in red blood cells. By monitoring the modulation of ambient light as it passes through tissue, the sensors can thus monitor blood flow and heart rate



Asymmetric Temperature Modulation for Extreme Fast Charging of Lithium-Ion Batteries



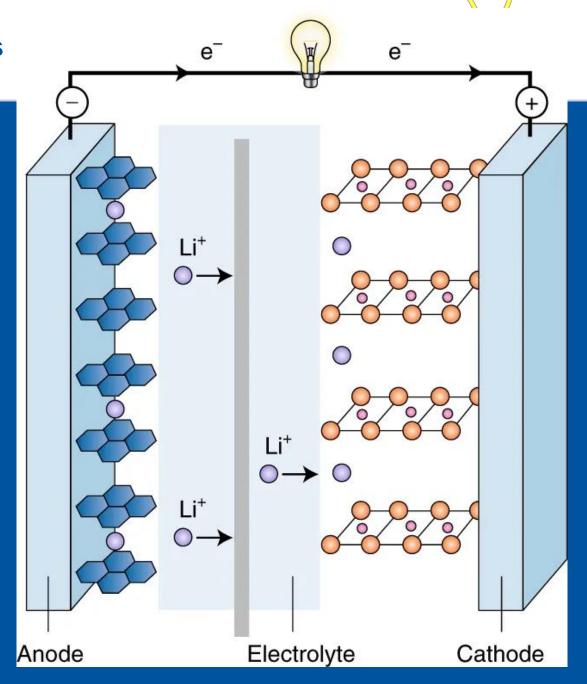


- Adding a 200-mile range in 10 min, so-called extreme fast charging (XFC), is the key to mainstream adoption of battery electric vehicles (BEVs). Joule, October 30, 2019
- https://www.cell.com/joule/fulltext/S2542-4351(19)30481-7

Nobel 2019: Li-ion batteries Eerste werk al uit jaren 70!

> https://www.nature.co m/articles/d41586-019-02965-y

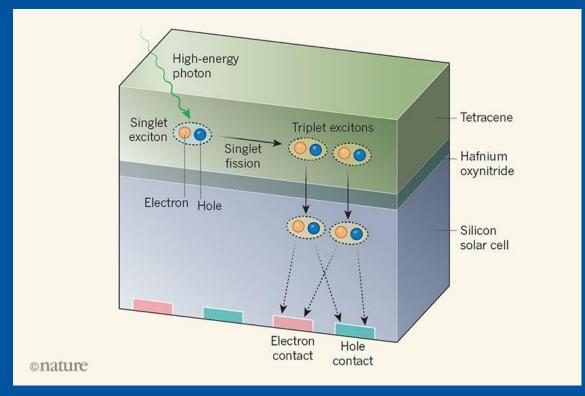


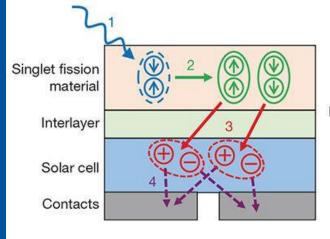


An exciting boost for solar cells



Silicon solar cells currently dominate the market, but have well-documented efficiency limitations. The most glaring deficiency, described in 1961, is that high-energy photons generate unwanted heat. Conventional silicon solar cells are therefore restricted to converting only 30% of incident solar energy into electricity in an otherwise perfect device. Strategies for overcoming this barrier include stacking different solar cells in series, or finding ways to split the energy of photons before collection.

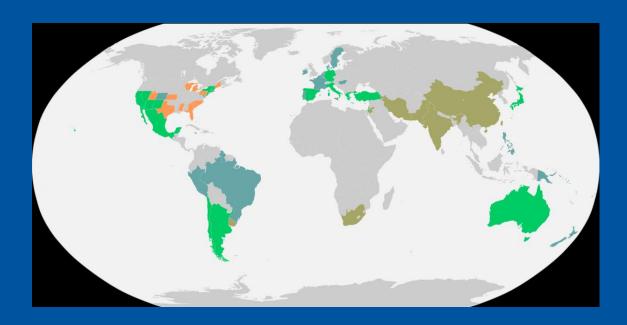




https://www.nature.com/articles/d41586-019-02014-8

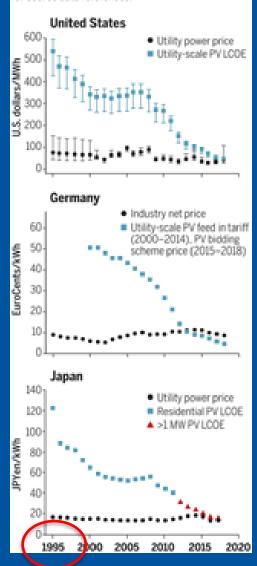
Coal and solar prices are now similar Breder dan alleen wetenschap (maatschappelijk belang)

Grid parity occurs when an alternative energy source can generate power at a price that is less than or equal to the price of power from the electricity grid. The term is most commonly used when discussing renewable energy sources, notably and Reaching grid parity is considered to be the point at which an energy source becomes a contender for widespread development without subsidies or government support. It is widely believed that a wholesale shift in generation to these forms of energy will take place when they reach grid parity.



Utility power and utility-scale PV prices

Error bars for U.S. power price indicate the average price for the least-cost and highest-cost market in a given year (excluding Hawaii); error bars for U.S. PV indicate LCOE in New York, NY (high bar), and Phoenix, AZ (low bar). See supplementary materials for source data references.



Investeren in windmolens en zonnepanelen wordt rendabeler dan investeren in de productie van diesel

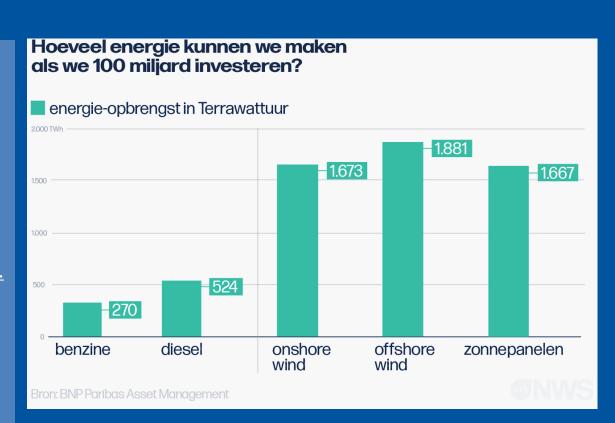


Dat blijkt uit een studie van BNP Paribas Fortis. Rijden op elektriciteit wordt steeds goedkoper. Benzine en diesel zullen op termijn het onderspit delven

Klimaat is altijd een ethische kwestie geweest," zegt Mark Lewis, "nu is het ook een economische kwestie geworden. Dat maakt dat het veel ernstiger genomen wordt

https://docfinder.bnpparibasam.com/api/files/1094E5B9-2FAA-47A3-805D-EF65EAD09A7F

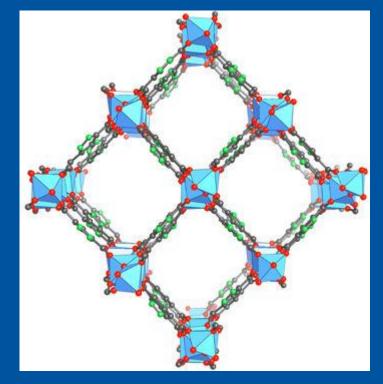
Echte ontwikkelingen zijn wetenschappelijk/economisch. Niet politiek (gelukkig?)



Crystalline nets snare water and make fuel from thin air



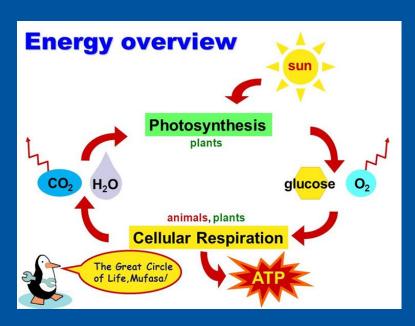
Over the past 2 decades, chemists have created thousands of spongelike crystalline materials known as metal-organic frameworks (MOFs). Each is made up of metal atoms that act like hubs in a Tinkertoy set, connected into a porous network by organic linkers designed to hold fast to the hubs and create openings to house molecular guests. By mixing and matching the metals and linkers, researchers found they could tailor the pores to capture gas molecules, such as water vapor and carbon dioxide. Because many of the early MOFs were expensive to make and degraded quickly, they did not live up to initial excitement. But in recent years, MOFmakers have figured out a broad set of design rules to make MOFs more robust. That has led to a bevy of new applications, such as harvesting water from desert air and turning carbon dioxide into liquid fuel.

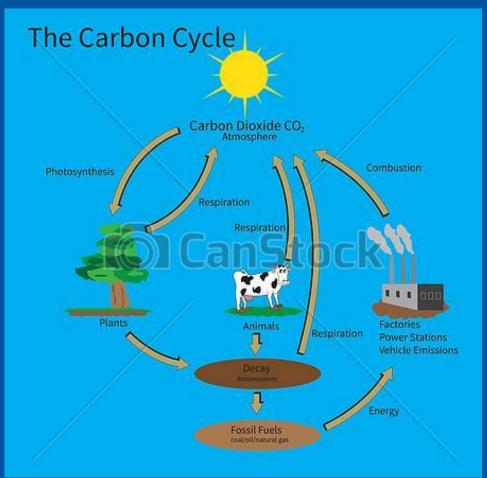


De koolstof cyclus



 Is niet gesloten door input van oude voorraad in de grond => extra energie, en opwarming

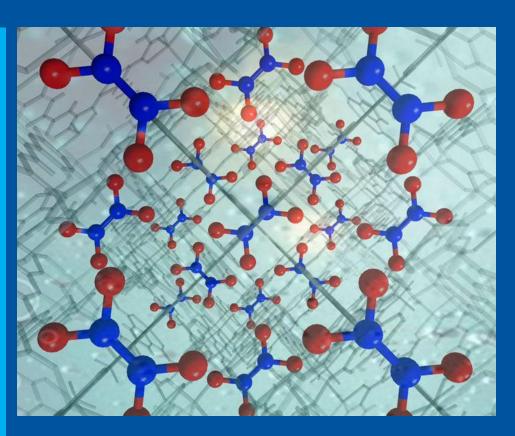




Porous material removes nitrogen dioxide from exhaust and transforms it into a valuable commodity.



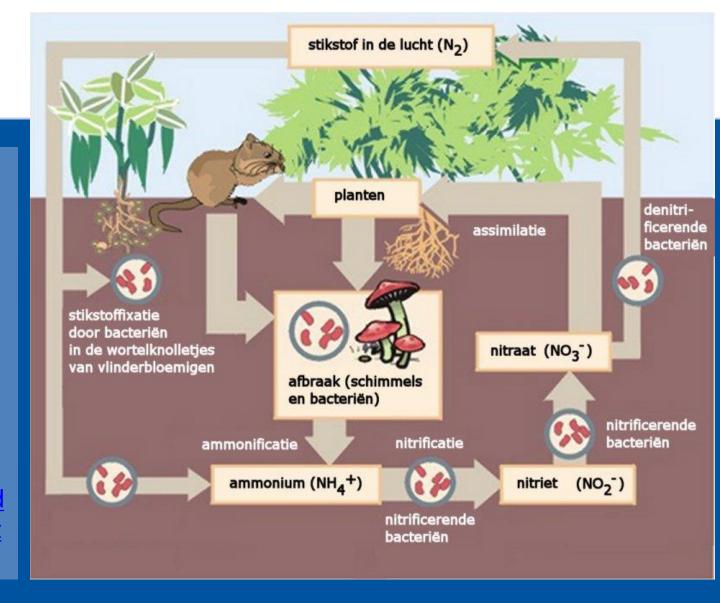
- Air pollution by nitrogen oxides, NO_x, is a major problem, and new capture and abatement technologies are urgently required. Here, we report a metal-organic framework (Manchester Framework Material 520 (MFM-520)) that can efficiently confine dimers of NO₂, which results in a high adsorption capacity of 4.2 mmol g⁻¹ (298 K, 0.01 bar) with full reversibility and no loss of capacity over 125 cycles.
- https://www.nature.com/articles/s41557-019-0356-0



De stikstof cyclus

 Is niet gesloten door import van stikstof => (mest)overschot

- NH3 = ammoniak = basis van kunstmest
- https://nl.wikiped ia.org/wiki/Kunst mest



Wetenschappelijke literatuur



Pubmed

https://www.ncbi.nlm.nih.gov/pubmed

Google scholar

https://scholar.google.nl/

Wetenschappelijk woordenboek

https://en.oxforddictionaries.com/

Science

http://science.sciencemag.org/

Nature

http://www.nature.com/nature/index.html

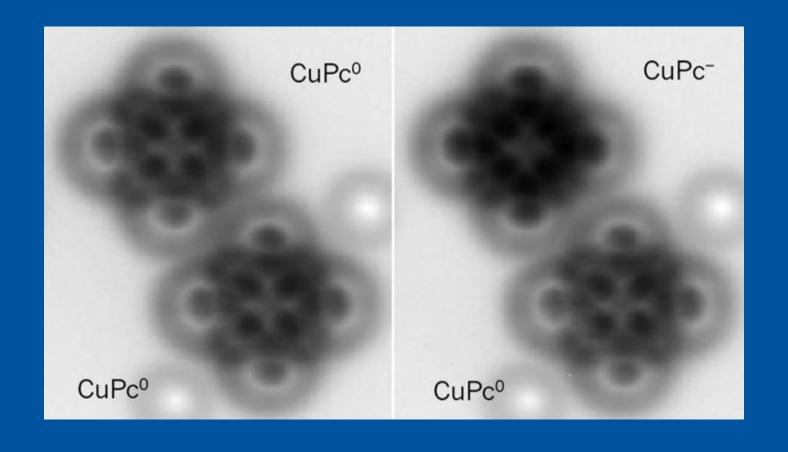
Cell

http://www.cell.com/cell/current

Volgde ik altijd al => nu cursus van gemaakt

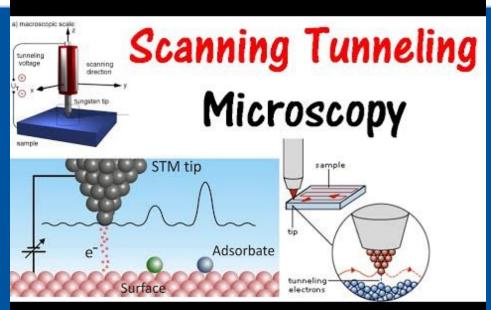
A microscope observes a single molecule as it gains an electron.

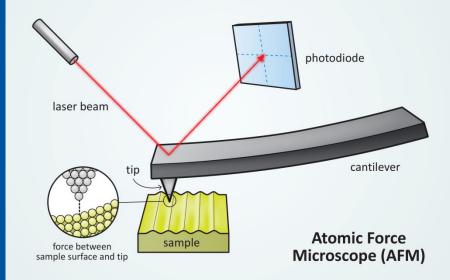




Scanning tunneling and atomic force microscopy









CRISPR's unwanted anniversary



- There are key moments in the history of every disruptive technology that can make or break its public perception and acceptance. For CRISPR-based genome editing, such a moment occurred 1 year ago—an unsettling push into an era that will test how society decides to use this revolutionary technology.
- Jennifer Doudna

Improving crop yield, 40%



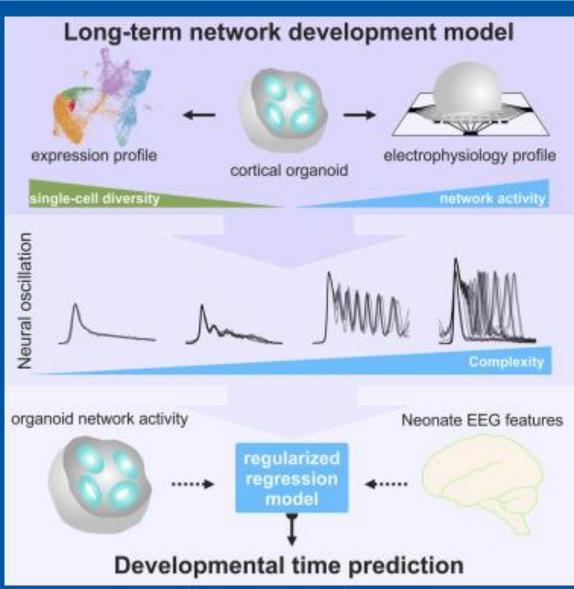
The enzyme ribulose 1,5-bisphosphate carboxylase-oxygenase (RuBisCO) is one of the most abundant proteins on Earth. During (RubisCO) is one of the most abundant proteins on Earth. During photosynthesis, it assimilates atmospheric CO_2 into biomass and hence is a major driver of the global carbon cycle. However, the enzyme is catalytically imperfect. It accepts not only CO_2 as a substrate, but also O_2 , which leads to the formation of a toxic byproduct, 2-phosphoglycolate (2-PGlycolate) (1). The metabolic pathway photorespiration detoxifies 2-PGlycolate, and it is essential for performing photosynthesis in an O_2 -containing atmosphere. Importantly, photorespiration causes a 20 to 50% yield penalty, depending on the environmental conditions and the type of photosynthesis employed (2). Multiple attempts have been undertaken to overcome this yield penalty and thereby increase biomass production in plants, with limited success to date. On page 45 of this issue, South et al. (3) present a synthetic pathway that fully detoxifies 2-PGlycolate inside plant chloroplasts. Transgenic tobacco plants expressing this pathway show strongly enhanced biomass production in field trials, suggesting that this could be used to improve crop yields.

Complex Oscillatory Waves Emerging from Cortical Organoids Model Early Human Brain Network Development (2019.08)



Toekomst:
Medicijnen
(bijv. antidepressiva)
testen op organoids
van individuele patient.

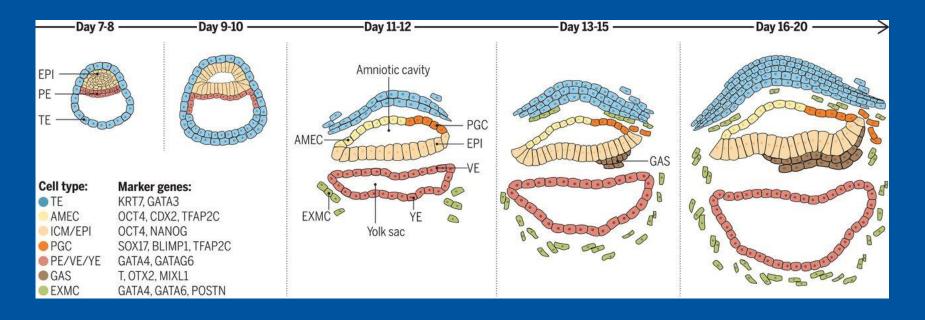
NB Eenvoudiger inzicht in de werking van organen (niet uit een lichaam hoeven halen, of in een lichaam bekijken





Monkey embryos cultured in vitro recapitulate primate postimplantation embryogenesis in vivo. => culture beyond 14 days





- Scheme of monkey postimplantation embryogenesis cultured in vitro. ICM, inner cell mass; EPI, epiblast; PE, primitive endoderm; TE, trophectoderm; AMEC, amniotic epithelium cell; PGC, primordial germ cell; VE, visceral endoderm; YE, yolk-sac endoderm; EXMC, extra-embryonic mesenchyme cell; and GAS, gastrulating cell.
- https://science.sciencemag.org/content/366/6467/eaaw5754

Pig brains kept alive outside body for hours after death => Filosofische implicaties





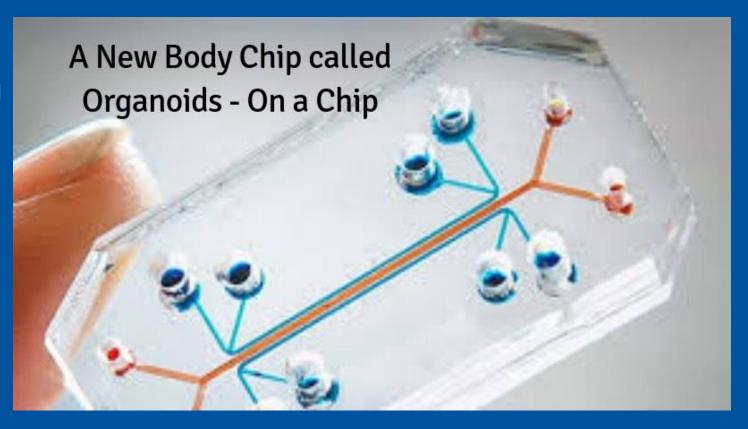
- "For most of human history, death was very simple."
- Now, we have to question what is reversible."
- => Wat is leven / bewustzijn

Homo Chippiens



Verschillende organoids die samen een heel lichaam vormen, in miniatuur.

Van 1 patient:
Personalized
medicine
Testen welke
therapie voor
die patient
werkt



Individuele Geneeskunde: Milasen



Scientists Designed <u>a</u>

<u>Drug for Just One Patient</u>.

Her Name Is Mila.

An achievement in ultrapersonalized medicine also raises questions about fairness and regulation.

Julia Vitarello with her daughter, Mila, 8, who has a rare neurological disorder. Scientists were able to create a drug to treat only the form of the illness she has.



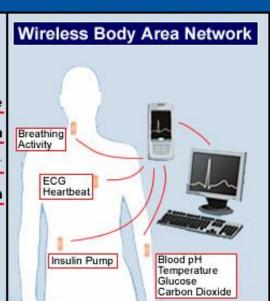
=> Personalized Medicine

How big data could be used to predict a patient's future.



Healthcare was once about trying to heal the sick patient. But organisations around the world now have an opportunity to shift this focus to one of keeping the public healthy and anticipating health issues before they become a problem.

Gauze
Antenna
Thin Battery Layer
Sensium



Big data can be collected to predict accurately when a health-issue will become a problem.

=> hospital for check-up

=> Predictive intelligence (already used for jet engines)



Reversal of epigenetic aging in humans



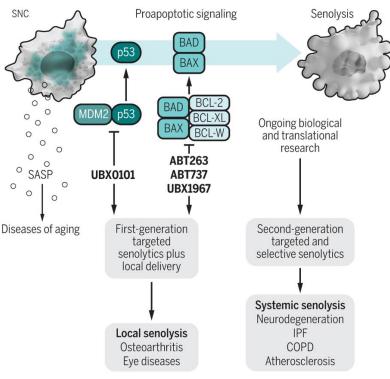
- https://onlinelibrary.wiley.com/doi/full/10.1111/acel.13028
- the trial included two widely used anti-diabetic drugs, dehydroepiandrosterone (DHEA) and metformin, in the treatment cocktail.
- First hint that body's 'biological age' can be reversed
- The effects of the widely prescribed diabetes drug metformin and the immune modulator rapamycin seem to mimic beneficial strategies — the equivalent of (respectively) exercising more and eating less, in pill form.

Senolytic therapies for healthy longevity



Senolytic therapies for optimized aging

Senescent cells (SNCs) resist apoptosis by activating prosurvival pathways and inhibiting proapoptotic pathways.



First-generation senolytics

Drugs developed to target key components of prosurvival pathways eliminate SNCs and thereby the SASP that drives diseases of aging.

Second-generation senolytics

Development of selective senolytics that safely and effectively eliminate SNCs upon systemic administration awaits further understanding of SNCs.

BAD, BCL-2—associated agonist of cell death; BAX, BCL2-associated X; BCL-2, B cell lymphoma 2; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; SASP, senescence-associated secretory phenotype.

The estimated "natural" life span of humans is ~30 years, but improvements in working conditions, housing, sanitation, and medicine have extended this to ~80 years in most developed countries. However, much of the population now experiences agingassociated tissue deterioration. Healthy aging is limited by a lack of natural selection, which favors genetic programs that confer fitness early in life to maximize reproductive output. There is no selection for whether these alterations have detrimental effects later in life. One such program is cellular senescence, whereby cells become unable to divide. Cellular senescence enhances reproductive success by blocking cancer cell proliferation, but it decreases the health of the old by littering tissues with dysfunctional senescent cells (SNCs). In mice, the selective elimination of SNCs (senolysis) extends median life span and prevents or attenuates age-associated diseases (1, 2). This has inspired the development of targeted senolytic drugs to eliminate the SNCs that drive age-associated disease in humans.

https://science.sciencemag.org/content/364/6441/636

Afweersysteem: Is zeer agressief, under-reaction =>





Evolutionaire selectie voor "over-reaction"

Mechanismen om dit in te beperken: => College 2

A Balanced Immune System

Internal Threat

Autoimmune problem

(type 1 diabetes, rheumatoid arthritis, psoriasis, multiple sclerosis, lupus, inflammatory bowel disease)

External Threat

Allergic Reaction

(hay fever, eczema, asthma, sinusitis)

Immune Over-reaction

BALANCED IMMUNE SYSTEM = OPTIMAL EFFECTIVENESS

Immune Under-reaction

Cancer

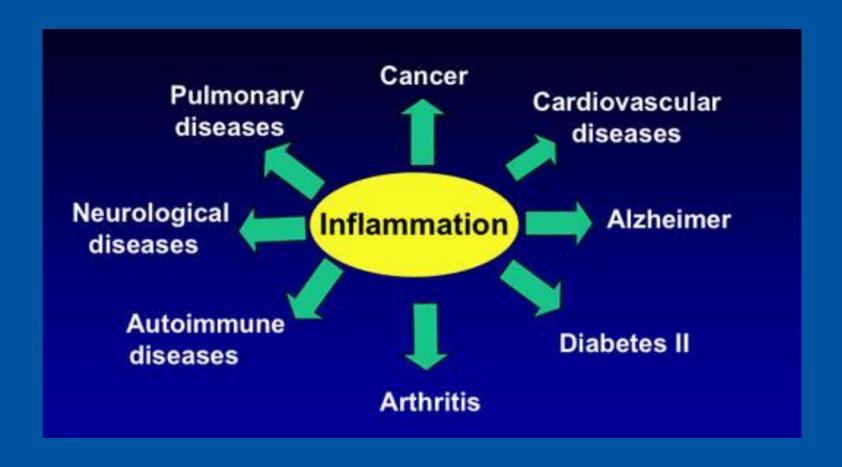
(hepatitis, HIV, shingles, TB)

Infection

(viruses, bacteria, fungi and parasites)

Chronische ontsteking en ziekte => college 4





Beginnen alzheimer en reuma met een ontstoken gebit?



- 'Voeding, gedrag, leefstijl, erfelijke aanleg: het speelt allemaal een rol', benadrukt Van Dijl. 'Maar we beginnen te beseffen dat er ook een microbiële component in het spel is. Bij opvallend veel vervelende ziekten is *Porphyromonas gingivalis* aanwezig. Hij zet bepaalde zaken op scherp.'
- => Floss to stay healthy
- https://www.volkskrant.nl/de-gids/beginnen-alzheimer-en-reumamet-een-ontstokengebit~b8300425/?referer=https%3A%2F%2Fwww.google.com%2F
- https://www.ncbi.nlm.nih.gov/pubmed/31297054

first vaccine against EBOLA approved

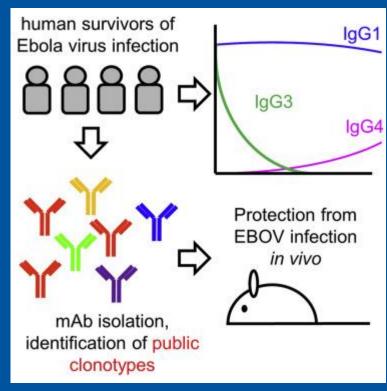


- The vaccine, first patented in 2003, has been administered on an emergency basis to quell the ongoing outbreak in the Democratic Republic of the Congo (DRC), which has killed some 2,000 people since it started last year. It was also used during another 2018 outbreak in that country, and in Guinea in 2015. In the current DRC outbreak, hundreds of thousands of people have received the Merck shot, including more than 60,000 health-care workers in the DRC and several neighbouring countries.
- ⇒ Anti-vax immunization?
- ⇒ Mazelen in .. (the pacific)

Longitudinal Analysis of the Human B Cell Response to Ebola Virus Infection



- Ebola virus infection causes massive recruitment of naive B cells
- Virus-specific antibodies continue to class-switch and mutate for months after acute infection
- Protective antibodies can be neutralizing or non-neutralizing and can appear early
- Convergent, protective antibody rearrangements are seen in multiple donors





Broadly protective human antibodies that target the active site of influenza virus neuraminidase



Better vaccines against influenza virus are urgently needed to provide broader protection against diverse strains, subtypes, and types. Such efforts are assisted by the identification of novel broadly neutralizing epitopes targeted by protective antibodies. Influenza vaccine development has largely focused on the hemagglutinin, but the other major surface antigen, the neuraminidase, has reemerged as a potential target for universal vaccines. We describe three human monoclonal antibodies isolated from an H3N2-infected donor that bind with exceptional breadth to multiple different influenza A and B virus neuraminidases. These antibodies neutralize the virus, mediate effector functions, are broadly protective in vivo, and inhibit neuraminidase activity by directly binding to the active site. Structural and functional characterization of these antibodies will inform the development of neuraminidase-based universal vaccines against influenza virus.

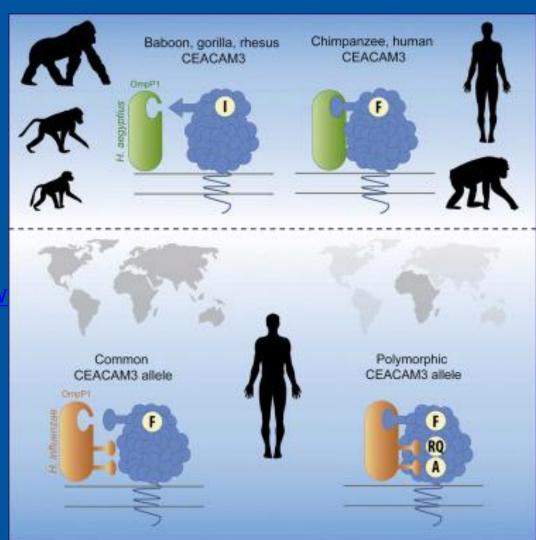
How measles causes the body to 'forget' infections



- https://science.sciencemag.org/content/366/6465/560
- Measles virus targets B cells, responsible for immune "memory."
- Two detailed studies of blood from unvaccinated Dutch children who contracted measles now reveal how such infections can also compromise the immune system for months or years afterward, causing the body to "forget" immunity it had developed to other pathogens in the past.

Adaptation to Host-Specific Bacterial Pathogens Drives Rapid Evolution of a Human Innate Immune Receptor

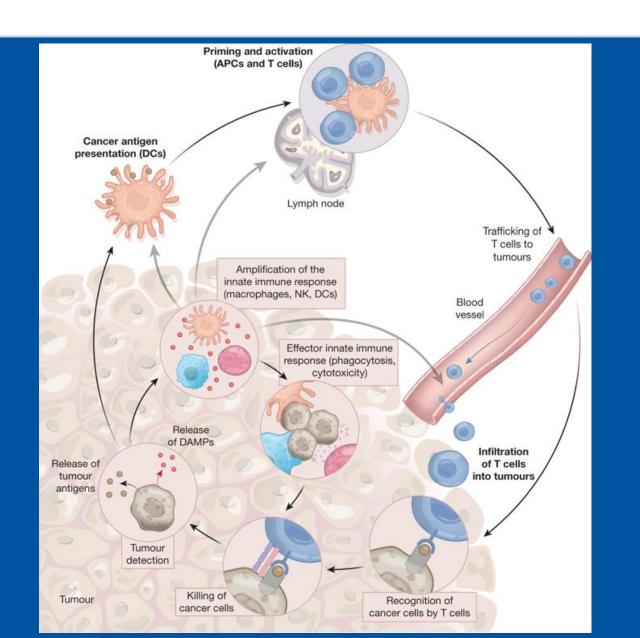




https://ww

Innate immunity in cancer therapy

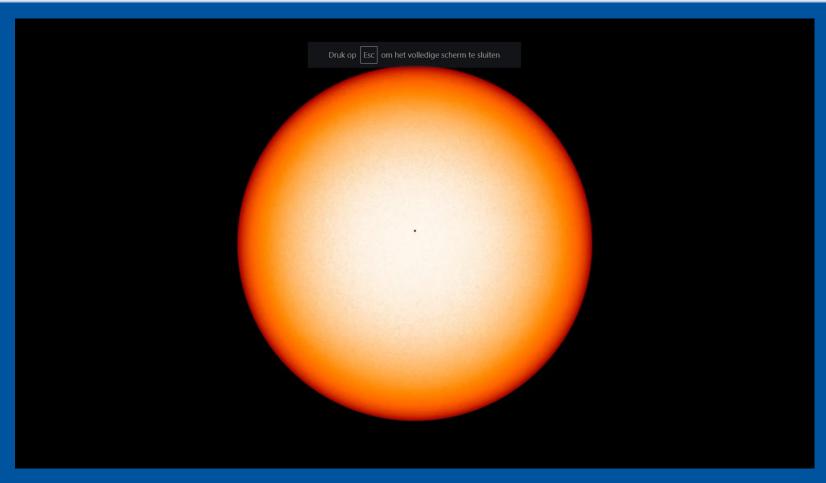




https://www.natur e.com/articles/s41 586-019-1593-5

Mercury Transit Planets are small





True distance between earth and the moon and size difference





https://joshworth.com/dev/pixelspace/pixelspace_solarsystem.html

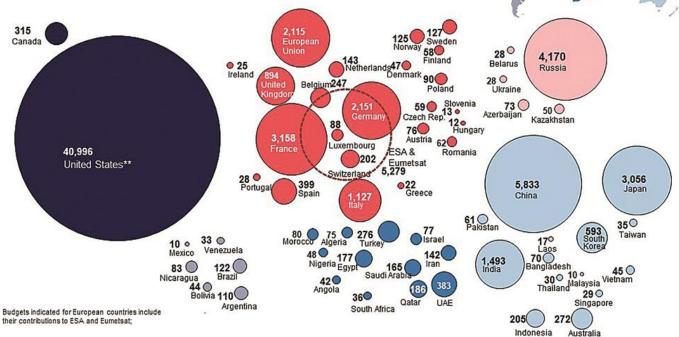
Rocket reuseability

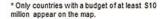


https://youtu.be/u0-pfzKbh2k

WORLD GOVERNMENT EXPENDITURES FOR SPACE PROGRAMS (2018)* TOTAL \$70.8 BILLION



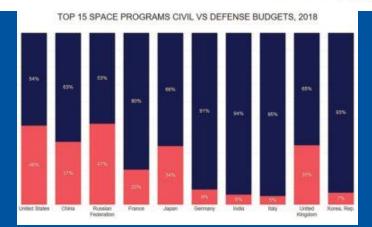




^{**} The United States is undersized (80%)



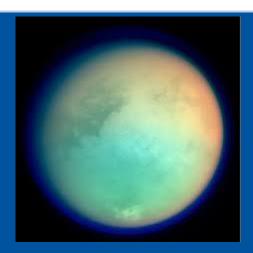
PROFILES OF GOVERNMENT SPACE PROGRAMS
© Euroconsult 2019 – Authorized for release



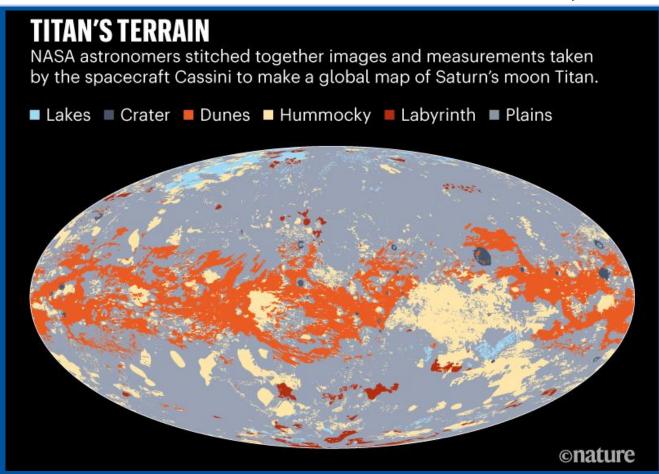


Titan, maan van Saturnus Is relatief groot, en interessant (proto-aar HOVO BRABANT SENIORENACADEMIE



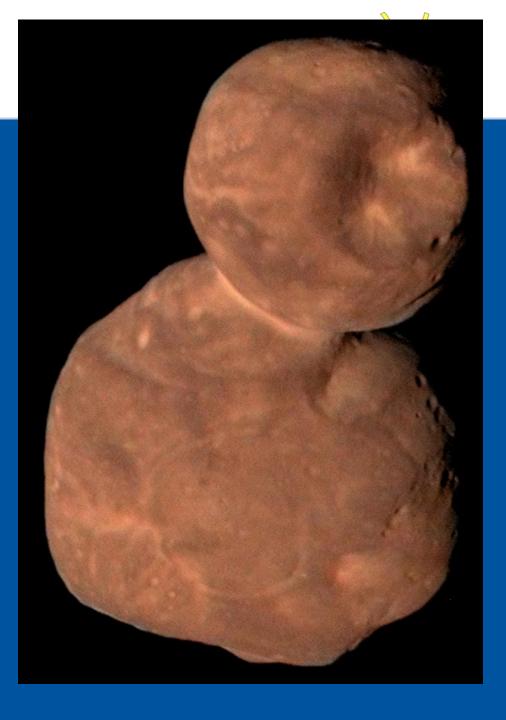


- There are surprisingly few impact craters, suggesting that the moon's surface is fairly young.
- Titan is the only world in the Solar System aside from Earth with known bodies of liquid (methane) on its surface.



Ultima Thule 1 januari 2019

- Ultima Thule is the first <u>unquestionably</u> <u>primordial</u> contact binary ever explored. Approach pictures hinted at a strange, snowman-like shape, but further analysis of images, taken near closest approach, uncovered just how unusual the KBO's shape really is. At 22 miles (35 kilometers) long, the binary consists of a large, flat lobe (nicknamed "Ultima") connected to a smaller, rounder lobe (nicknamed "Thule").
- This strange shape was the biggest surprise of the flyby. Nothign like it has been anywhere in the solar system -sending the planetary science community back to the drawing board to understand how planetesimals (the building blocks of the planets) form. New Horizons scientists have also seen evidence for methanol, water ice and organic molecules on the surface -- a spectrum similar to some of the most extreme objects we've seen in the outer solar system.



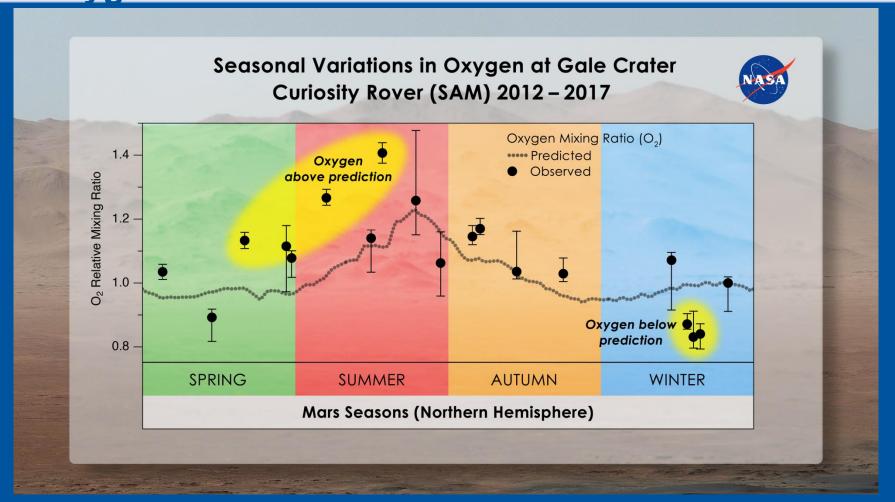
Exoplanets => exobiology Life is a numbers game



- https://youtu.be/SjkWi9pf0dM
- https://videos.space.com/m/rEKpFhpS/stunning-southern-sky-panoroma-created-with-nasa-tess?list=6DUiA9a3

With Mars Methane Mystery Unsolved, Curiosity Serves Scientists a New One: Oxygen





Methane and Oxygen; signs of life? https://mars.nasa.gov/news/8548/with-mars-methane-mystery-unsolved-curiosity-serves-scientists-a-new-one-oxygen/?site=msl

Wetenschappelijke vragen



- Als leven op een andere planeet is ontstaan zou het dan anders zijn? => astrobiologie
- Als leven nog een keer op aarde zou ontstaan, zou dit dan anders zijn, of nog een keer mensen opleveren? => nee
- Hoe is het leven ontstaan?
- Why is the chemistry of life the way it is?
- => verbeteren!
- https://www.youtube.com/watch?v=GEhPVhap44w
- https://www.youtube.com/watch?v=V6ycmQJOaBQ

How two intruders from interstellar space are upending astronomy

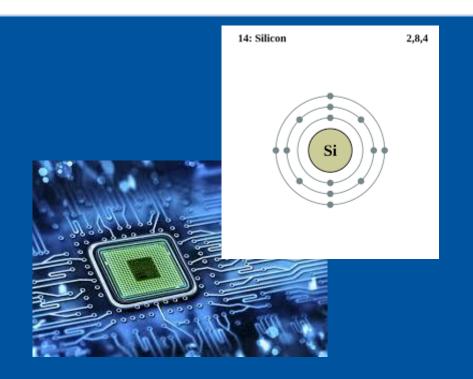


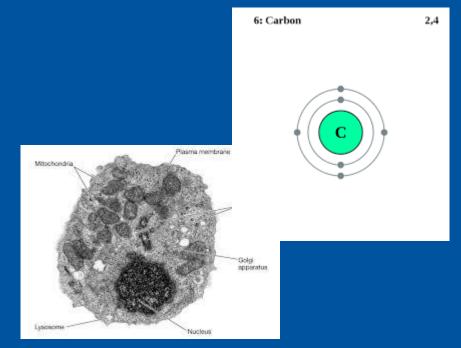
Once astronomers have 10 or 20 interstellar objects under their belts, they should have a much better picture of what these deep-space wanderers are really like. "Eventually we'll be talking about the Galaxy as something in which we are exchanging the products of planetary systems," says Bannister. "It will be an entirely different way of doing astronomy."

=> Stars are Islands but not totally secluded

Silicium en elektronen => elektronica Koolstof en ionen => biologie



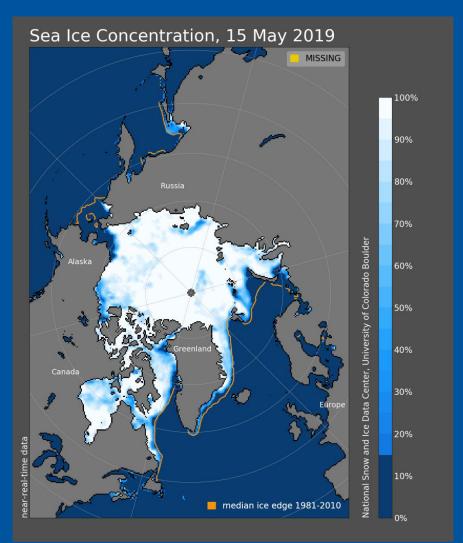


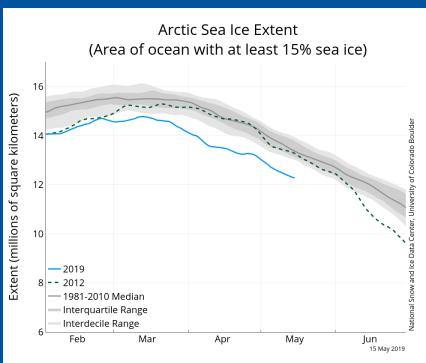


Silicon is the eighth most common element in the universe by mass, but very rarely occurs as the pure element in the Earth's crust. <u>Carbon is more available => life.</u>
But, the more an electron is near to the nucleus, the stronger is the covalent bond. Since carbon has only 2 shells, the valence electrons are pretty tightly bonded, while in case of silicon, its ideal i.e. 3 shells. Carbon has no free electrons available so it cannot conduct electricity => Silicon for electricial purposes (semi-conductor)

Earth from space: Vanishing ice





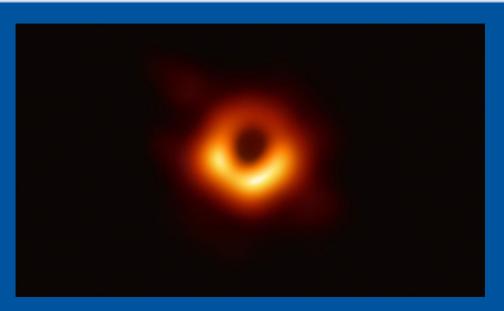


- https://science.sciencemag.org/content/ 364/6441/616
- http://nsidc.org/arcticseaicenews/

Black hole pictured for first time in spectacular detail



- In context
- Werk van jaren
- Multidisciplinair team
- Hele wereld (letterlijk en figuurlijk)
- ⇒ Hoe werkt wetenschap
- ⇒ Quantum gravity
- => Quantum biology



- Wetenschappelijke ontwikkelingen komen altijd voort uit langdurige processen en bouwt voort op reeds opgedane kennis (telescoop, optica, vuur, taal)
- https://www.space.com/event-horizon-telescope-blackhole-movie-funded.html
- https://youtu.be/uyMtsyzXWd4

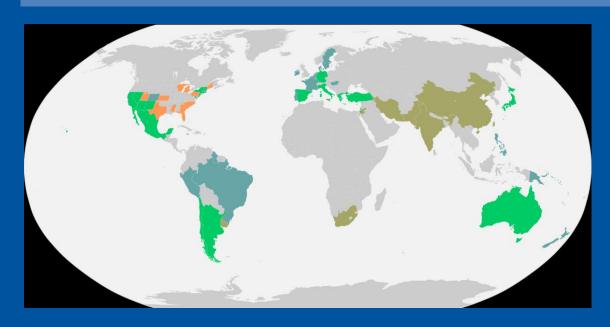
https://www.space.com/milky-way-center-black-hole-deepest-sharpest-images





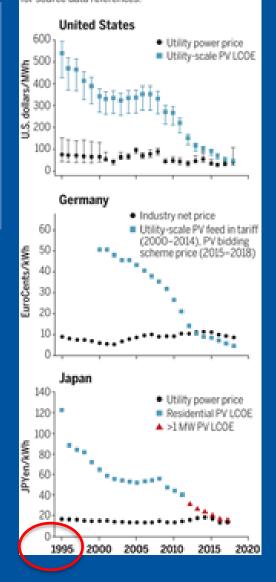
Coal and solar prices are now similar (maatschappelijk belang!)

Grid parity occurs when an alternative energy source can generate power at a price that is less than or equal to the price of power from the electricity grid. The term is most commonly used when discussing renewable energy sources, notably solar power and wind power. Reaching grid parity is considered to be the point at which an energy source becomes a contender for widespread development without subsidies or government support. It is widely believed that <u>a</u> wholesale shift in generation to these forms of energy will take place when they reach grid parity.



Utility power and utility-scale PV prices

Error bars for U.S. power price indicate the average price for the least-cost and highest-cost market in a given year (excluding Hawaii): error bars for U.S. PV indicate LCOE in New York, NY (high bar), and Phoenix, AZ (low bar). See supplementary materials for source data references.

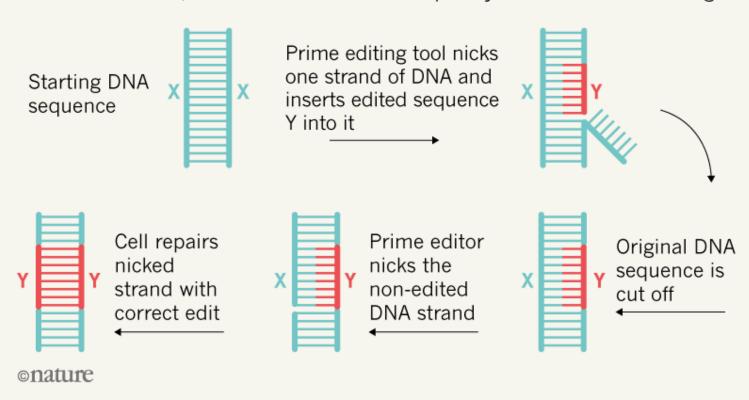


Super-precise new CRISPR tool allows researchers more control over DNA changes



PRECISION EDITOR

Prime editing reduces the number of unintended changes to a genome by inserting the edits researchers want to make into the DNA itself. This contrasts with CRISPR-Cas9, which relies on the cell's repair system to make the changes.



Pig brains kept alive outside body for hours after death => Filosofische implicaties

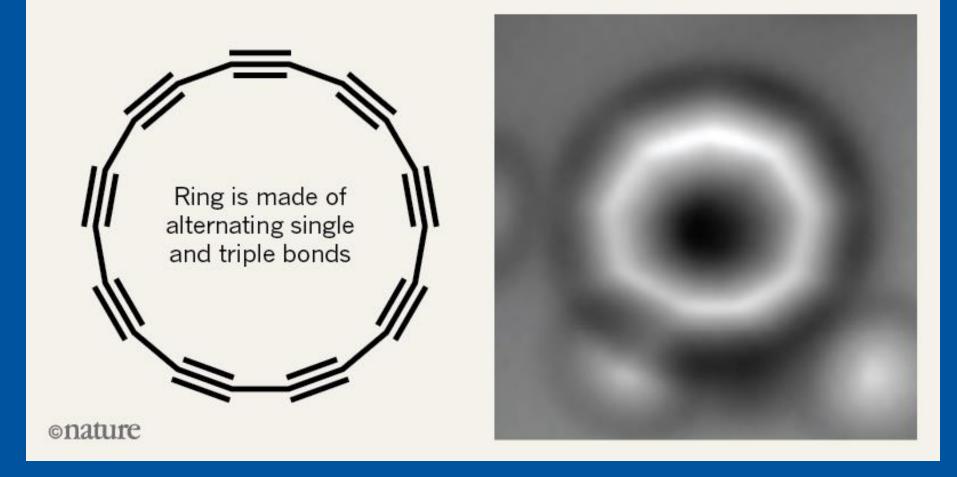




- "For most of human history, death was very simple."
- Now, we have to question what is reversible."
- => Wat is leven / bewustzijn

FULL CIRCLE

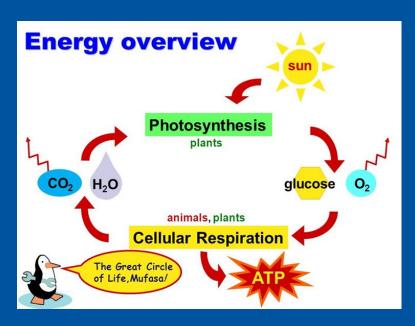
Chemists have created the first-ever ring molecule made purely of carbon, C_{18} , and imaged it with an atomic-force microscope.

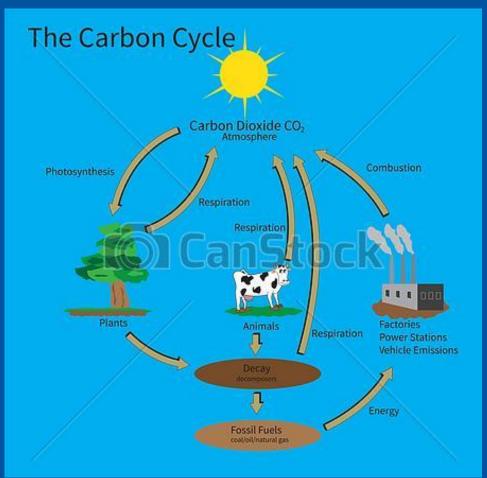


De koolstof cyclus



 Is niet gesloten door input van oude voorraad in de grond => extra energie, en opwarming





Sugar Synthesis from CO₂ in *Escherichia coli*https://www.nature.com/articles/d41586-019-03679-x
Nov. 2019 => Quick fix for the climate !?

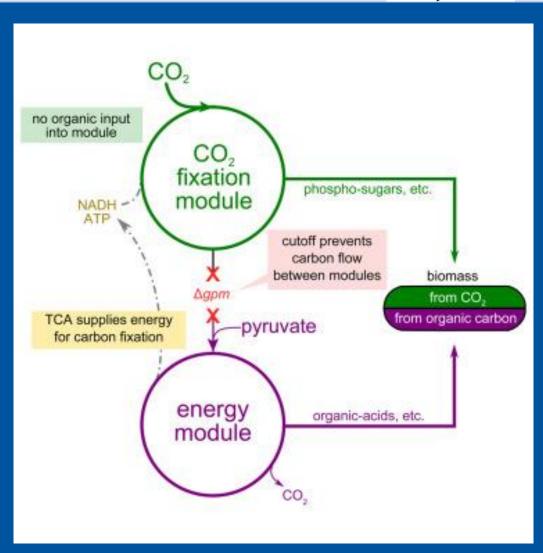


Biomass from CO₂ directly by E.coli.

- ⇒ Toepassing bij CO2 productie
- ⇒ Of zelfs uit atmosfeer halen

Here, we demonstrate how a combination of rational metabolic rewiring, recombinant expression, and laboratory evolution has led to the biosynthesis of sugars and other major biomass constituents in *E. coli*. But no net. negative CO2

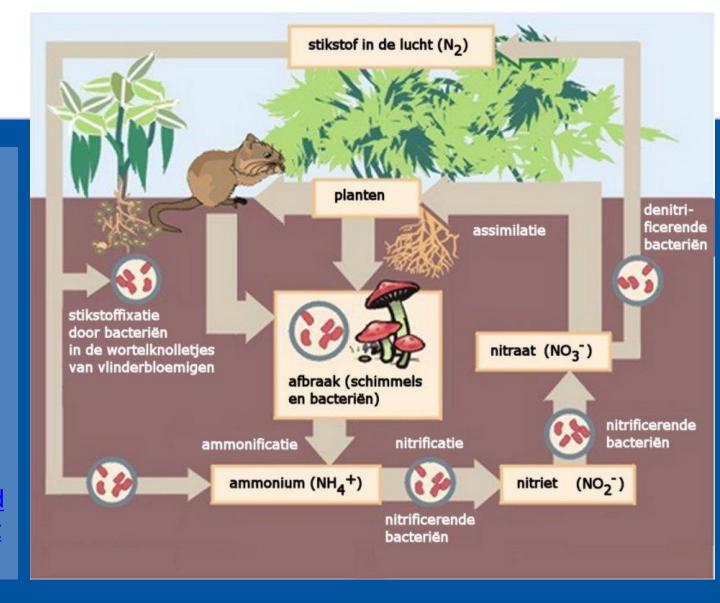
⇒ Wel hoogstandje in synth.biol. Maar (nog) geen revolutie



De stikstof cyclus

 Is niet gesloten door import van stikstof => (mest)overschot

- NH3 = ammoniak = basis van kunstmest
- https://nl.wikiped ia.org/wiki/Kunst mest



Wetenschappelijke literatuur



Pubmed

https://www.ncbi.nlm.nih.gov/pubmed

Google scholar

https://scholar.google.nl/

Wetenschappelijk woordenboek

https://en.oxforddictionaries.com/

Science

http://science.sciencemag.org/

Nature

http://www.nature.com/nature/index.html

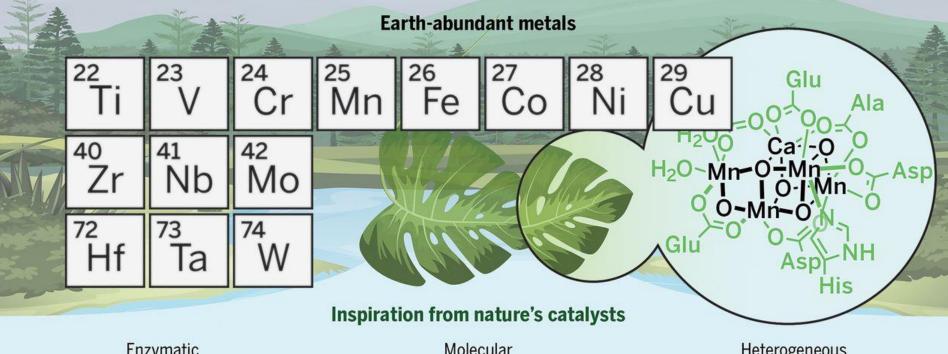
Cell

http://www.cell.com/cell/current

Volgde ik altijd al => nu cursus van gemaakt

Using nature's blueprint to expand catalysis with Earthabundant metals





Enzymatic

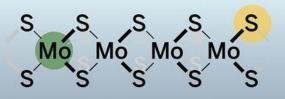
Nitrogenase

Molecular



Metalloporphyrins

Heterogeneous



Metal chalcogenides

explaining-extreme-events-from-a-climate-perspective



 https://www.ametsoc.org/ams/index.cfm/publications/bulletin-of-theamerican-meteorological-society-bams/explaining-extreme-eventsfrom-a-climate-perspective/

emerging-technologies-to-watch-in-2022



 https://www.economist.com/the-world-ahead/2021/11/08/what-next-22-emerging-technologies-to-watch-in-2022