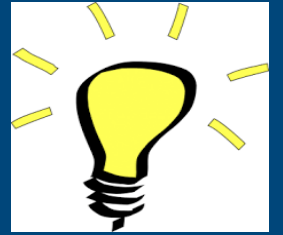


College 3

Biotechnologie.



DNA/RNA-technologie

=> gentherapie/mRNA therapie

Afweersysteem

=> Immunotherapie

Stamcellen

=> stamceltherapie

Cybernetica

=> verbeteren (integratie technologie en biologie)

Synthetic biology

=> wat is leven?

Evolutie

- Langzaam
- Slordig
- Moet functioneel zijn

=> Gevaar!

⇒ ethiek!

⇒ Permanente aanpassing (van de soort)

v

Gentechnologie

v

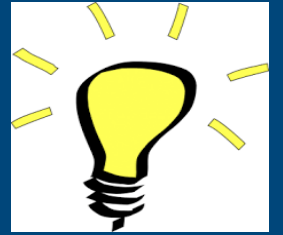
Snel

v

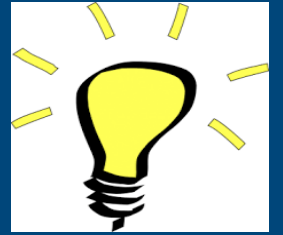
Precies

v

Kan alles zijn wat je wilt



Gen => RNA => Eiwit
filmpjes, **biologische nanotech**



<https://www.youtube.com/watch?v=nHM4UUVHPQM>

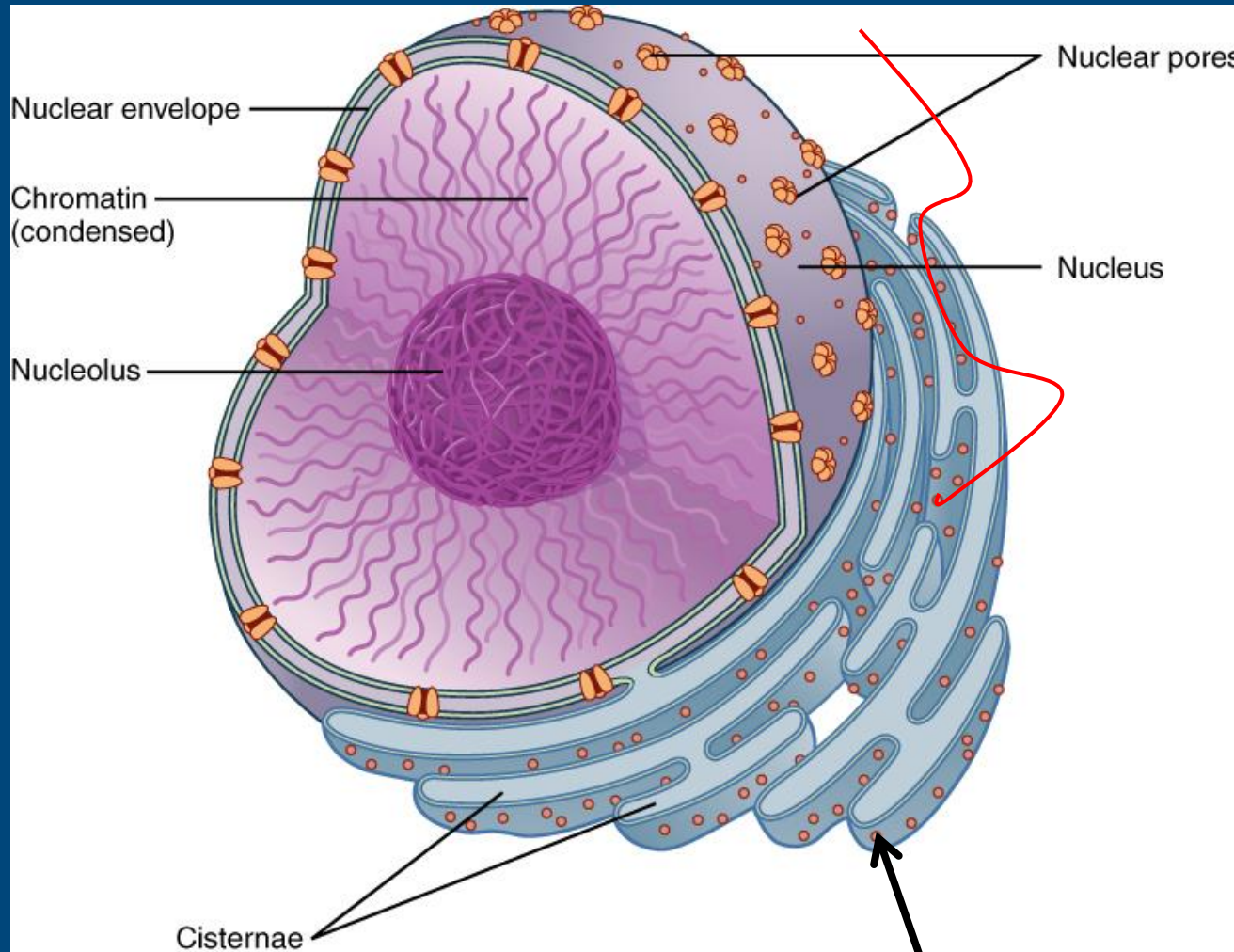
<https://www.youtube.com/watch?v=gG7uCskUOrA>

IKEA vergelijking:

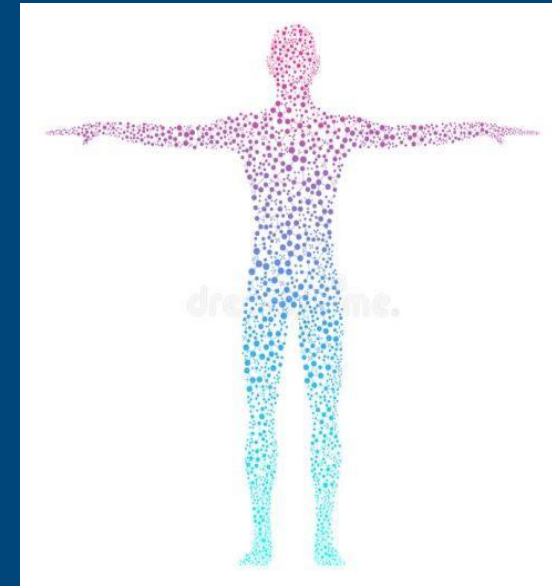
DNA is de gebruiksaanwijzing (informatie),

Eiwitten vormen de kast (deze bouwen iets)

De celkern, met daarin DNA

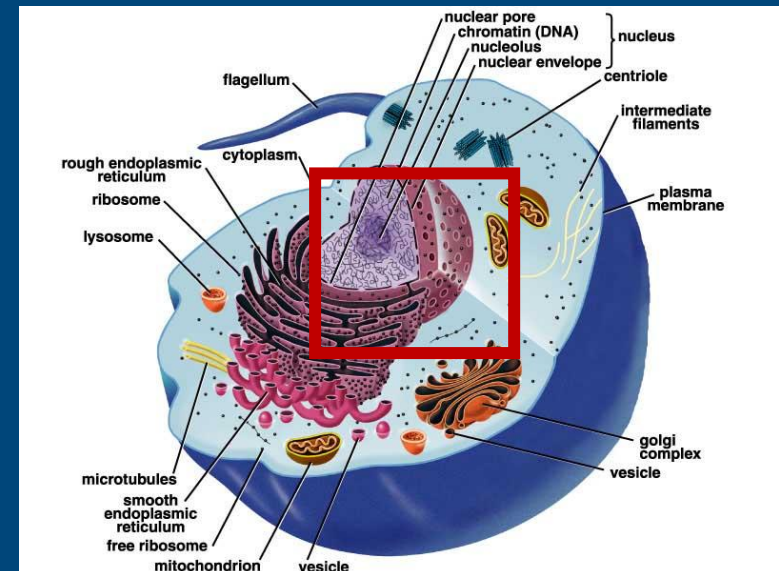


Ruw Endoplasmatisch Reticulum met ribosomen (mRNA => eiwit)

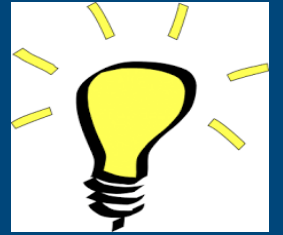


Leven bestaat uit cellen
<https://youtu.be/SEejivHRIbE>

Een (eukaryote) cel met celkern



mRNA technologie is **transient**



- Geen translocatie naar celkern en integratie in genoom nodig

=> veel directer

- RNA is veel minder stabiel dan DNA

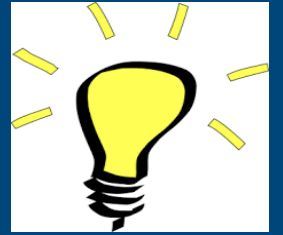
=> Wordt snel afgebroken (minuten-dagen)

⇒ Eigenlijk dus geen gentherapie

⇒ Geschikt voor (kanker) vaccinatie, en meer

Intracellulaire afweer (tegen virussen)

De interferon respons



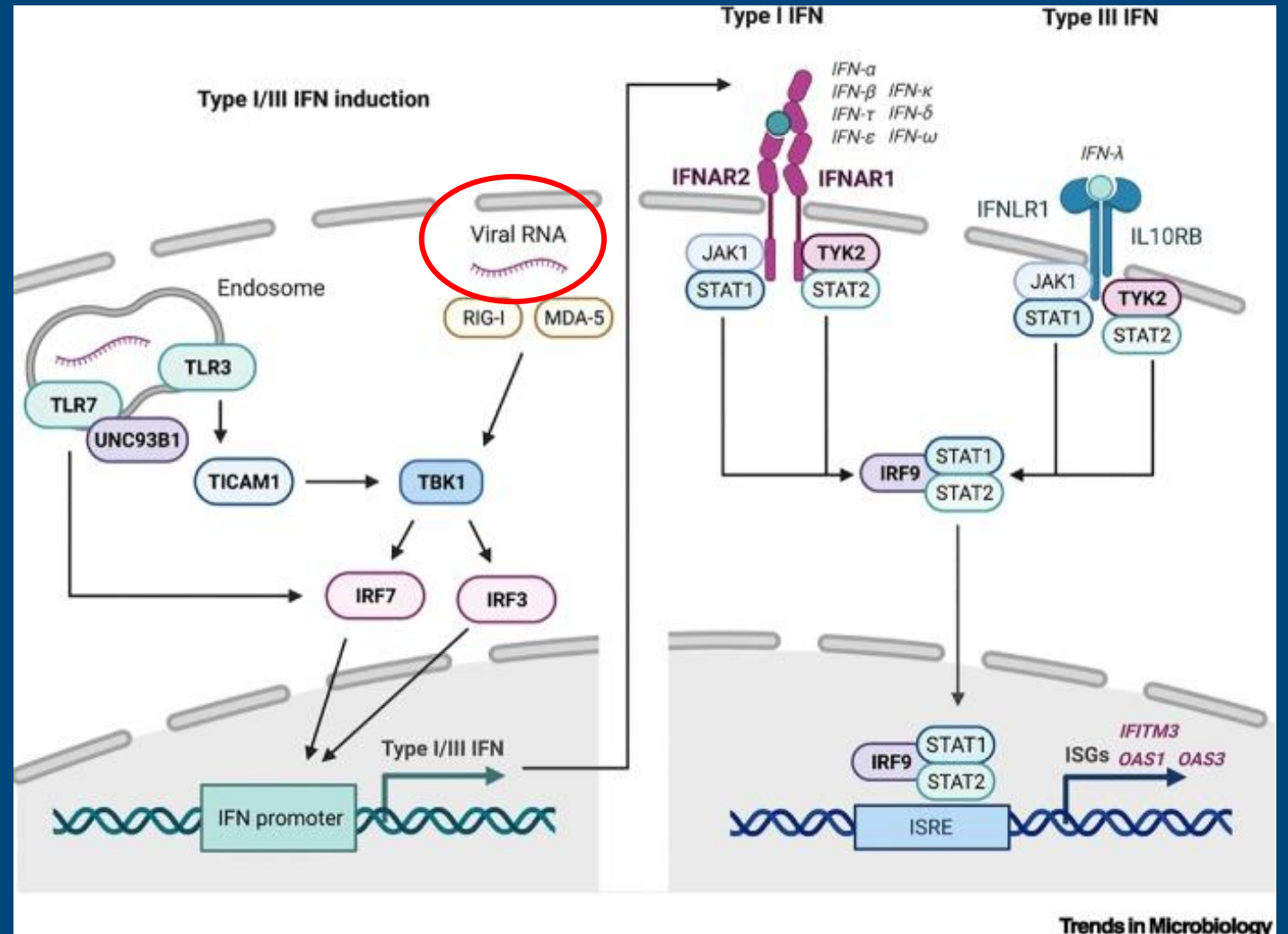
Simplified signaling cascades leading to transcription of type I/III interferon genes following infection with an **RNA virus** (*left panel*).

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

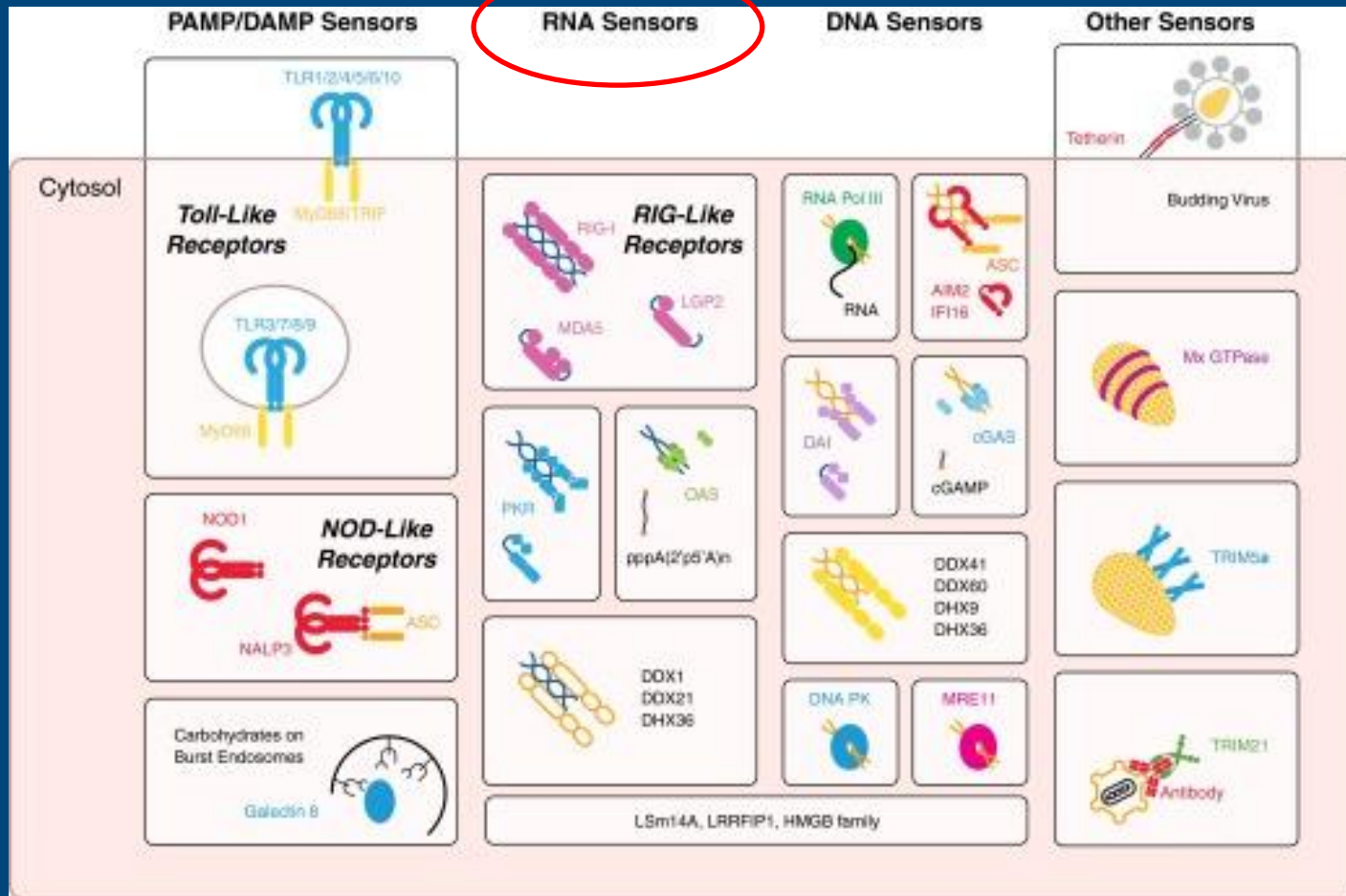
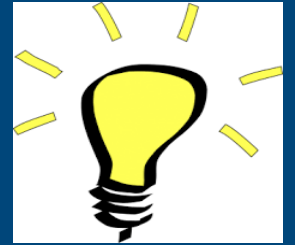
⇒ Meer MHC

⇒ Pro-inflammatoire cytokines

⇒ gevaar

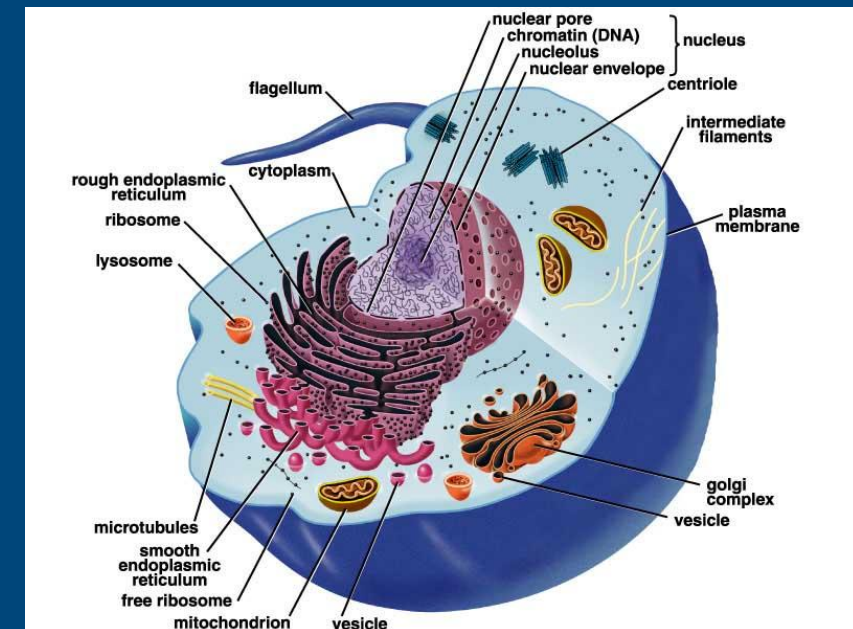


Intracellulaire afweer: interferon => aspecifiek!



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

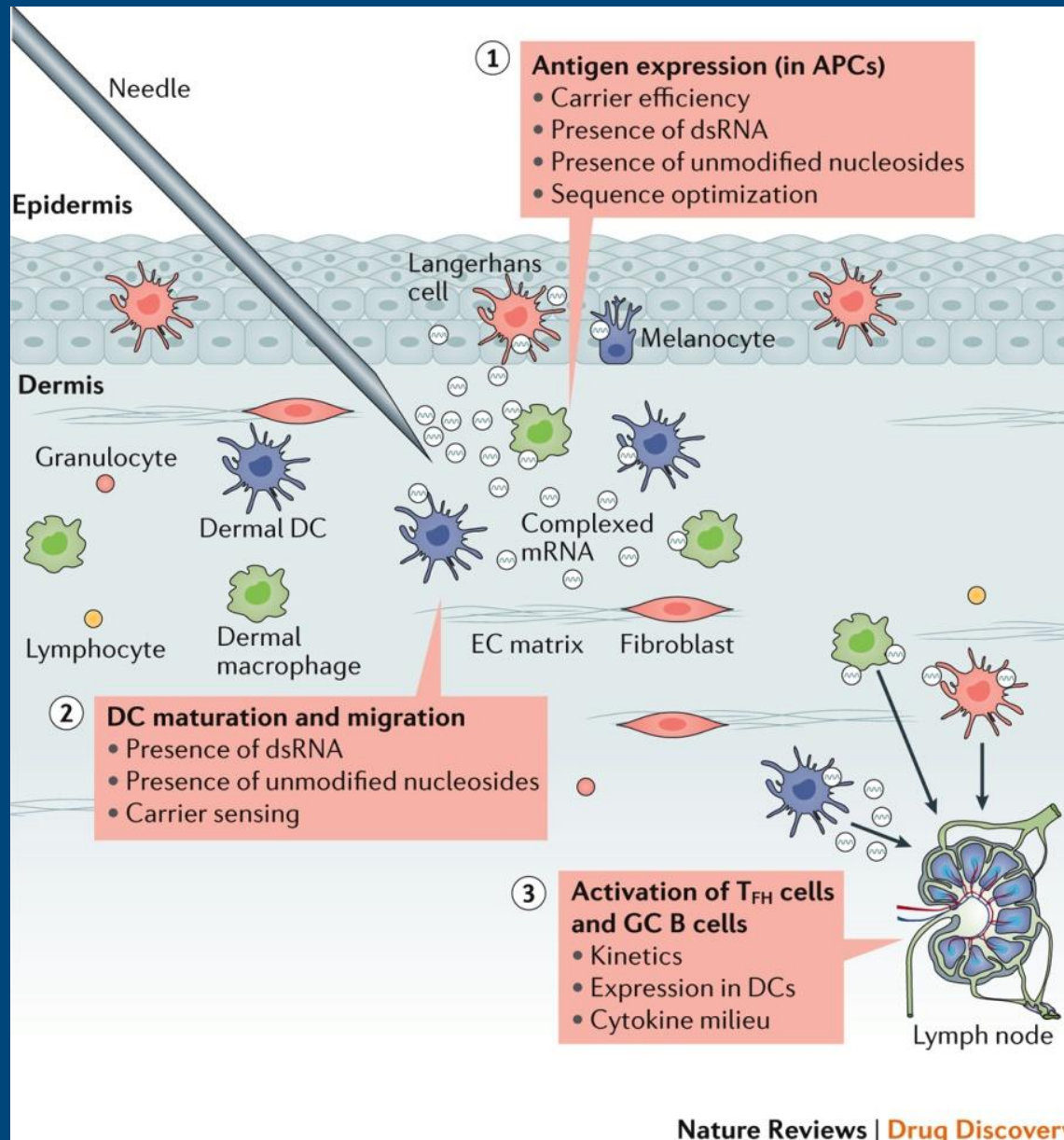
RNA komt in het cytoplasma normaal niet voor => virus!



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

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

The delivery problem, solved



mRNA vaccins
(Moderna, BioNtech)

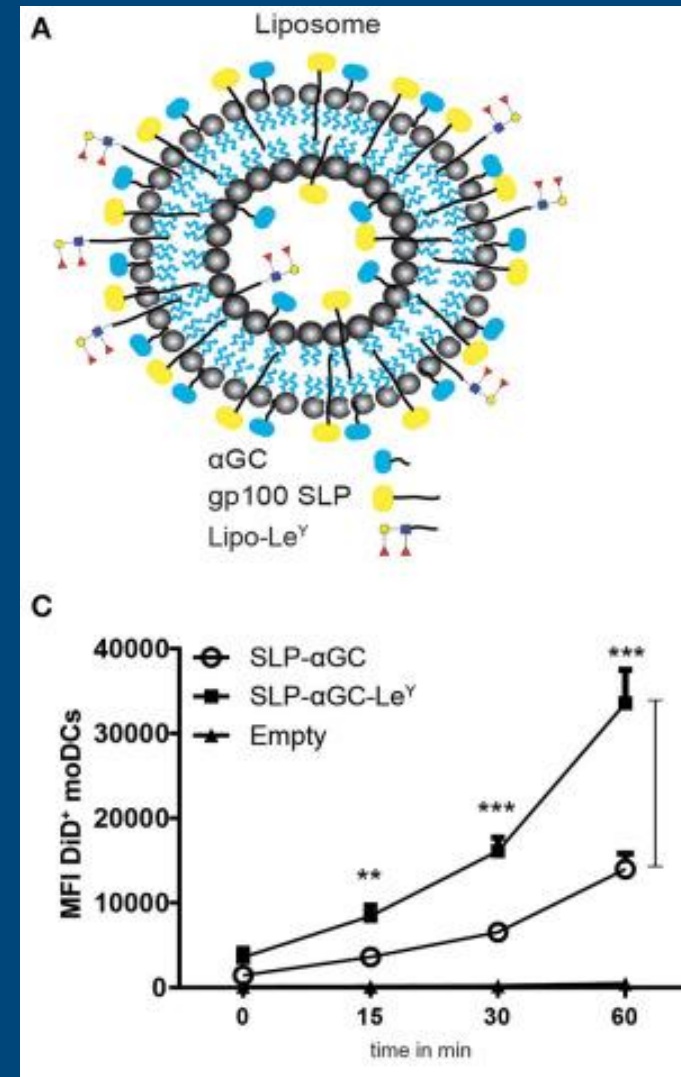
Zijn verpakt in liposomen die specifiek worden opgenomen door DC's in LK, die ze ziet als ziekmaker => presentatie in lymfeklier

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

Targeting DC's with liposomes => delivery

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

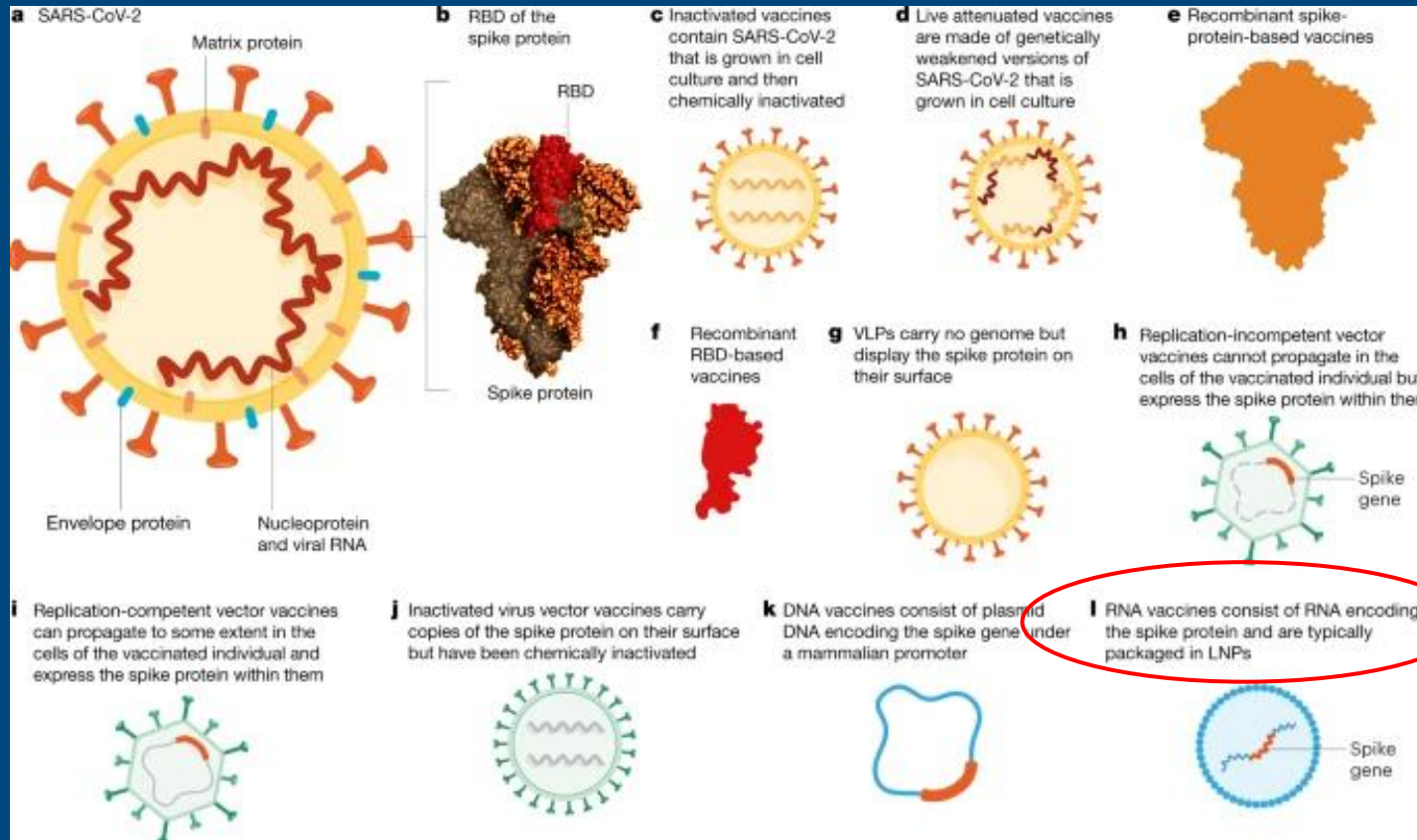
=> MHC-II loading?



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

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

(SARS-CoV-2) vaccines



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

Versie 2.0
Geinactiveerd (c) mazelen

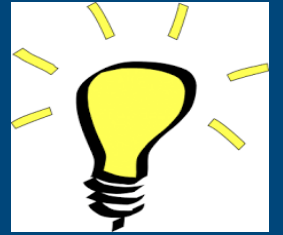
Versie 3.0
Uitgekleed (h)

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

<https://www.nature.com/articles/s41586-020-2798-3>

<https://www.nature.com/nature/volumes/586/issues/7830>

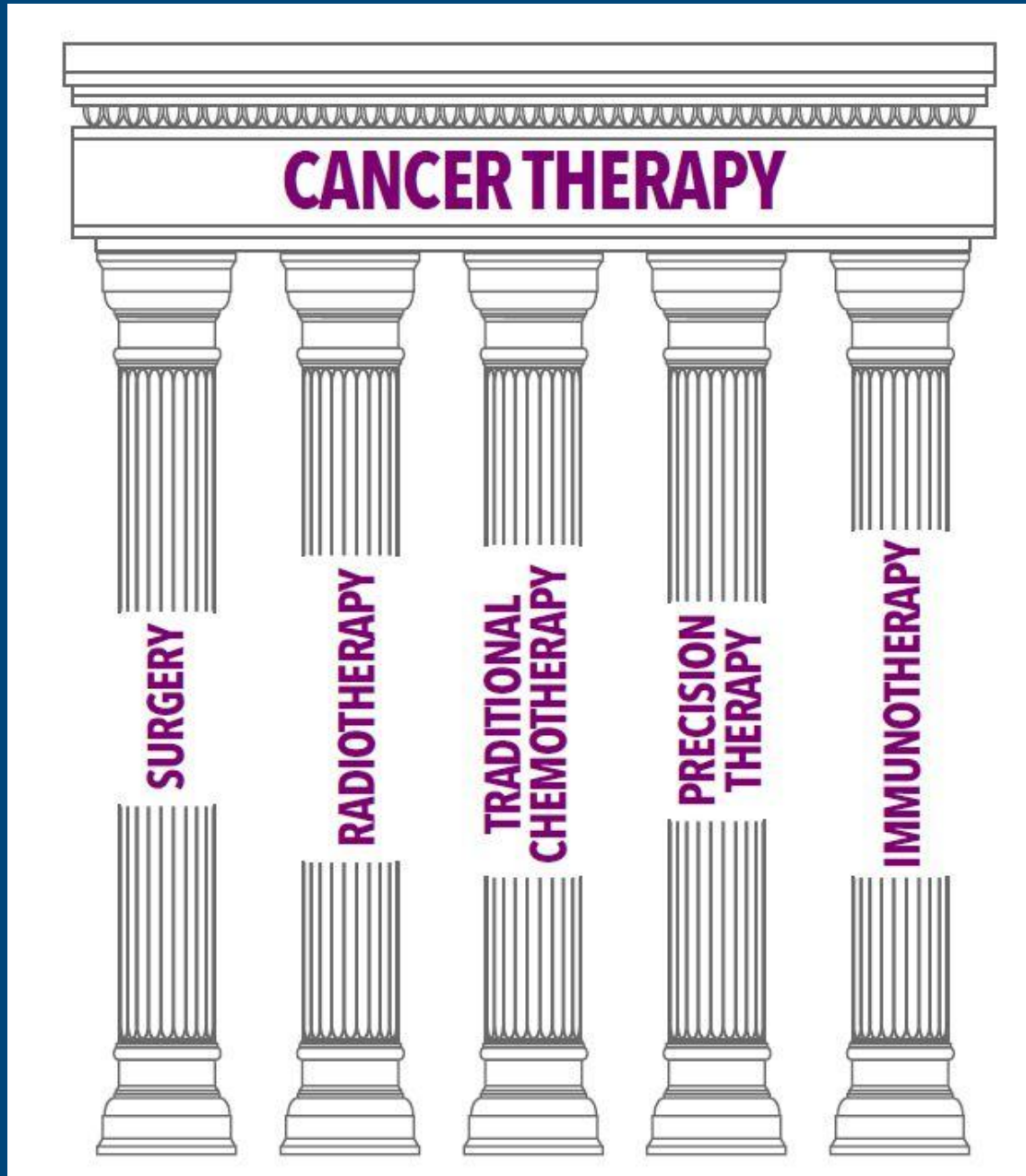
mRNA tegen kanker



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

Sunday with Laura Kuennsberg | 16th October 2022

Immunotherapy:



Surgery: wegsnijden

Radio: bestraling

Chemo: doden (alle) snel delende cellen

Precision: doden specifieke cellen
(antilichamen)

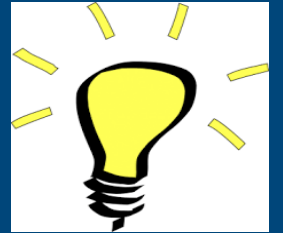
Immuuntherapie:

Afweercellen opleiden tot tumor bestrijders

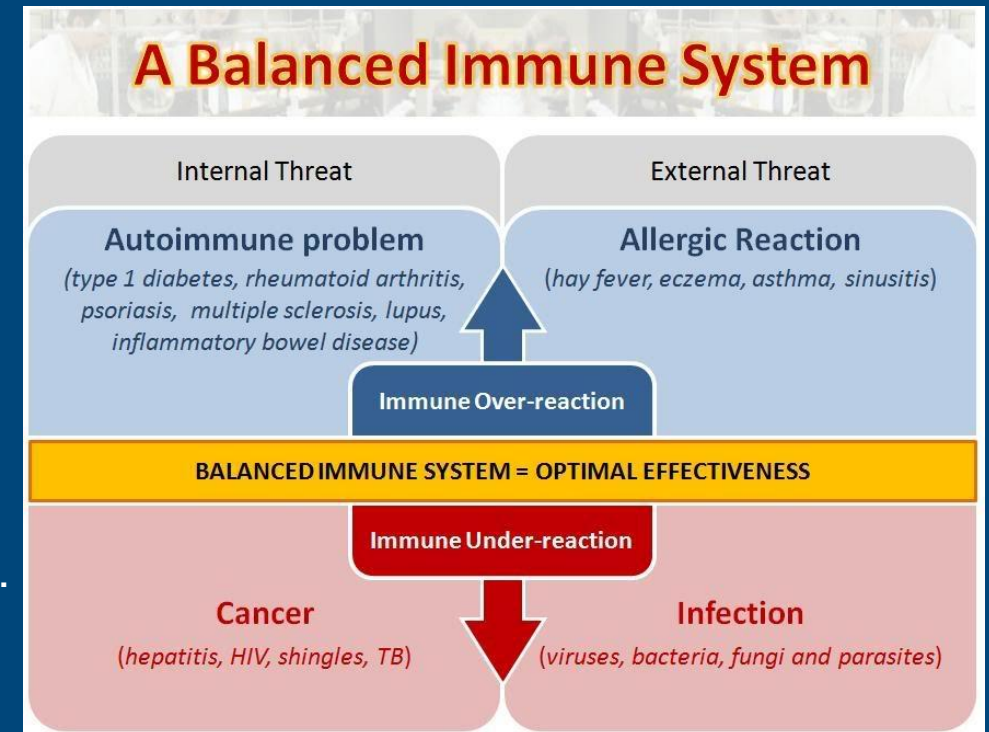
Verminderen suppressie (antilichamen)

mRNA

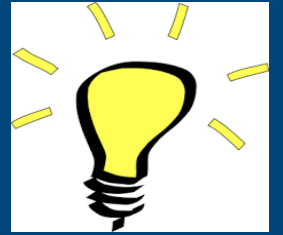
Reageren op lichaamsvreemd en gevaar Voor de rest moet het tolerant zijn.



- Alleen lichaamsvreemd moet worden aangevallen
 - ⇒ **Centrale Tolerantie (Opleiding)**
 - ⇒ “Self non-self discrimination”
 - ⇒ **Kanker is lichaamseigen**
- Maar niet alles wat lichaamsvreemd is (pollen), is gevaarlijk.
 - ⇒ **Perifere Tolerantie (Controle)**
 - ⇒ “Danger hypothesis”

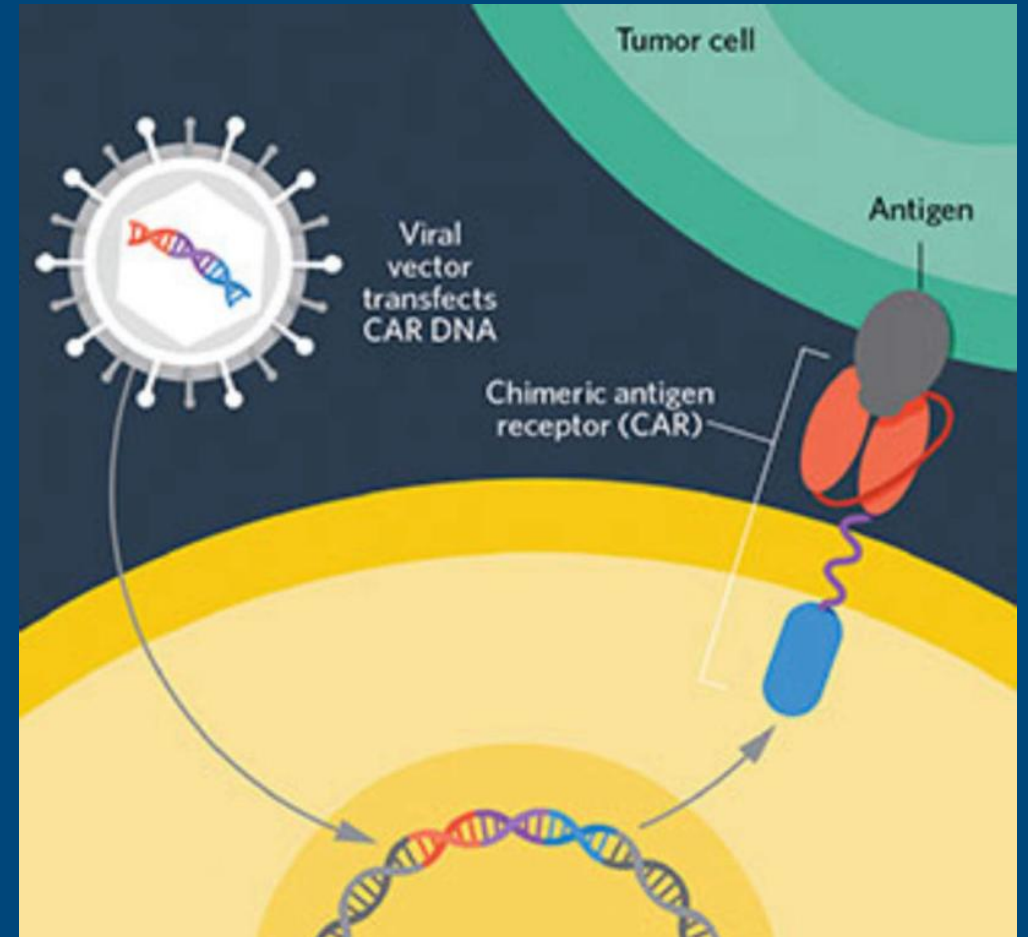


Immunotherapie: CAR-T



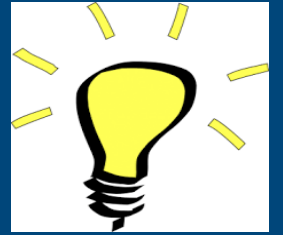
- Opvoeden van de afweer om kanker te herkennen
- Levend medicijn
- **Biologische robot**
- If there isn't a cure for their cancer today, there's a reasonable chance that around the corner, there's going to be one.

<https://www.nature.com/articles/d41586-022-00241-0>



College 3

Biotechnologie.



DNA/RNA-technologie

=> gentherapie/mRNA therapie

Afweersysteem

=> Immunotherapie

Stamcellen

=> stamceltherapie

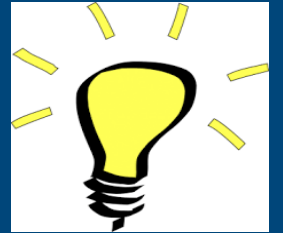
Cybernetica

=> verbeteren (integratie technologie en biologie)

Synthetic biology

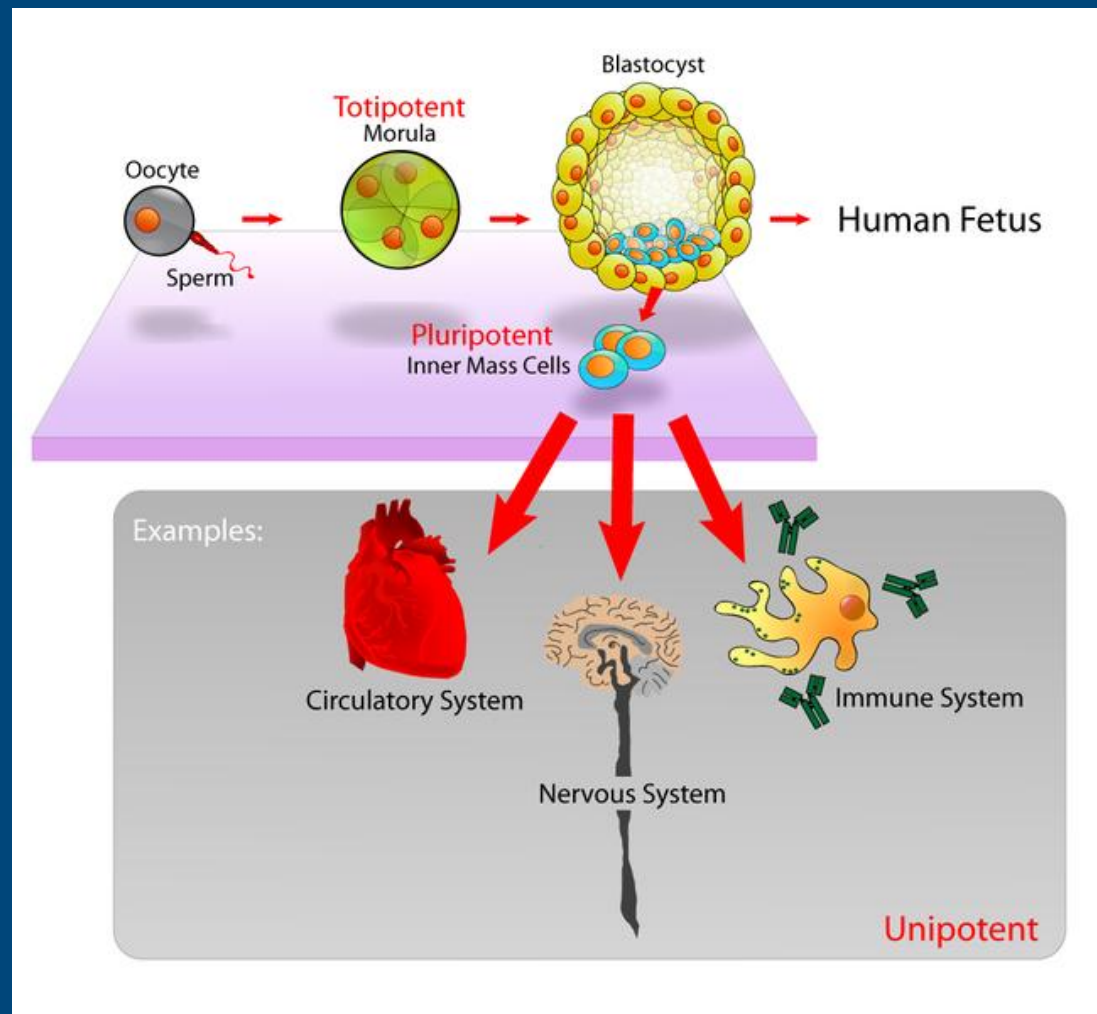
=> wat is leven?

Stamcellen => gebruiken voor therapie

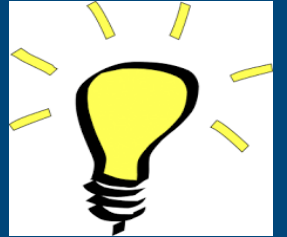


Al onze miljarden cellen komen voort uit 1 enkele stamcel: de bevruchte eicel
=> Pluripotent (kan nog van alles worden)

Na de embryonale ontwikkeling blijven stamcellen actief
=> **adult stem cells**
=> Multipotent (kunnen nog een beperkt aantal dingen worden)

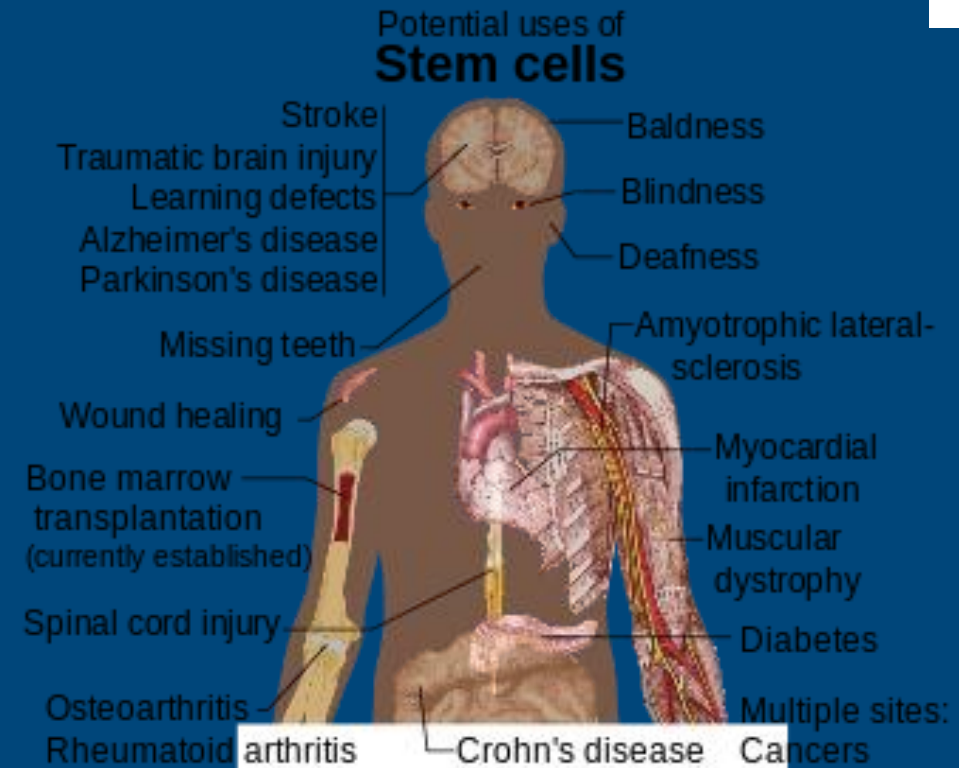


Stamcel therapie

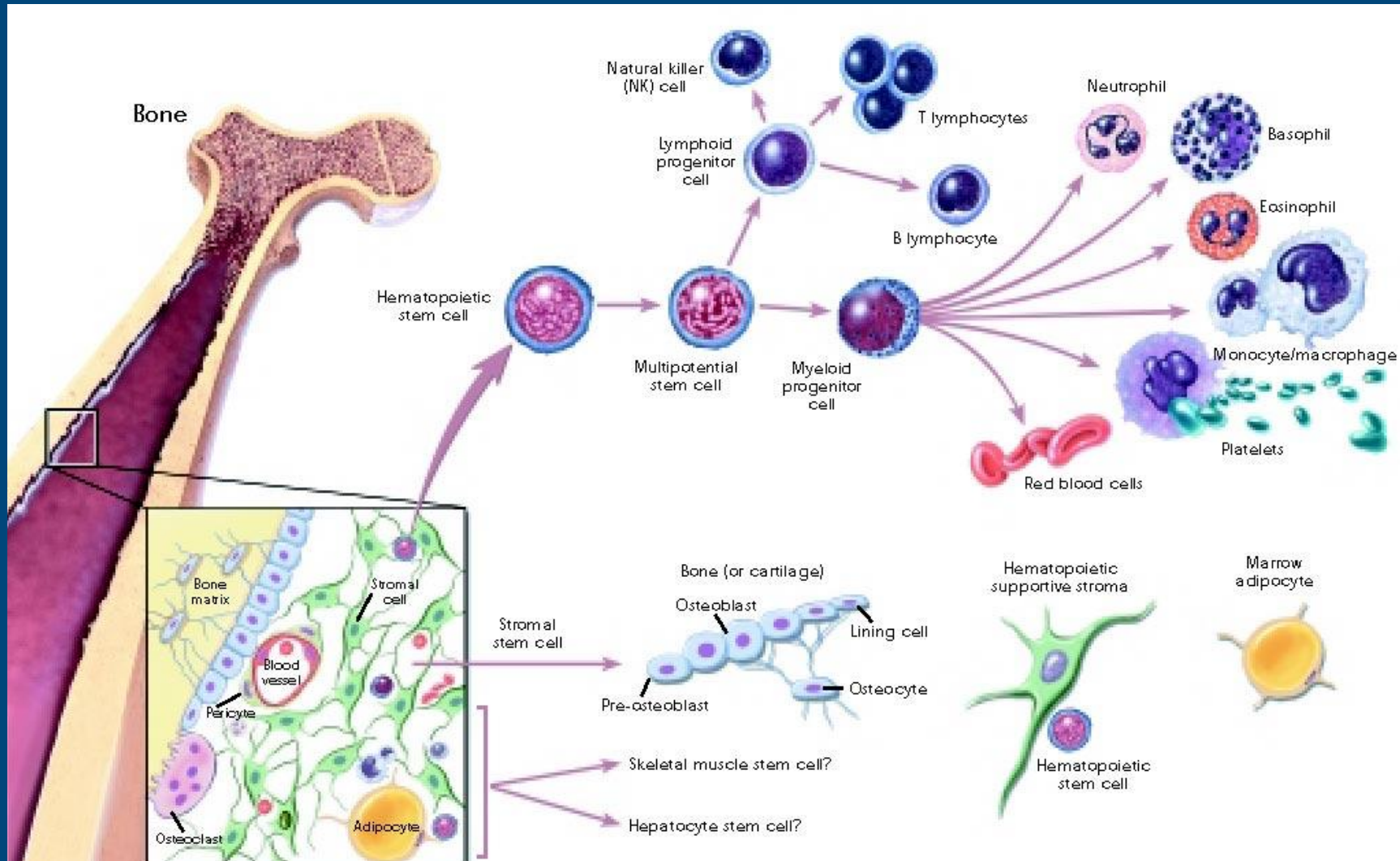


- Lichaam bestaat uit >100 miljard cellen
- Voortgekomen uit 1 cel
- Bevruchte eicel is ultieme stamcel

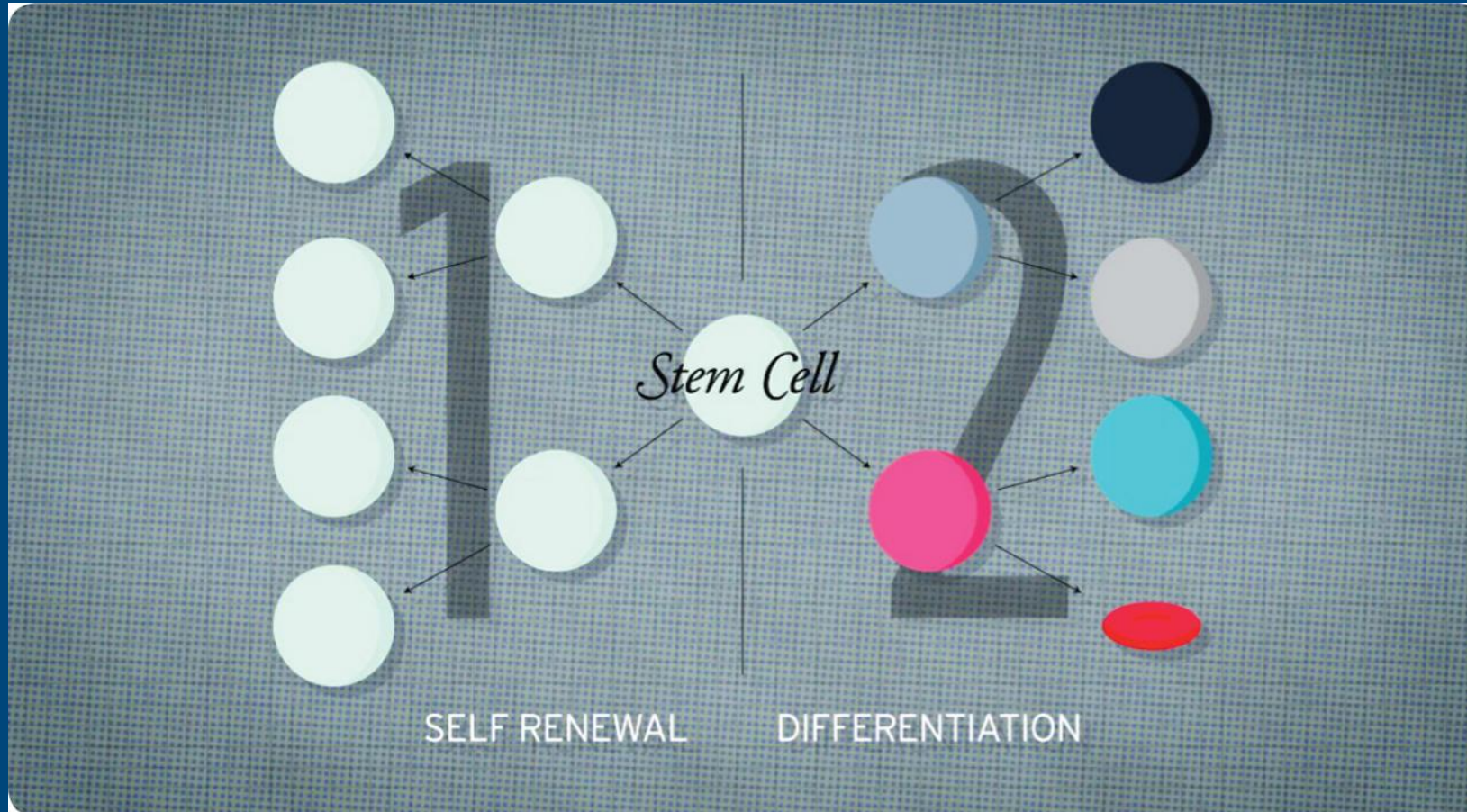
- Embryonic stem cells (ethiek)
- **Adult stem cells => veilig**
- Induced pluripotent stem cells



Celbio 2: Stamcellen in het beenmerg



Stamcellen delen en dochtercellen vormen functioneel weefsel

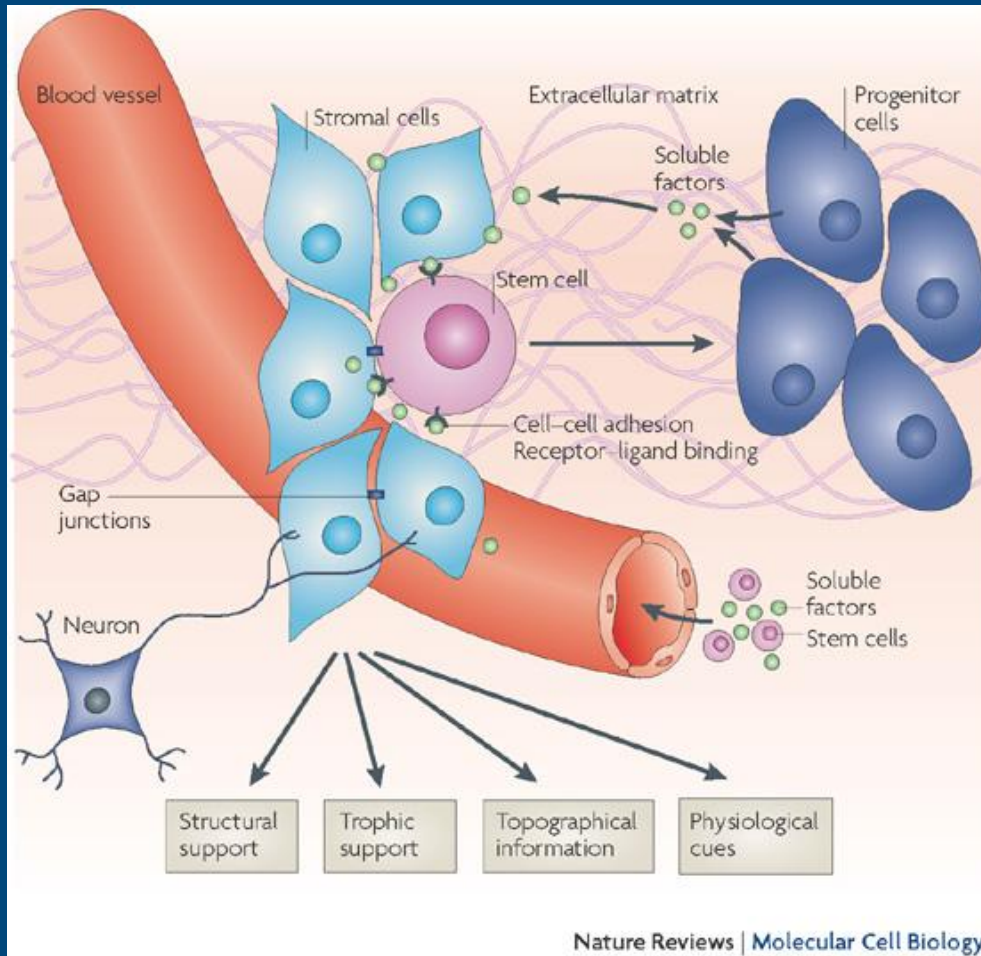
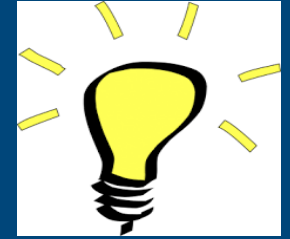


https://www.youtube.com/watch?v=_hbgeQzmU9U

American Association for the Advancement of Science
Science 2014;343:600-610



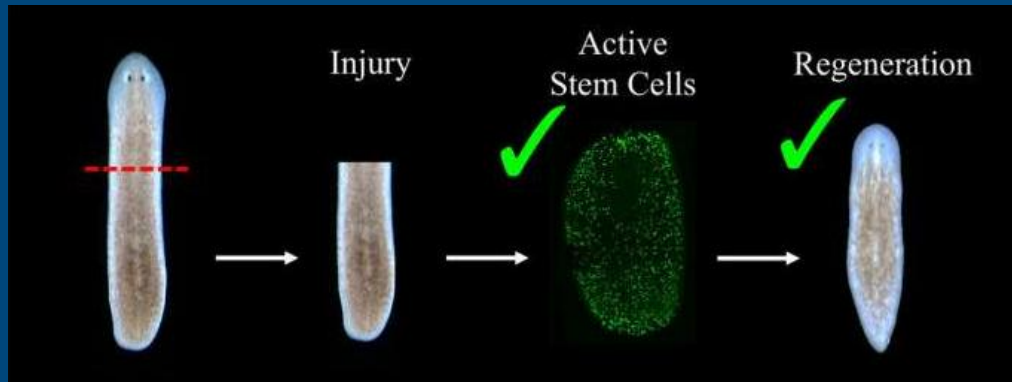
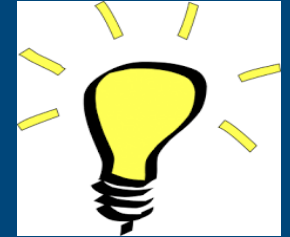
Stem cell niche, signalen



The niche is a complex and dynamic structure that transmits and receives signals through cellular and acellular mediators. This schematic depicts a hypothetical niche composite, which summarizes known components of previously described mammalian and non-mammalian niches: the stem cell itself, stromal cells, soluble factors, extracellular matrix, neural inputs, vascular network and cell adhesion components. It is important to note that although many niche components are conserved, it is unlikely that every niche necessarily includes all of the components listed. Instead, niches are likely to incorporate a selection of these possible avenues for communication, specifically adapted to the particular functions of that niche, which might be to provide structural support, trophic support, topographical information and/or physiological cues.

D. Leanne Jones & Amy J. Wagers
Nature Reviews Molecular Cell Biology **9**, 11-21

Planaria: Kampioen regeneratie. Waarom kunnen wij dit niet?



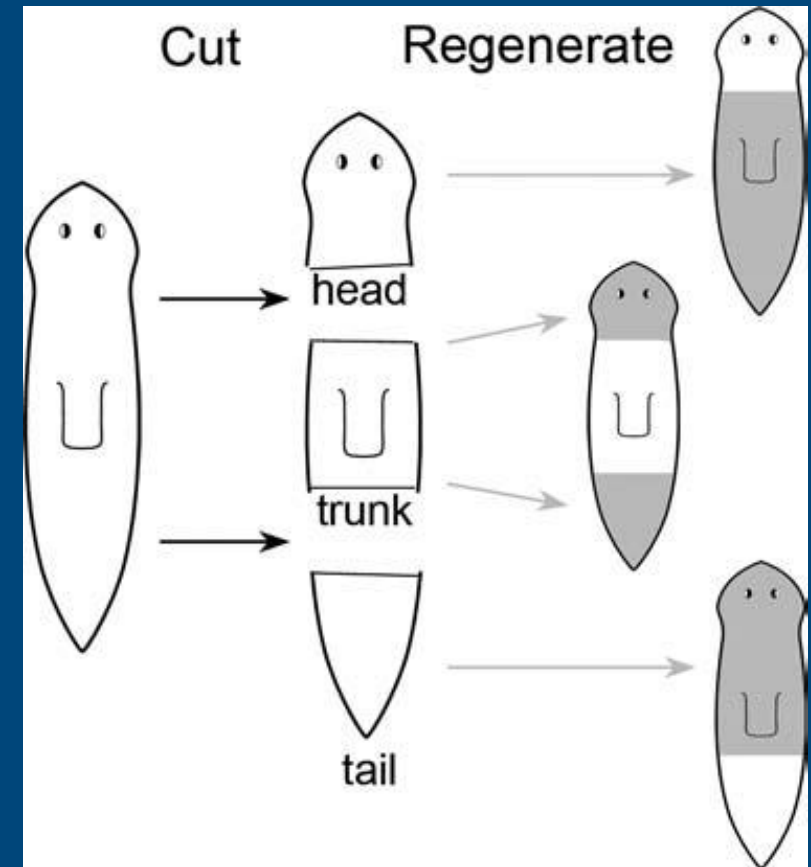
Platwormen (Planaria) zijn relatief eenvoudig.

Een **ingewikkelder** organisme zoals de mens is moeilijker te regenereren. En is **warmbloedig**.

⇒ Kan maar kort inactief zijn. We moeten door..

⇒ Scarring = **litteken**weefsel (**fibrose**) als methode om de rest van het weefsel weer snel te laten functioneren.

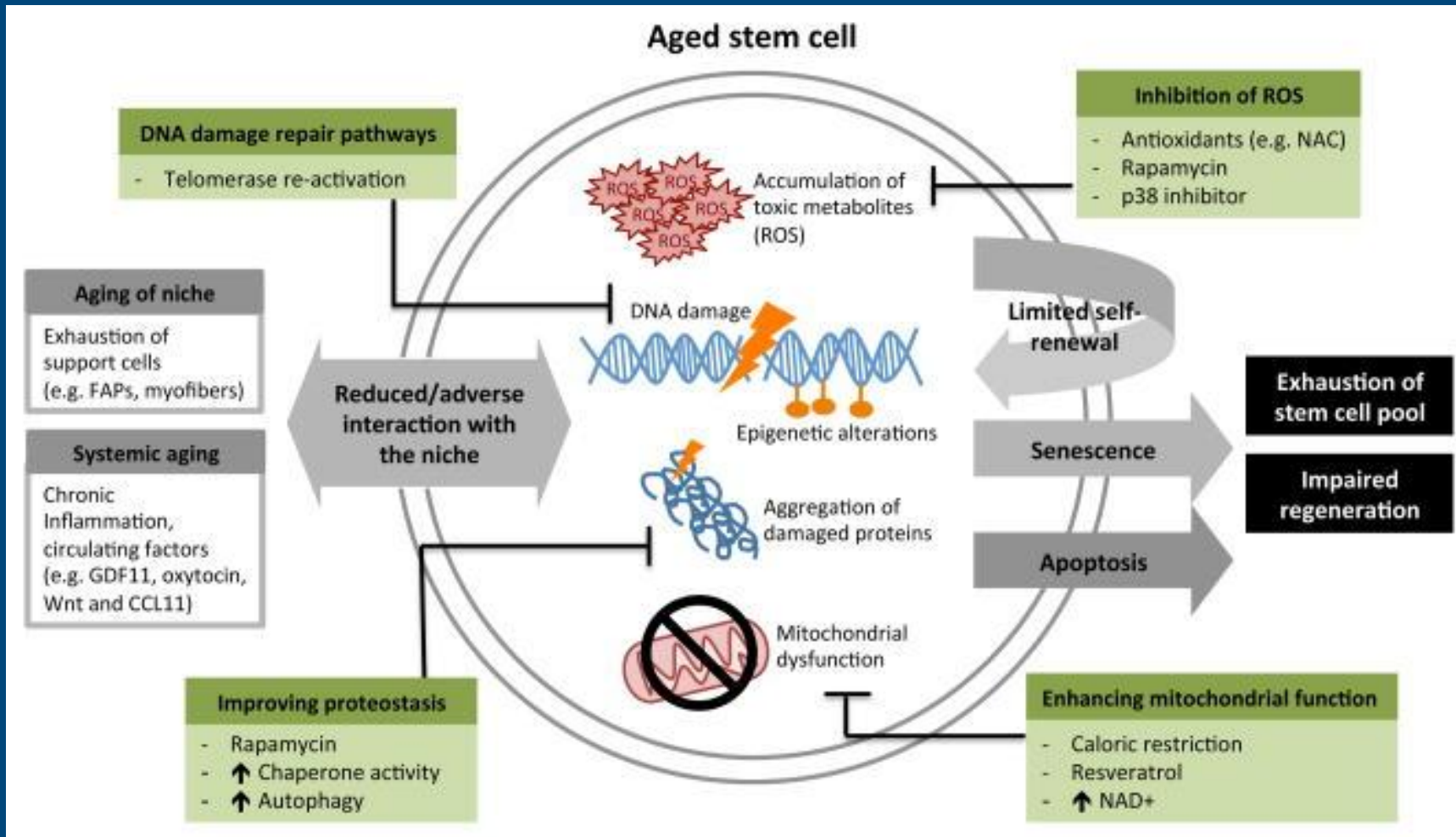
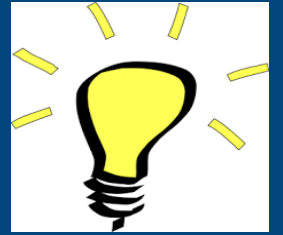
⇒ Gebeurt ook na beschadiging stamcelcompartiment



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

<https://onlinelibrary.wiley.com/doi/full/10.1111/trf.14836>

Stem cell aging loss of quality and quantity (of niche)



Stamcellen

Kanker en veroudering



- Stamcellen kunnen nog volop delen. Maar ongecontroleerd delen = kanker
=> **stamcel controle is essentieel (Niche!)**
- Te sterke stamcelcontrole => te weinig deling => veroudering ??
- Veroudering hoort bij lang leven, want kanker moet worden voorkomen ??
- Onderzoek naar stimulatie en remming stamcellen zorgt voor betere therapieën (adult stamcel + iPS techniek)

Halfwaardetijd cellen

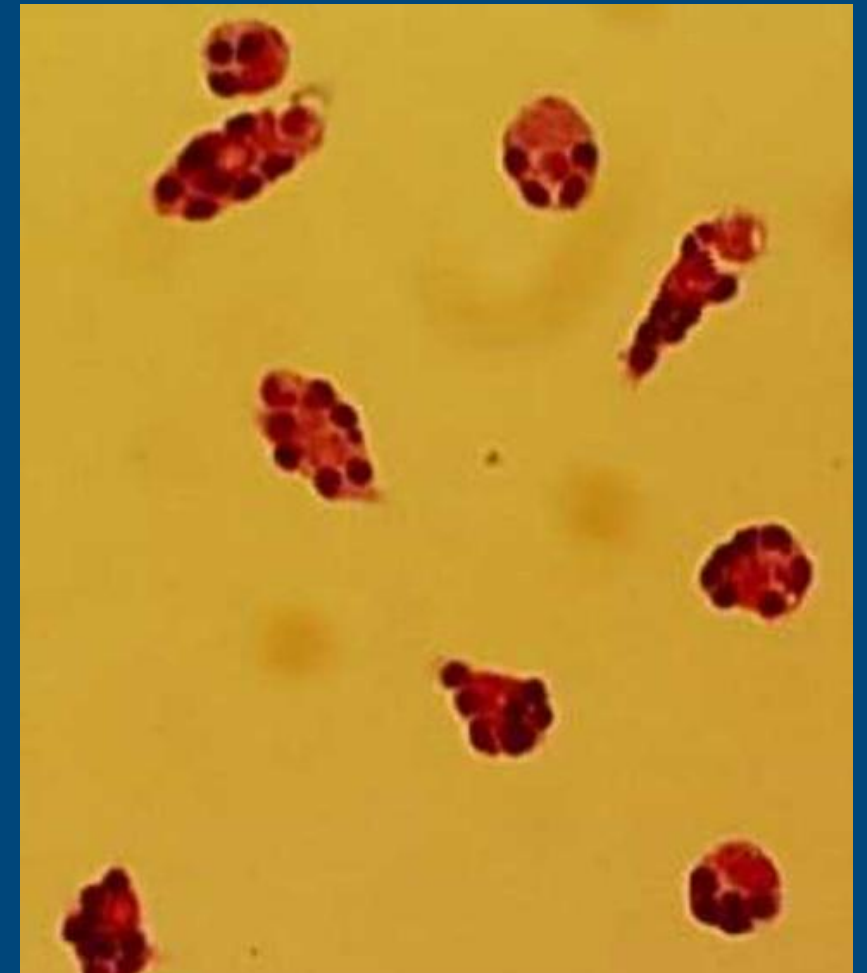
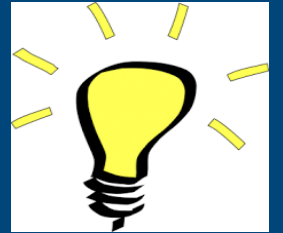
- Rode bloedcel 110 dagen
- Huidcel 21 dagen
- Darm epitheel 2 dagen => hans cleevers
- Long epitheelcel 2 jaar => long-covid

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

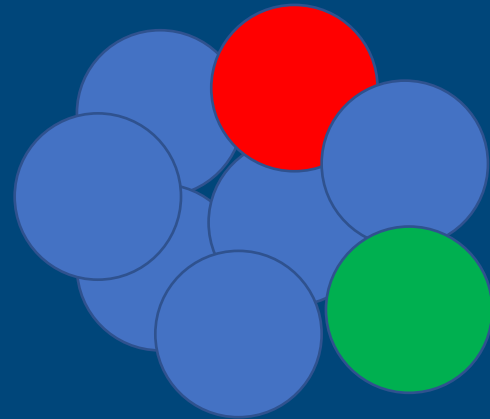
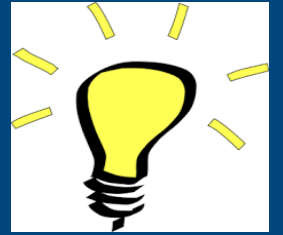
NB Meeste cellen gaan ordelijk dood via apoptose,
en worden verwijderd door macrofagen

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

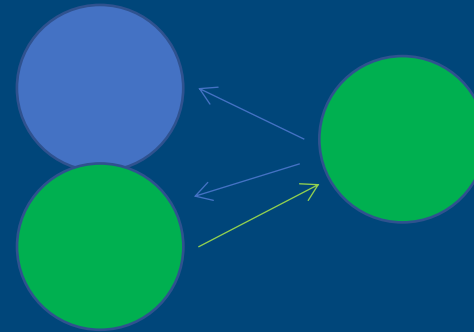
<http://www.uptodate.com/contents/red-blood-cell-survival-normal-values-and-measurement>



Leven is een fluide verzameling Atomen / Cellen / Organismen



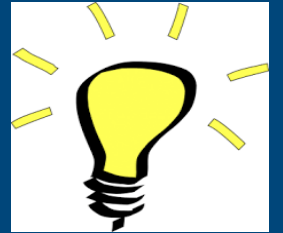
Dode cel
stamcel



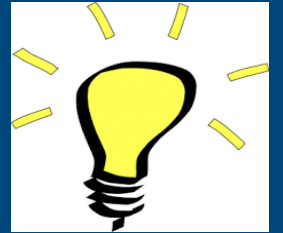
Elke cel wordt op termijn vervangen.
En uit een stamcel die deelt ontstaan 2
nieuwe cellen (1 wordt de nieuwe stamcel)

Leven is..

- Een informatie systeem
- Manipuleerbaar met informatietechnologie
- Individuele processen kunnen ook buiten een levend systeem plaatsvinden
- **Modulair**

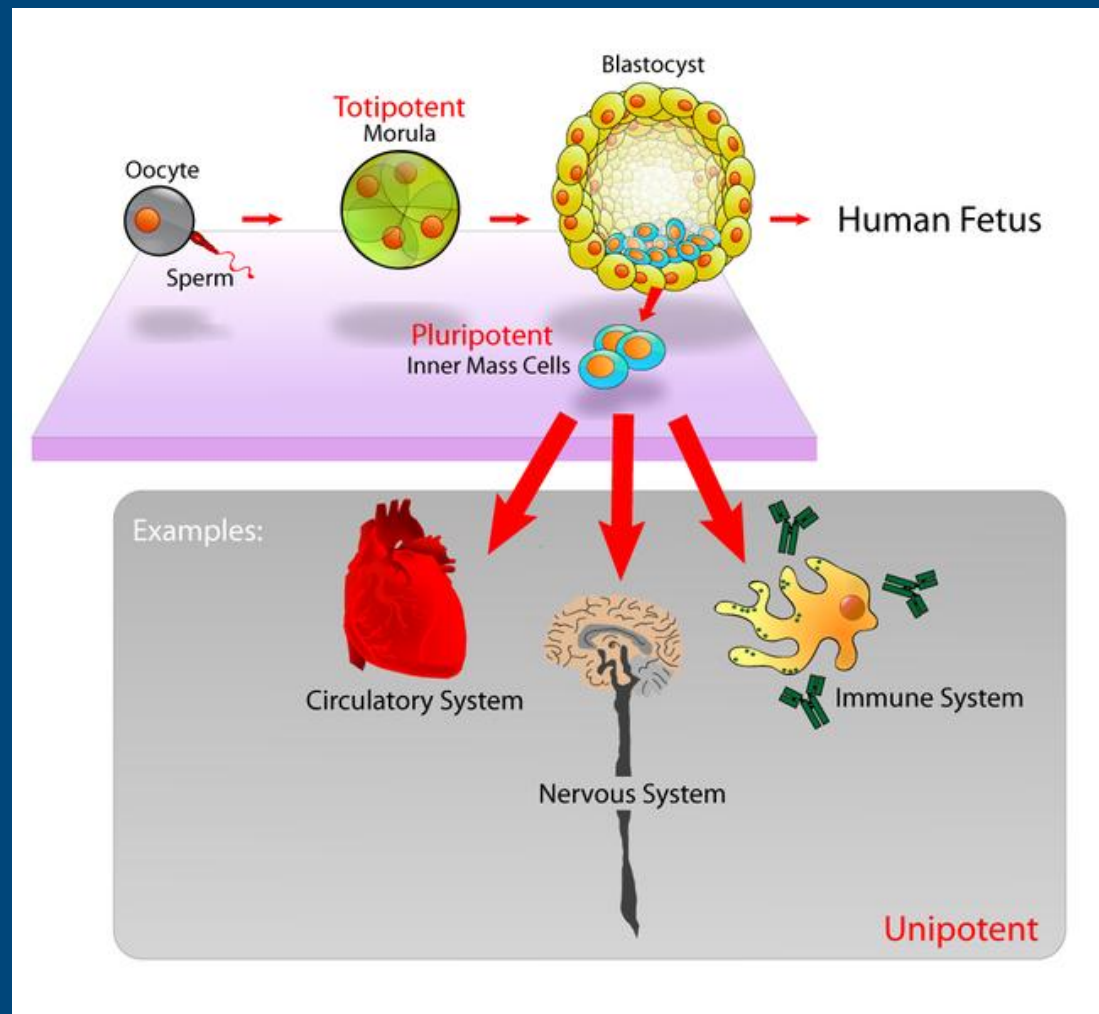


Stamcellen => gebruiken voor therapie

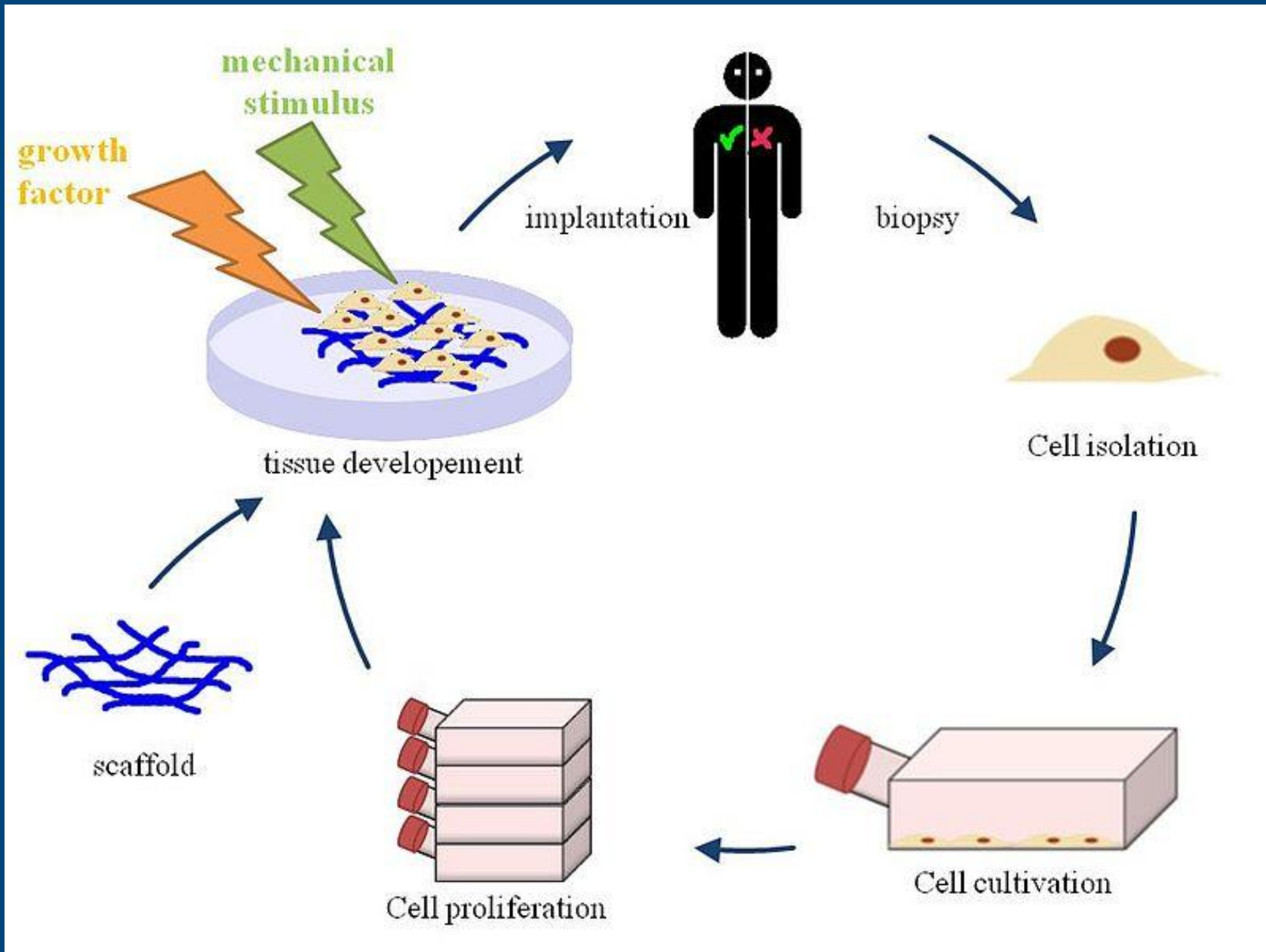


Al onze miljarden cellen komen voort uit 1 enkele stamcel: de bevruchte eicel
=> Pluripotent (kan nog van alles worden)

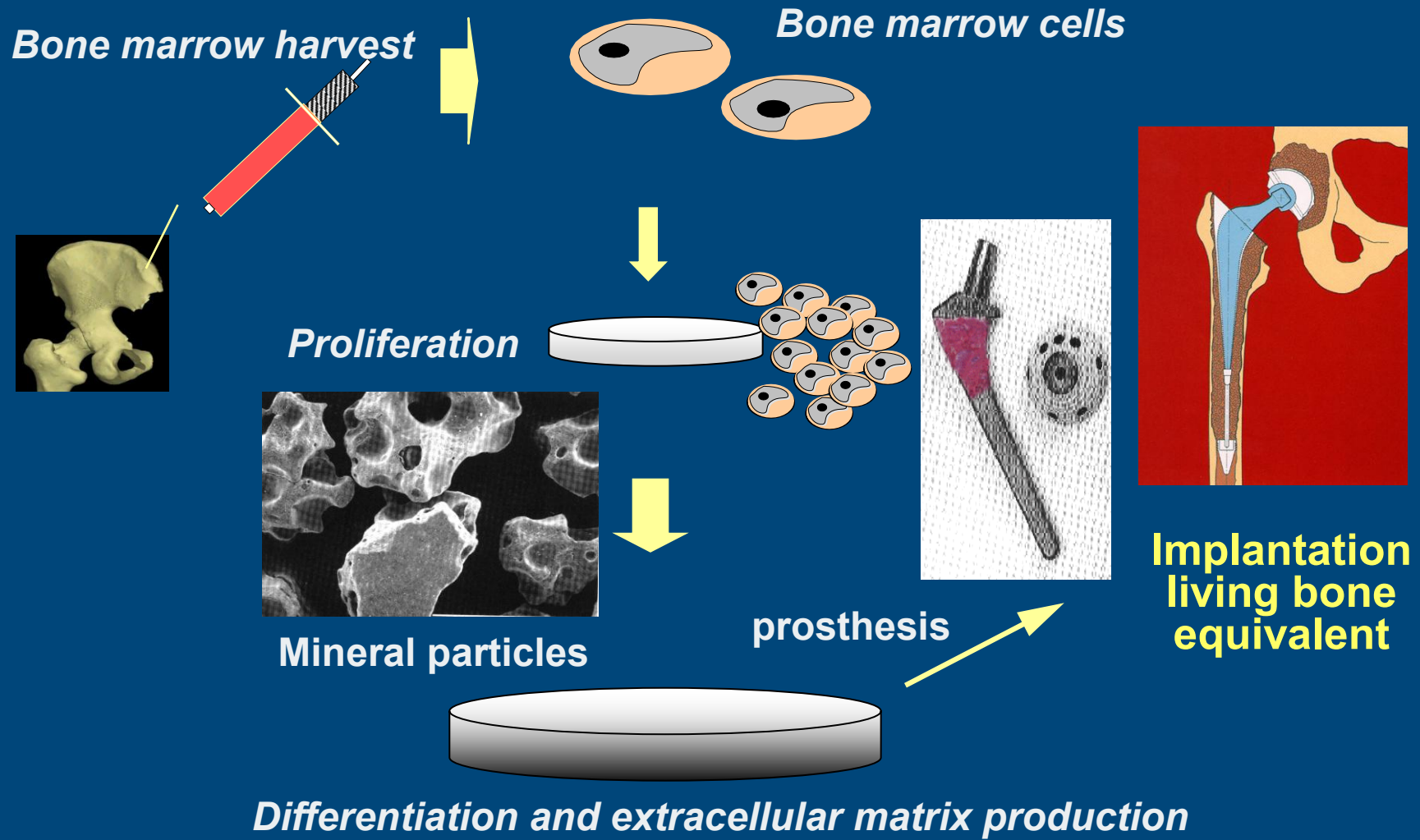
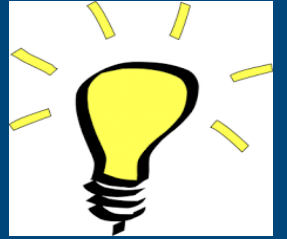
Na de embryonale ontwikkeling blijven stamcellen actief
=> **adult stem cells**
=> Multipotent (kunnen nog een beperkt aantal dingen worden)



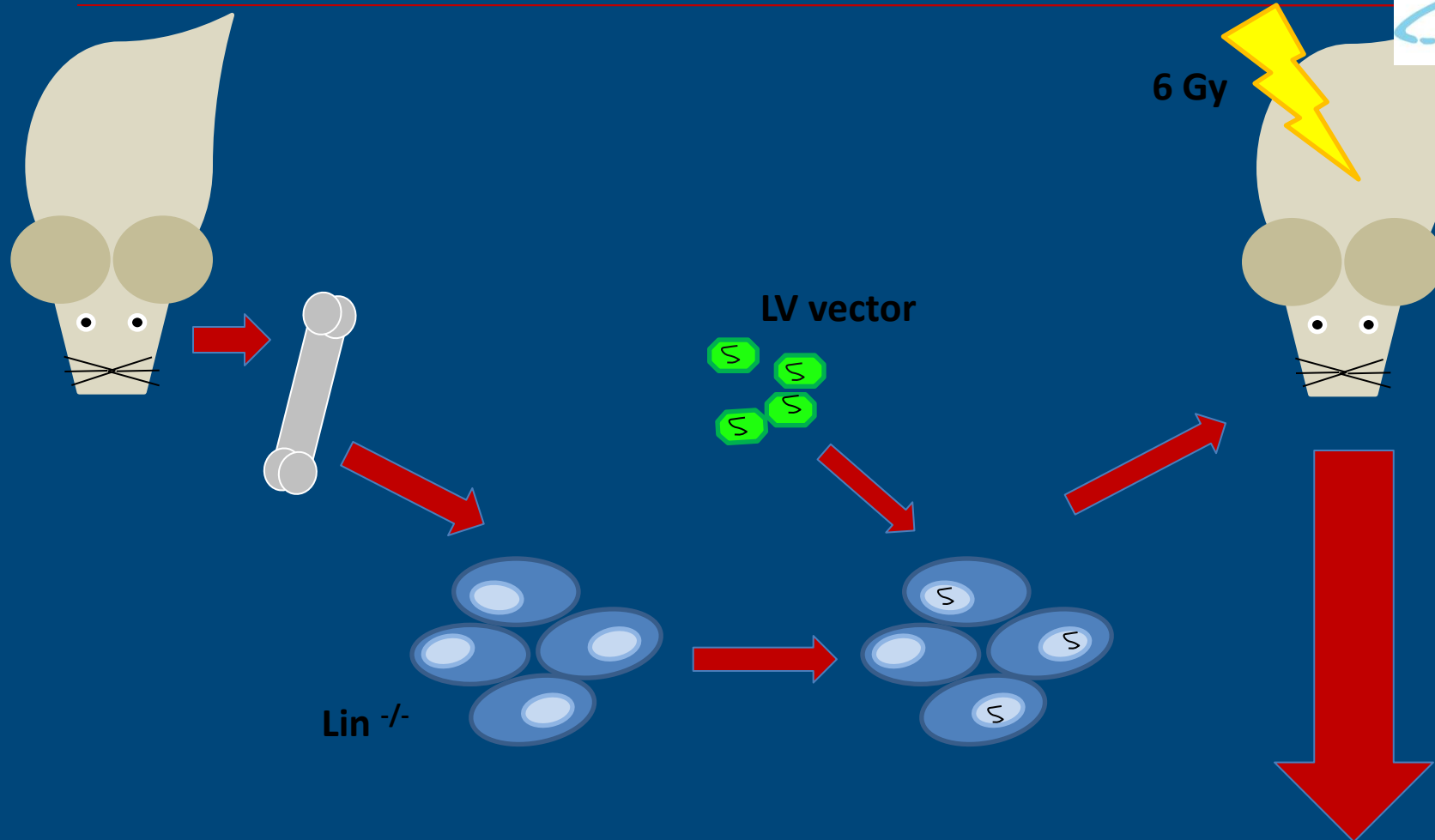
Tissue-engineering



Tissue-engineered bone coated on titanium.



Experimental Approach (ex vivo)



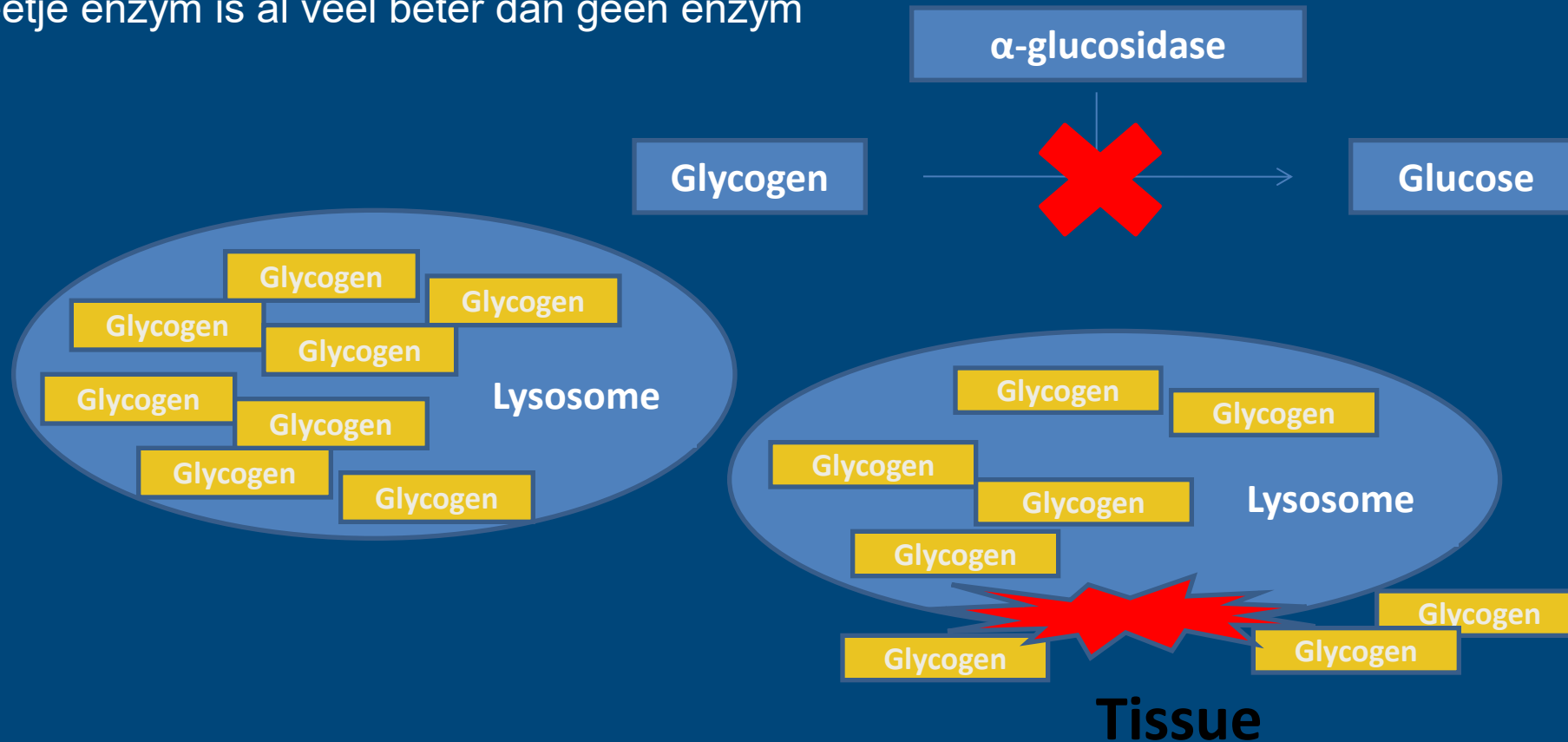
Expression of the transgene in all hematopoietic cells
Ex vivo possible through use of stem cells (quality control)

stamcel => college 2

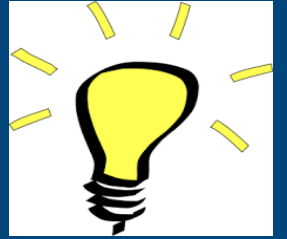
Gen/stamceltherapie: Pompe Disease

Autosomal recessive lysosomal storage disorder
Deficiency in α -glucosidase (GAA)

=> Klein beetje enzym is al veel beter dan geen enzym

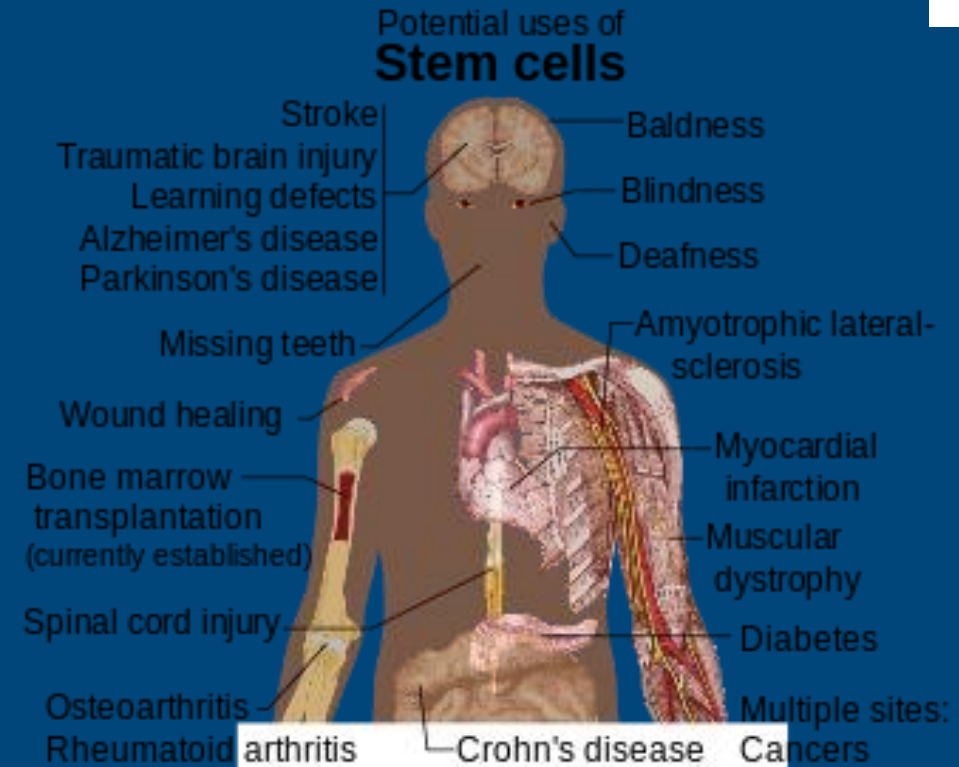


Stamcel therapie



- Lichaam bestaat uit >100 miljard cellen
- Voortgekomen uit 1 cel
- Bevruchte eicel is ultieme stamcel

- Embryonic stem cells
- Adult stem cells => veilig
- **Induced pluripotent stem cells**



Stamcel Nobel 2012

John B. Gurdon and Shinya Yamanaka
(Nobel al binnen 10 jaar na ontdekking!)

Mature cells can be reprogrammed (iPS)
to become pluripotent

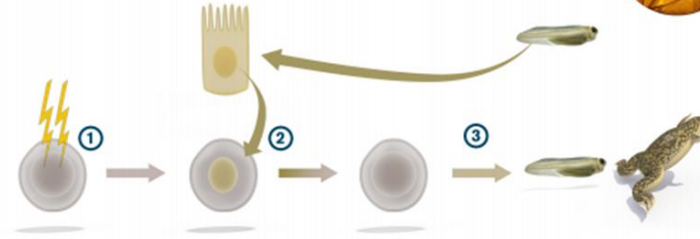
Elke cel heeft nog al het DNA

Patient levert eigen materiaal voor
therapie !

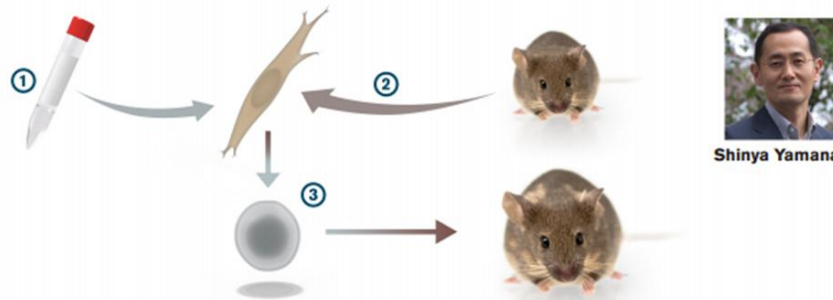
The Nobel Prize in Physiology or Medicine 2012



John B. Gurdon

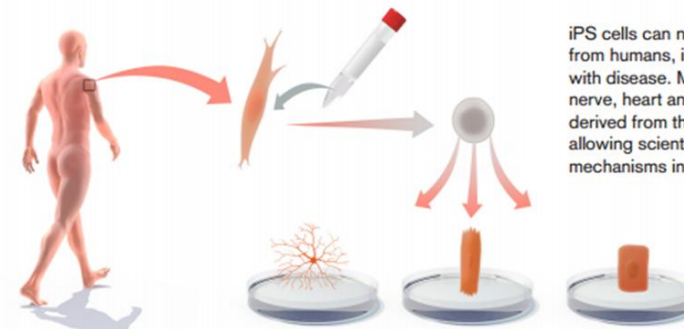


John B. Gurdon eliminated the nucleus of a frog egg cell (1) and replaced it with the nucleus from a specialised cell taken from a tadpole (2). The modified egg developed into a normal tadpole (3). Subsequent nuclear transfer experiments have generated cloned mammals (4).

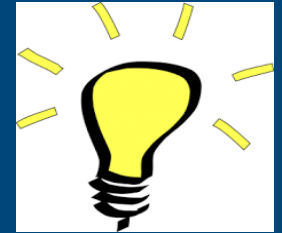


Shinya Yamanaka

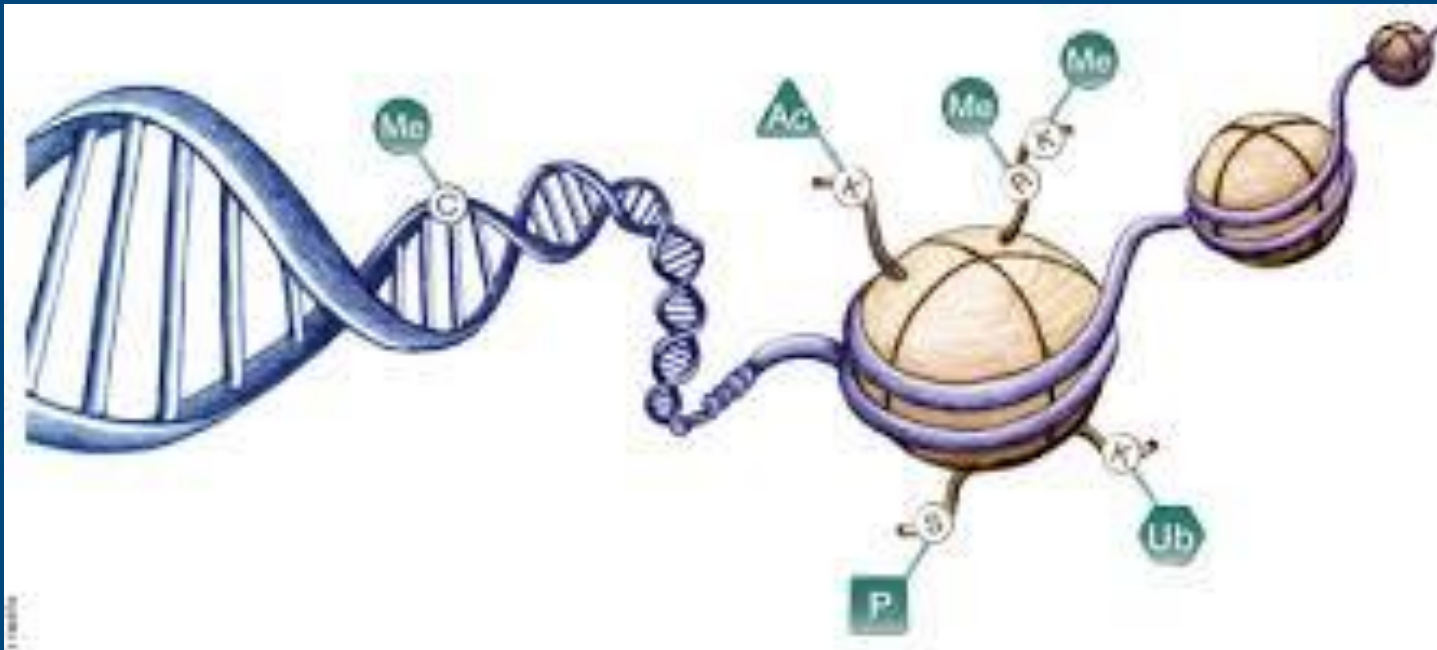
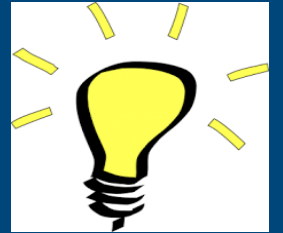
Shinya Yamanaka studied genes that are important for stem cell function. When he transferred four such genes (1) into cells taken from the skin (2), they were reprogrammed into pluripotent stem cells (3) that could develop into all cell types of an adult mouse. He named these cells induced pluripotent stem (iPS) cells.



iPS cells can now be generated from humans, including patients with disease. Mature cells including nerve, heart and liver cells can be derived from these iPS cells, thereby allowing scientists to study disease mechanisms in new ways.



Celbio 1: Epigenetische modificatie



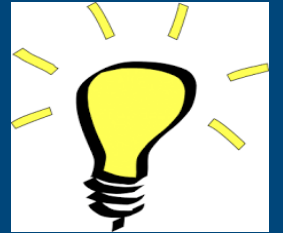
<https://www.youtube.com/watch?v=mHak9EZjySs&list=PL761BC3F8B2447983>

- **Differentiatie** van cellen: van stamcel tot weefsel
=> Kanker, Veroudering
=> **Non coding RNA**

MCB H.18, p.309

Organoids

Growing new tissues outside the body => ex vivo

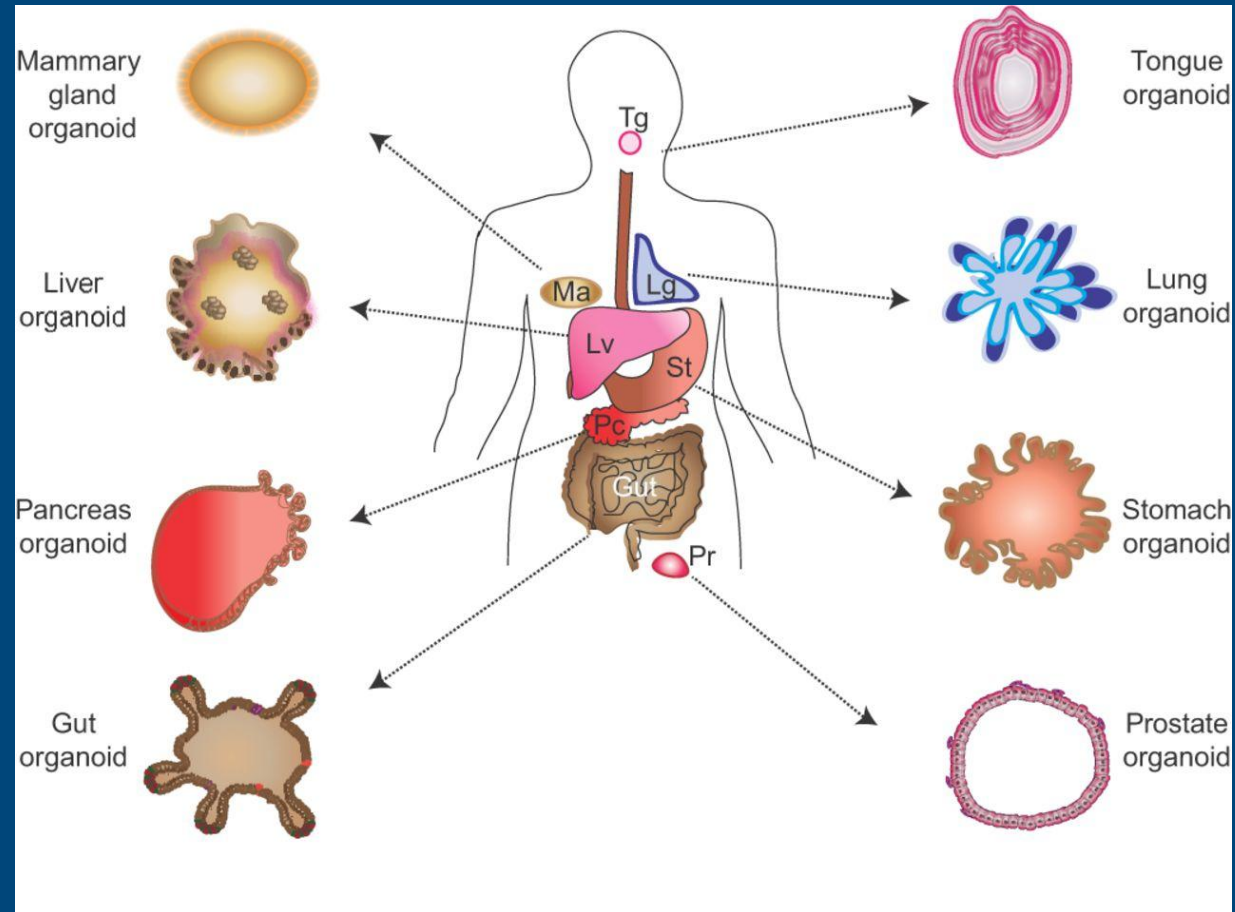


(Stam)cellen uit het lichaam van een patients worden in het lab (via iPS) gestimuleerd en opgekweekt tot mini-orgaantjes

=> Volledige differentiatie

Die kunnen dan worden gebruikt voor onderzoek, en therapie

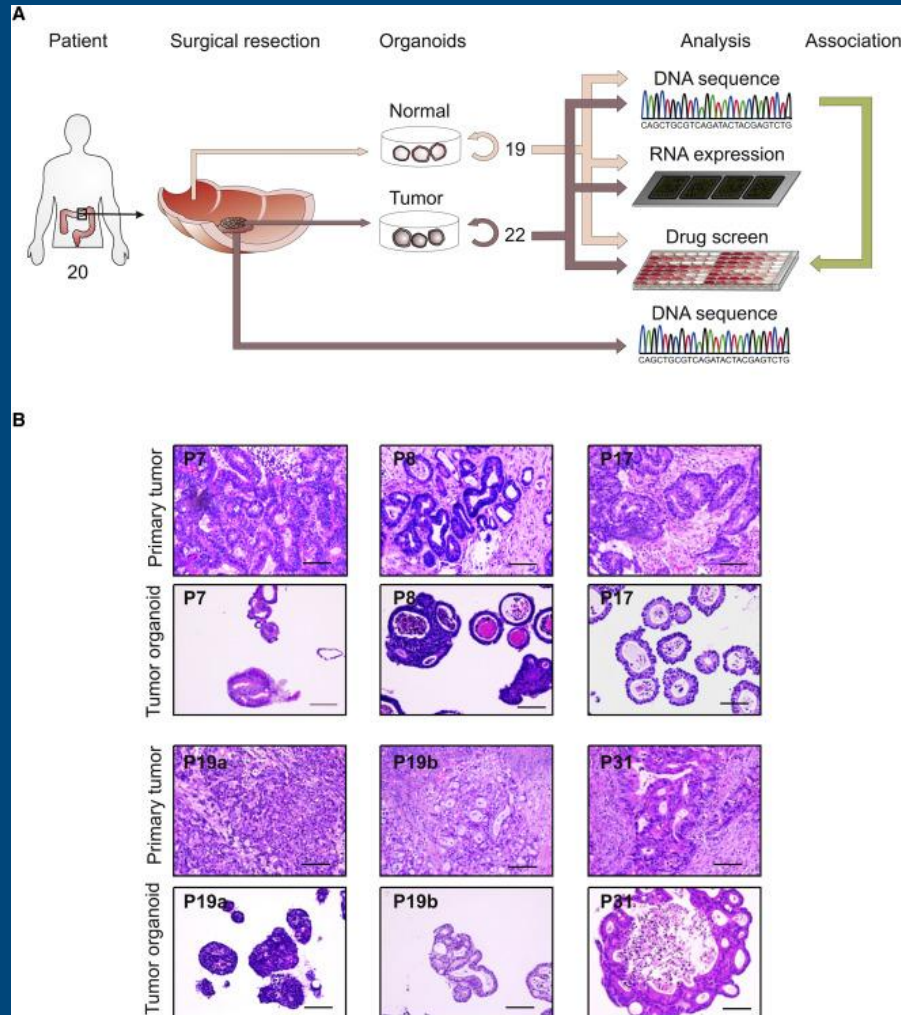
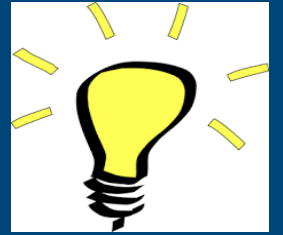
=> Individuele geneeskunde



NB iPS cellen zijn nu in principe volledig gedifferentieerd, maar er hoeft maar 1 cel van een organoid zich niet aan de spelregels te houden => kanker. Veiligheid is dus nog een issue.

Hans CleEVERS

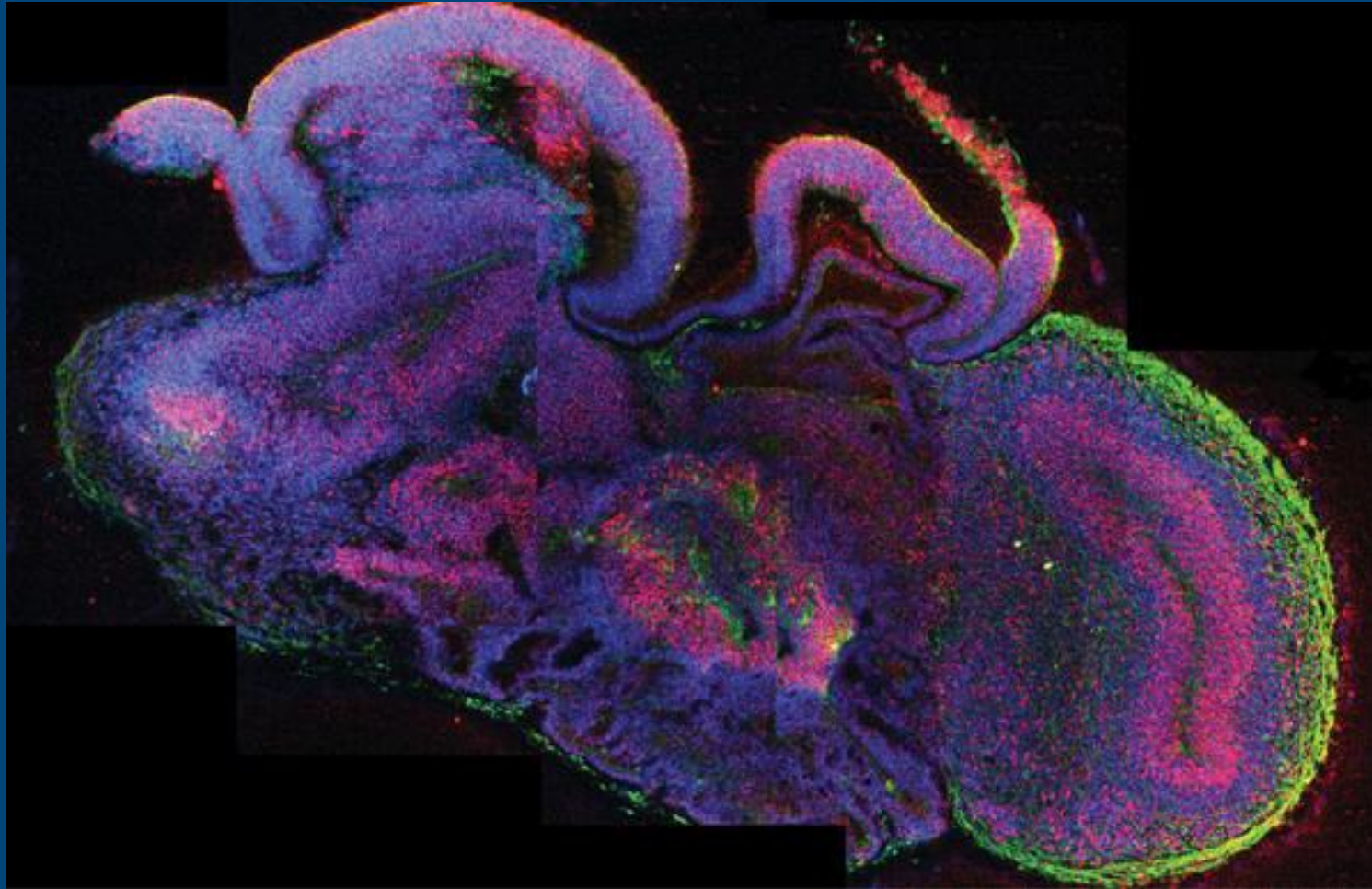
Darm stamcellen => organoids



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

[http://www.cell.com/cell/fulltext/S0092-8674\(15\)00373-6?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867415003736%3Fshowall%3Dtrue](http://www.cell.com/cell/fulltext/S0092-8674(15)00373-6?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867415003736%3Fshowall%3Dtrue)

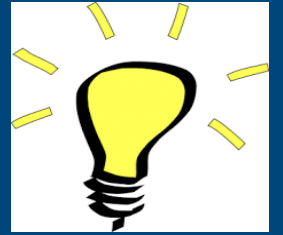
Brain Organoids



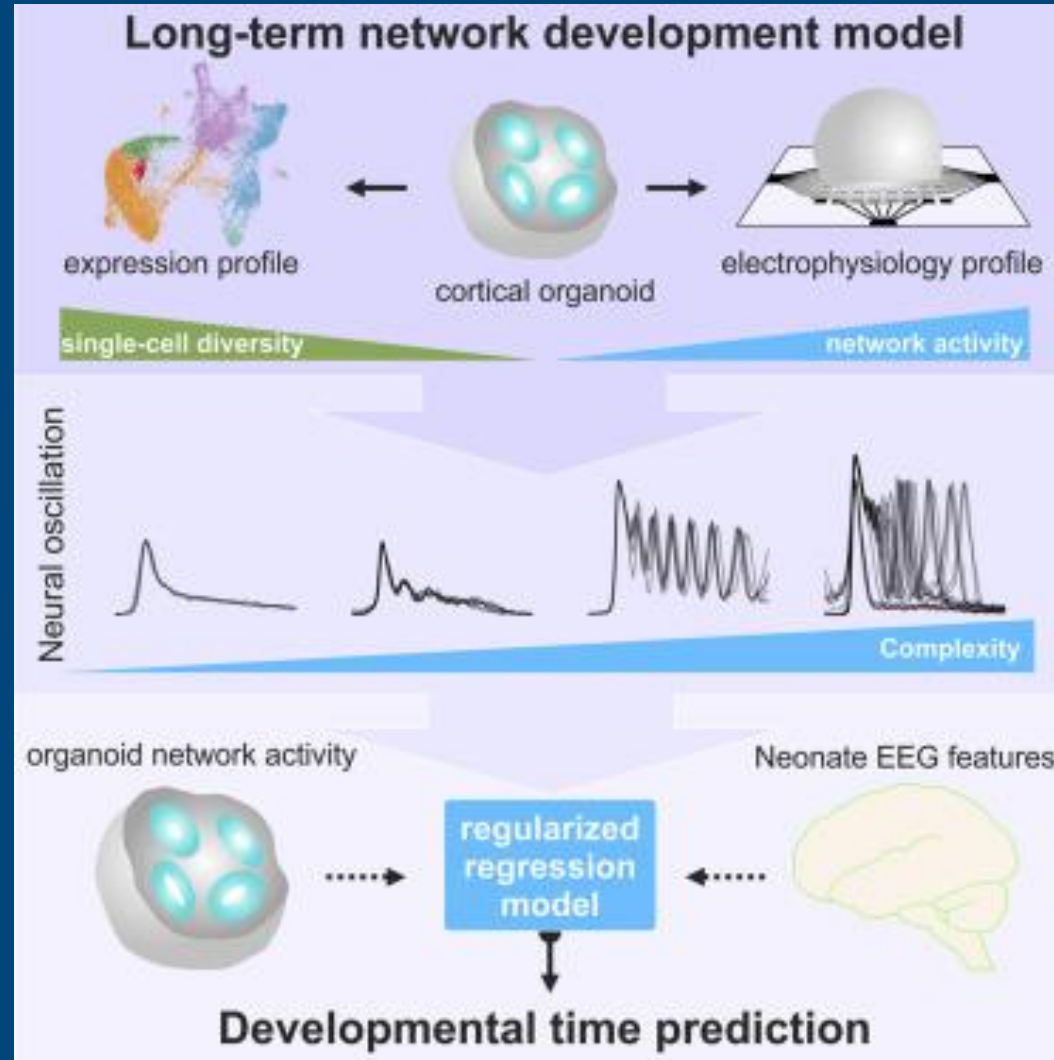
Vooral onderzoek, patientspecifiek
Ook hier is de kliniek nog ver weg
ivm veiligheid

- <https://www.youtube.com/watch?v=76CQ1kLGbNs>
- <http://hub4organoids.eu/organoid-technology/>

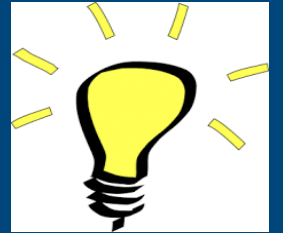
Complex Oscillatory Waves Emerging from Cortical Organoids Model



- 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)
- Testen voor bewustzijn?
- Heeft een organoid als bewustzijn? Of in ieder geval waarde



Celbio 2



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

=> bioelectricity

=> biological computation

=> cells have agency

(reageren op hun omgeving)

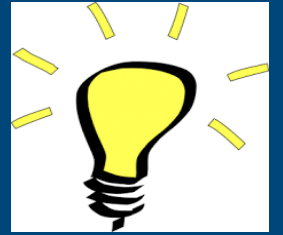
=> cel is een (levende) basis bouwsteen

=> degrees of freedom (controle!?)

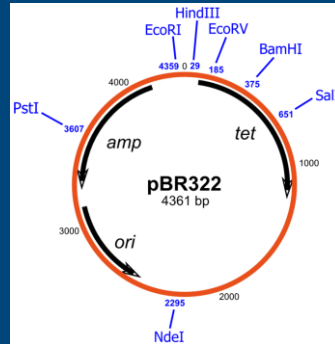
Informatie in het netwerk



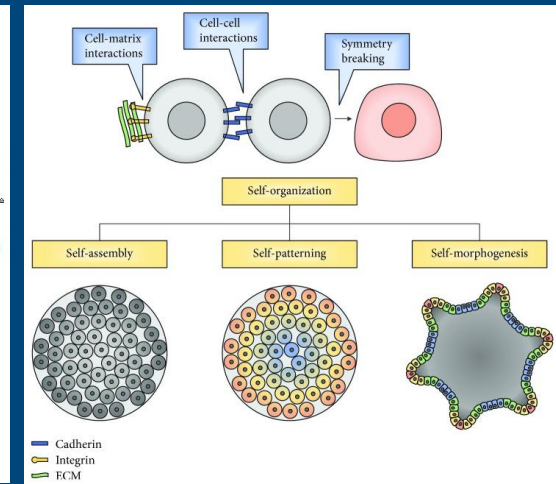
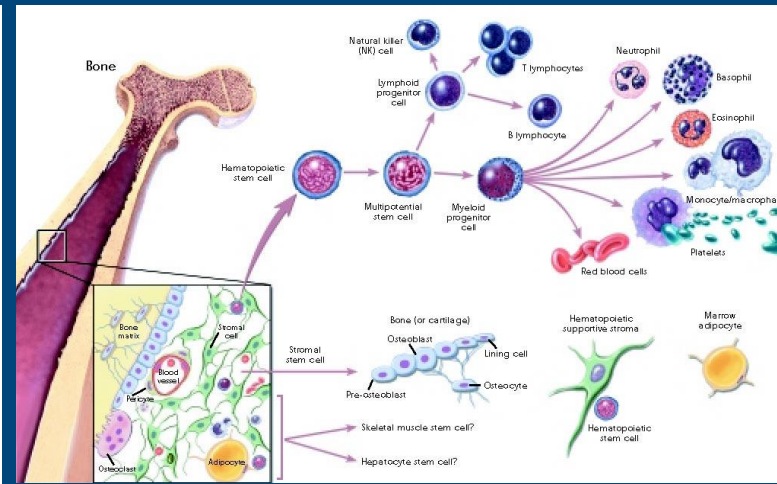
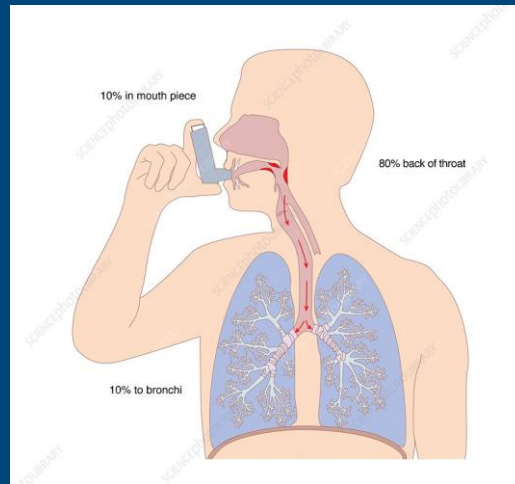
The delivery problem: solutions



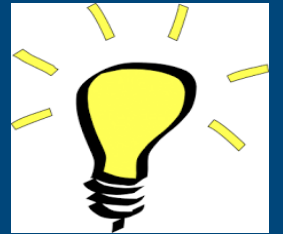
- Pflanzen, bacterien
=> plasmide



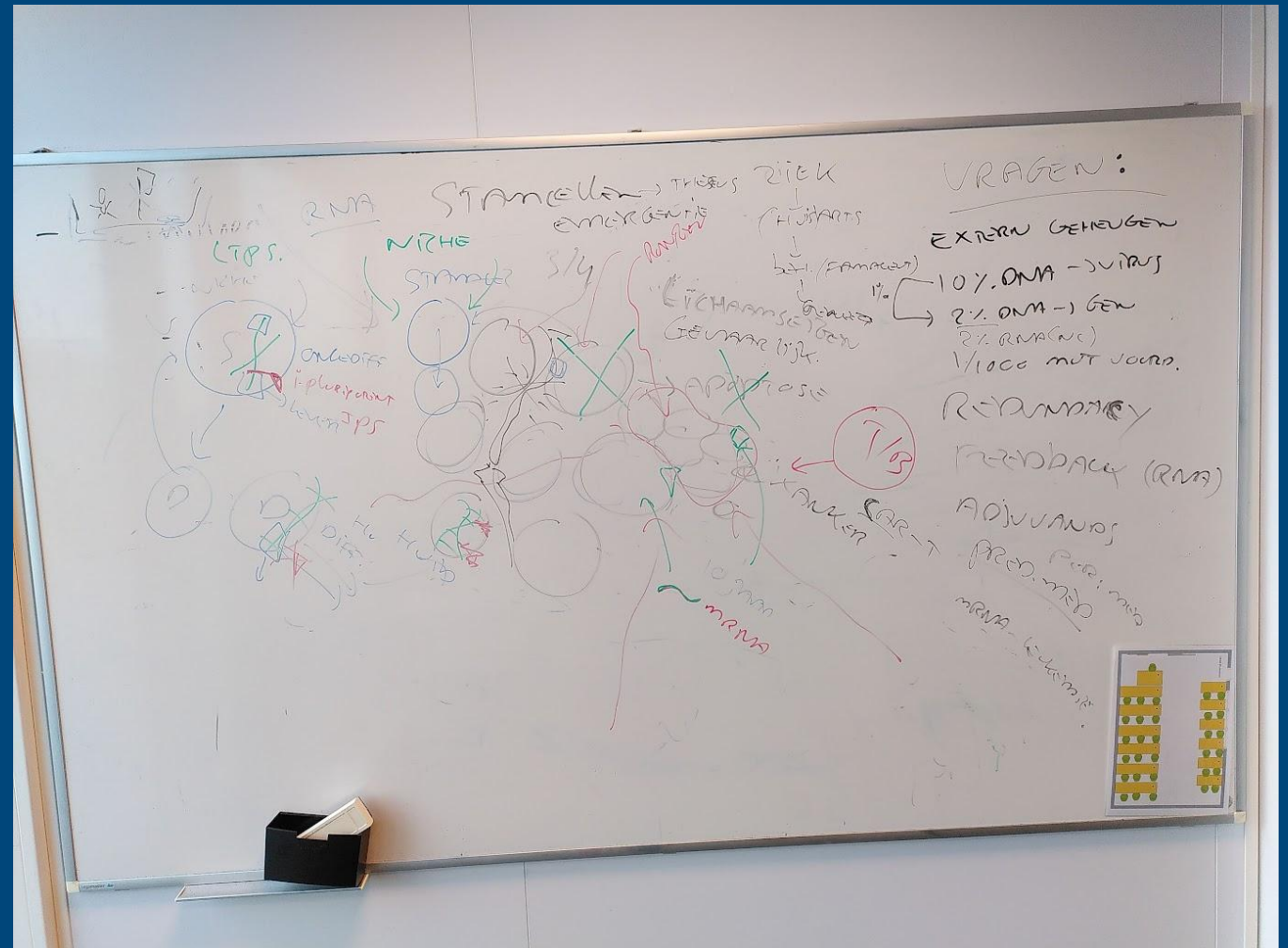
- Mens
=>Virus
=>Stamcel
=>Organoid (TE)



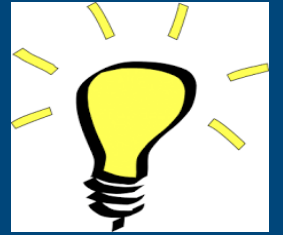
Vragen



- RNA world
 - Mutaties/evolutie
 - Emergentie
 - Redundancy
 - Feedback
 - Adjuvans
 - Kanker (stamcel)
-
- Personalised medicine
 - Predictive medicine
 - Extern geheugen
- => college 4



De RNA wereld



Human genome project in 2000:
1-2% DNA codeert voor eiwit (via mRNA).

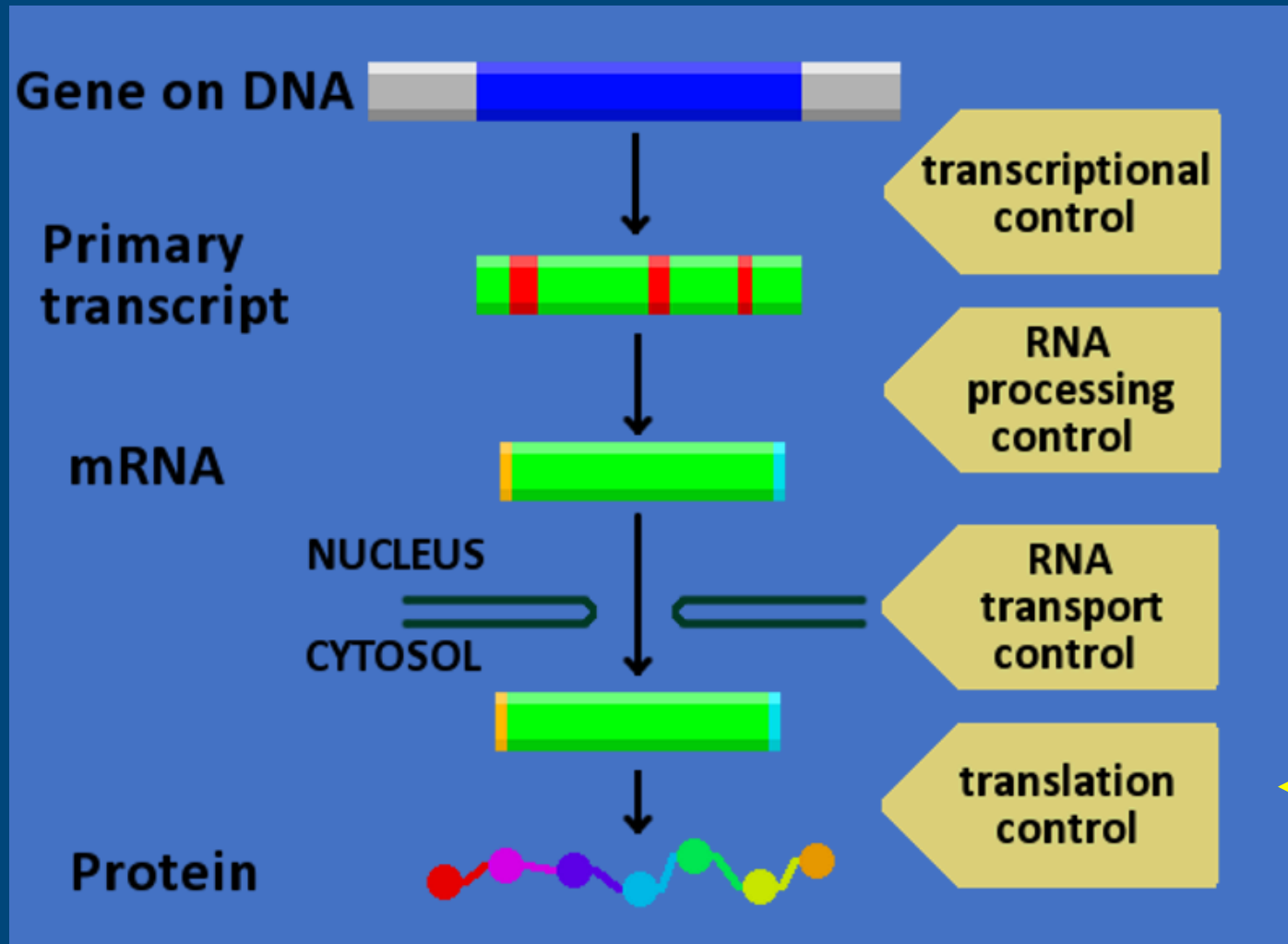
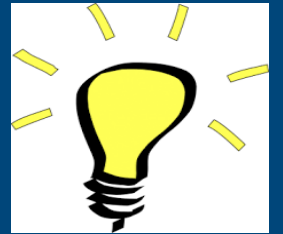
The Encyclopedia of DNA Elements (ENCODE) project reported in 2012 that over 80% of DNA in the human genome "serves some purpose"
=> no junk

1-2% DNA codeert voor **non-coding RNA's** (microRNA)
=> Belangrijke **extra regelniveaus** in de celkern
=> fine-tuning genexpressie (belangrijk met maar 20.000 genen)

=> Encode link
<http://www.nature.com/encode/#/threads>

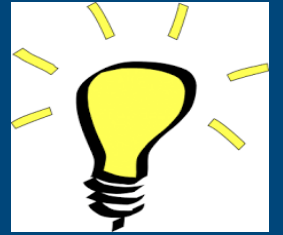
The screenshot shows a web browser displaying a Nature journal article. The browser's address bar shows the URL: <http://www.nature.com/encode/#/threads>. The page header includes navigation links: Home, News & Comment, Research, Careers & Jobs, Current Issue, Archive, Audio & Video, and For Authors. The article title is "MicroRNAs 103 and 107 regulate insulin sensitivity" by Mirko Trajkovski, Jean Hausser, Jürgen Soutschek, Bal Bhat, Akinc Akin, Mihaela Zavolan, Markus H. Heim & Markus Stoffel. The article is categorized as a "LETTER" in "NATURE". The publication details are: Nature 474, 649–653 (30 June 2011) | doi:10.1038/nature10112. The article text begins with: "Defects in insulin signalling are among the most common and earliest defects that predispose an individual to the development of type 2 diabetes^{1, 2, 3}. MicroRNAs have been identified as a new class of regulatory molecules that influence many biological functions, including metabolism^{4, 5}. However, the direct regulation of insulin sensitivity by microRNAs *in vivo* has not been demonstrated. Here we show that the expression of microRNAs 103 and 107 (miR-103/107) is upregulated in obese mice. Silencing of miR-103/107 leads to improved glucose homeostasis and insulin sensitivity. In contrast, gain of miR-103/107 function in either liver or fat is sufficient to induce impaired glucose homeostasis. We identify caveolin-1, a critical regulator of the insulin receptor, as a direct target gene of miR-103/107. We demonstrate that caveolin-1 is upregulated upon miR-103/107 inactivation in adipocytes and that this is concomitant with stabilization of the insulin receptor, enhanced insulin signalling, decreased adipocyte size and..." On the right side of the article, there is a sidebar with a "日本語要約" (Japanese Summary) link and several sharing options: print, email, download citation, order reprints, rights and permissions, and share/bookmark.

RNA: Levels of control



Belangrijk is niet het aantal genen, maar wat je er mee doet

← RNase
<https://nl.wikipedia.org/wiki/Ribonuclease>
=> RNA wordt snel afgebroken



Variatie is nodig voor **selectie**
=> evolutie

Mutaties (beperkt en relatief langzaam)

=> Mutaties zijn essentieel, maar random en leiden meestal niet tot verbetering

Sexuele voortplanting => **recombinatie** (nieuwe combinaties van bestaande eigenschappen)

=> Natuurlijke selectie (omgeving)

=> Sexuele selectie (partnerkeuze)

=> Culturele selectie (gewenste eigenschappen)

Epigenetische veranderingen (genen aan/uit)

<https://www.youtube.com/watch?v=hOfRN0KihOU>

<https://www.youtube.com/watch?v=-mPCqYxB4d4>

MCB H.21

Emerging properties Voorbij **reductionisme**



- http://www.npo.nl/de-volmaakte-mens/10-06-2015/VPWON_1231937



Celbio 4: Integratie van verschillende signalen



2nd messengers

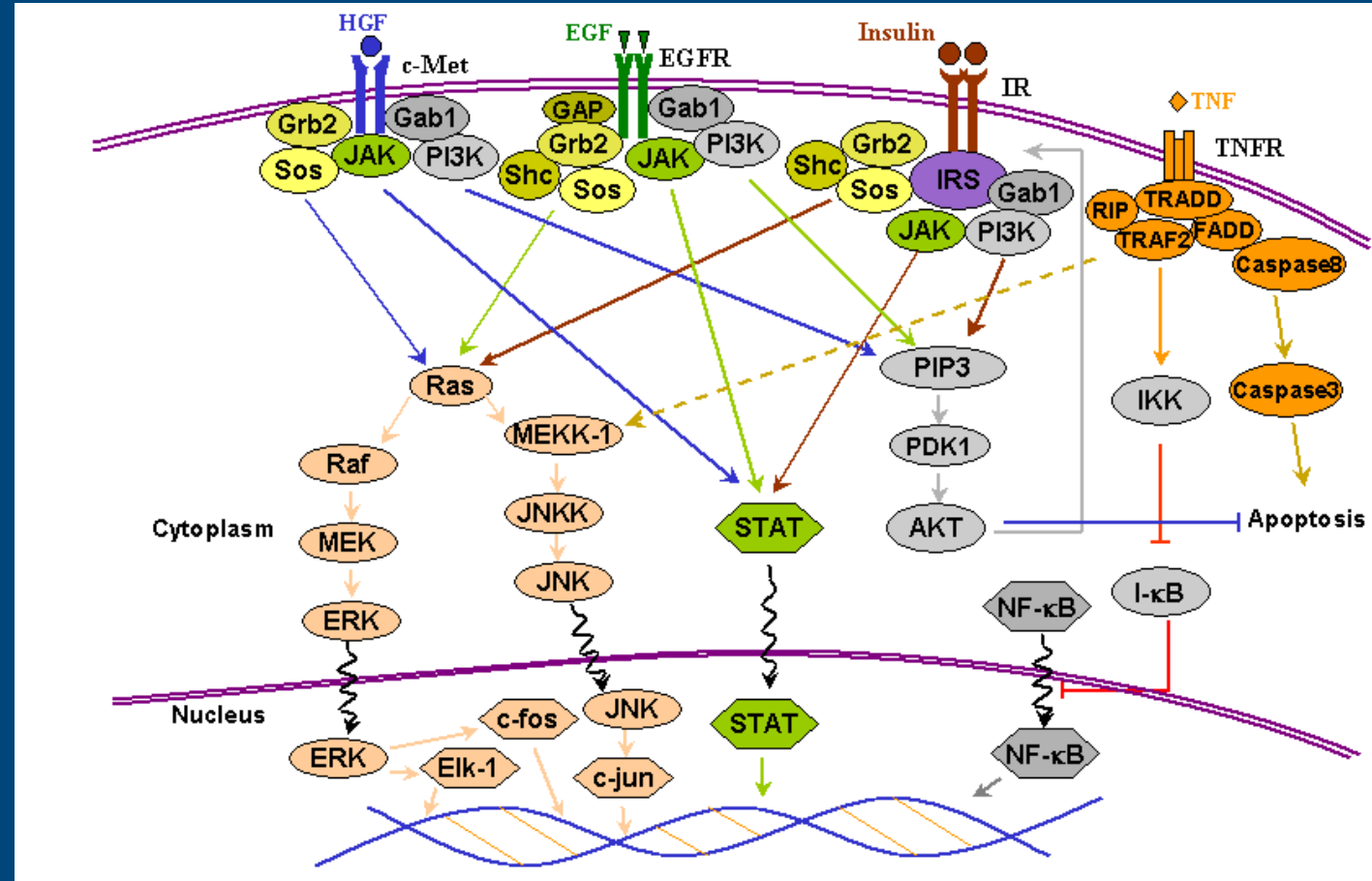
Genexpressie

⇒Stabiliteit!

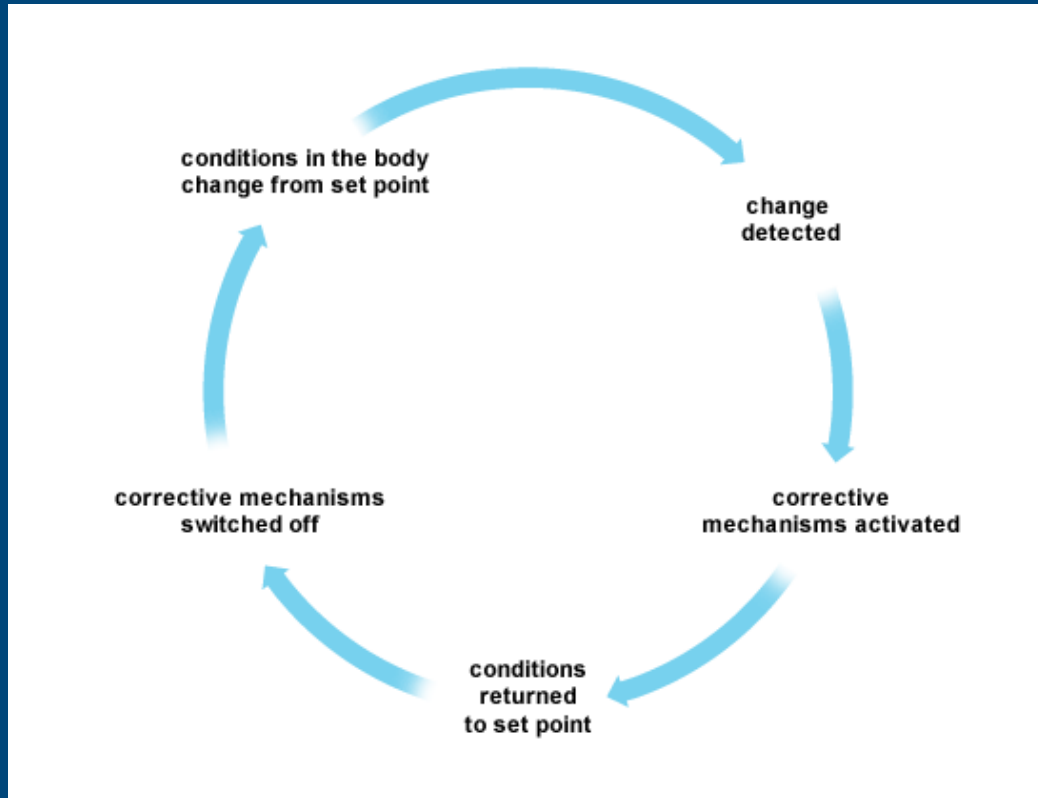
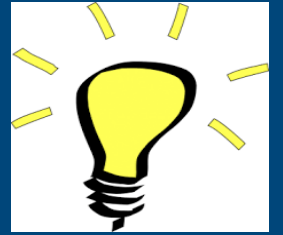
Als 1 signaal uitvalt kunnen anderen dit compenseren

(Redundancy)

Feedback op elk niveau



Celbio 4: Feedback is continuous



For example: Biological clock, or Nerve cell firing, where input generates output, which generates input, which generates output...

Analogie is een stad:

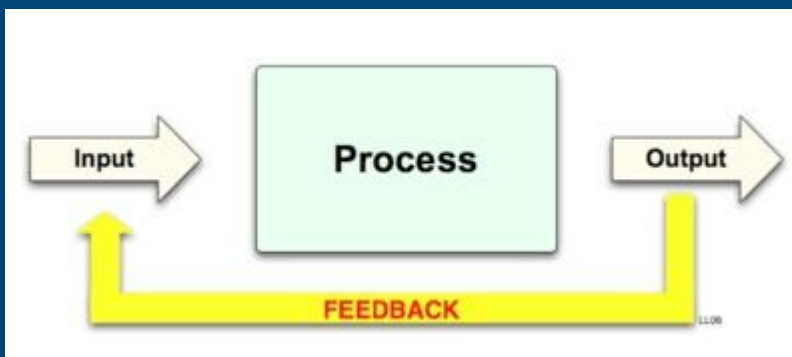
Beetje centrale aansturing maar eigenlijk gevolg van activiteit van individuele onderdelen.

Bottom-up ipv top-down (vgl spons)

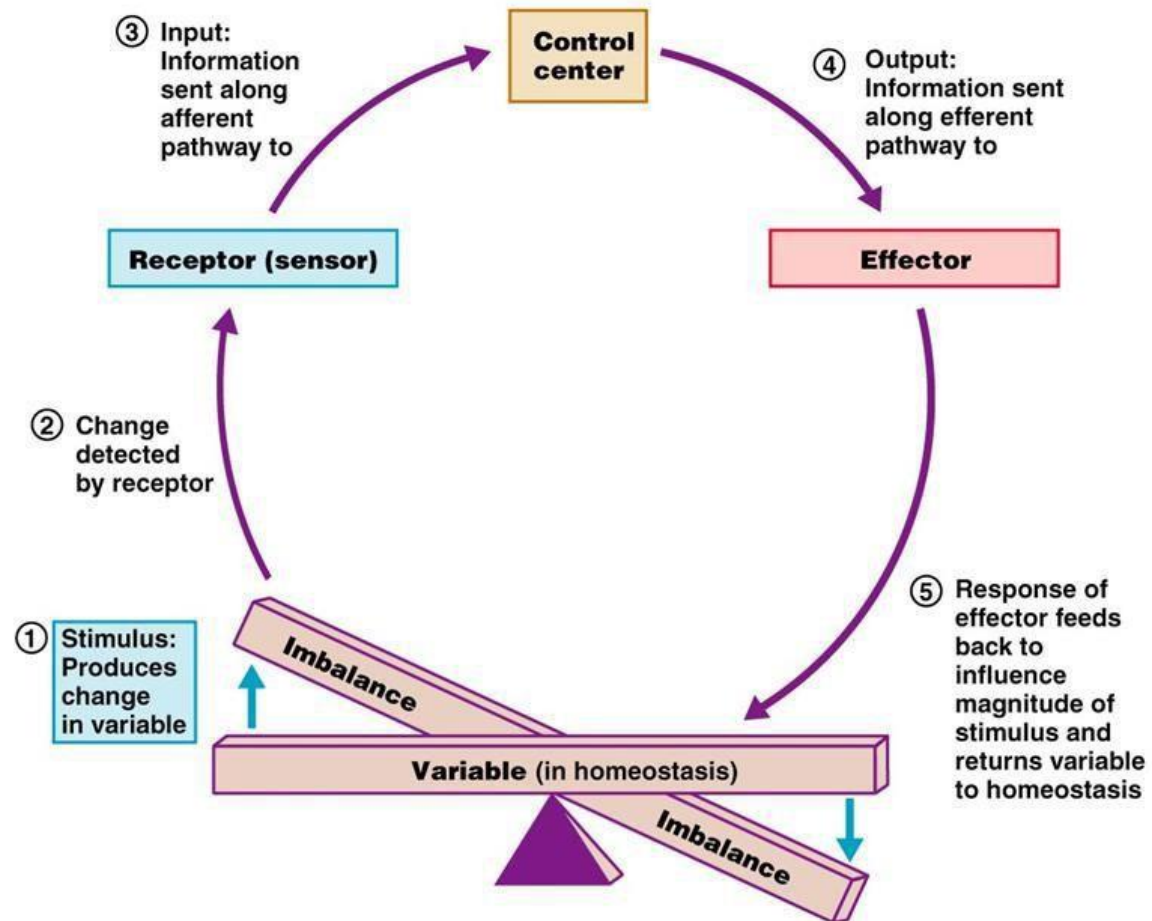
En, er is altijd iets dat het evenwicht verstoord (al is het maar entropie), dus er is continue correctie

Behoud van ordening mbv feedback (kost energie).
Proces is metastabiel, maar bestaat al 4 miljard jaar

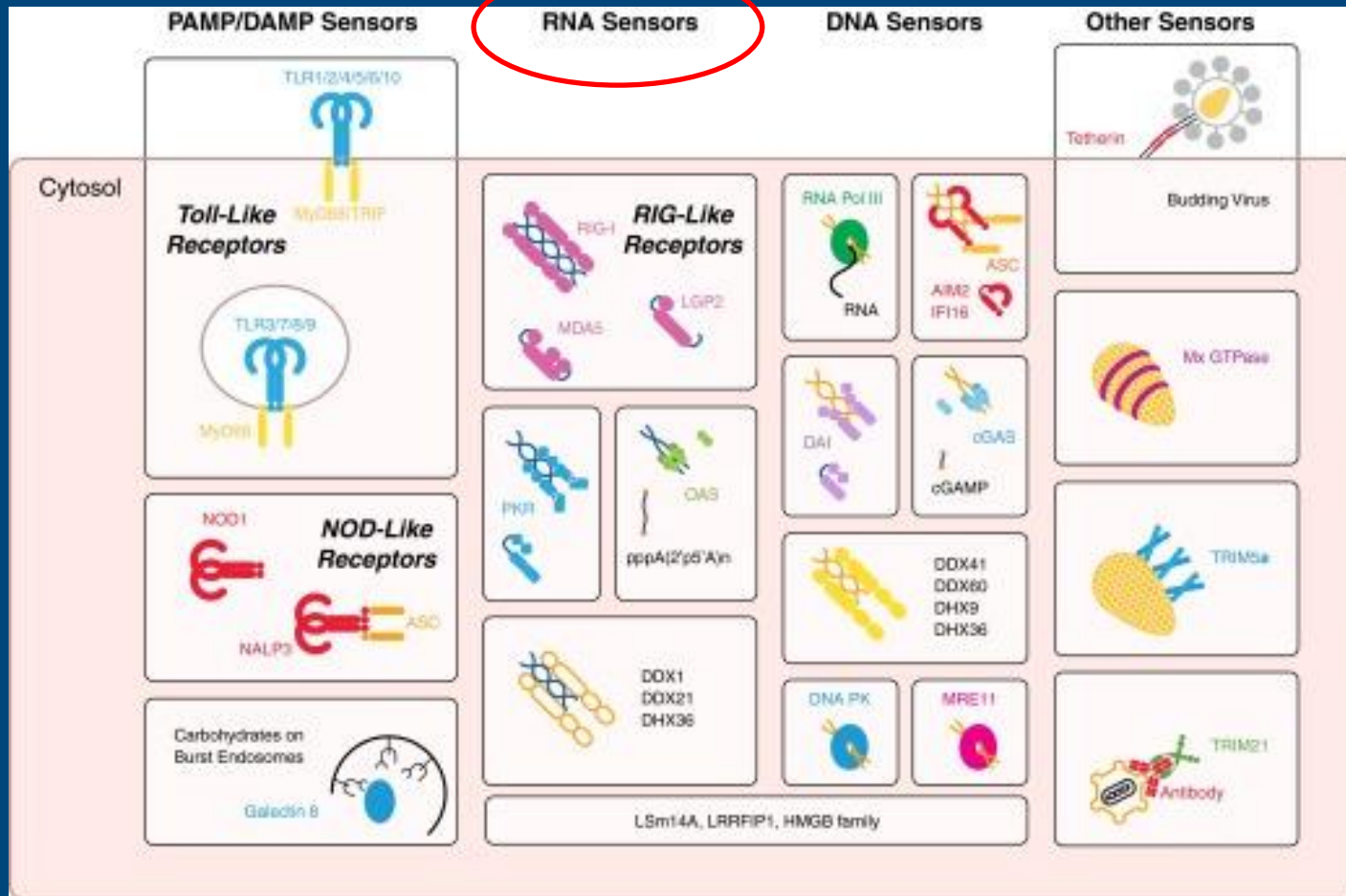
https://www.youtube.com/watch?v=AZUeKoD_3y0



Feedback en Homeostase

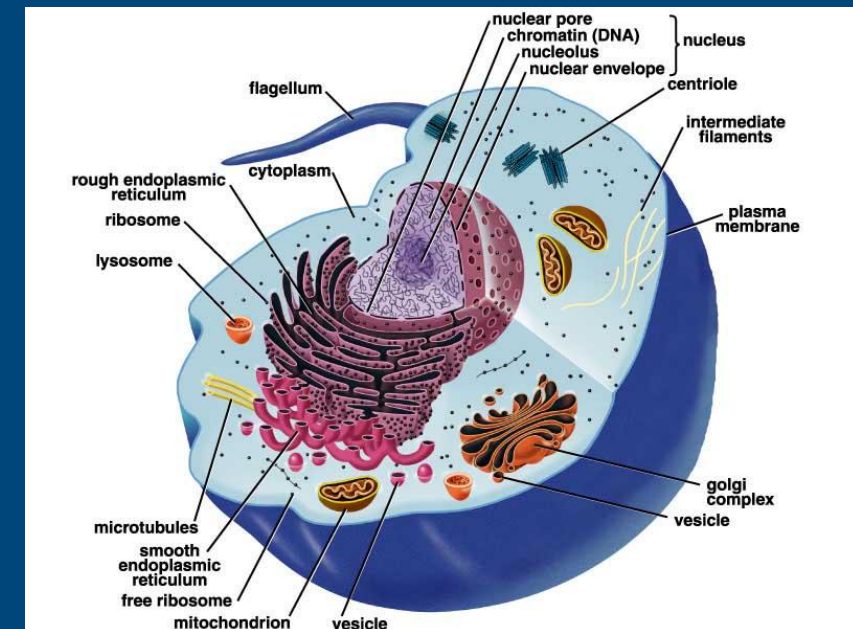


Intracellulaire afweer: interferon => aspecifiek!



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

RNA komt in het cytoplasma normaal niet voor => virus!



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

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

Kanker:



Etymologie:

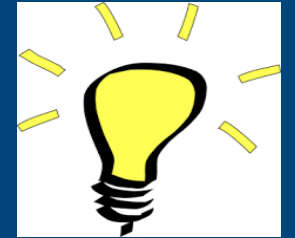
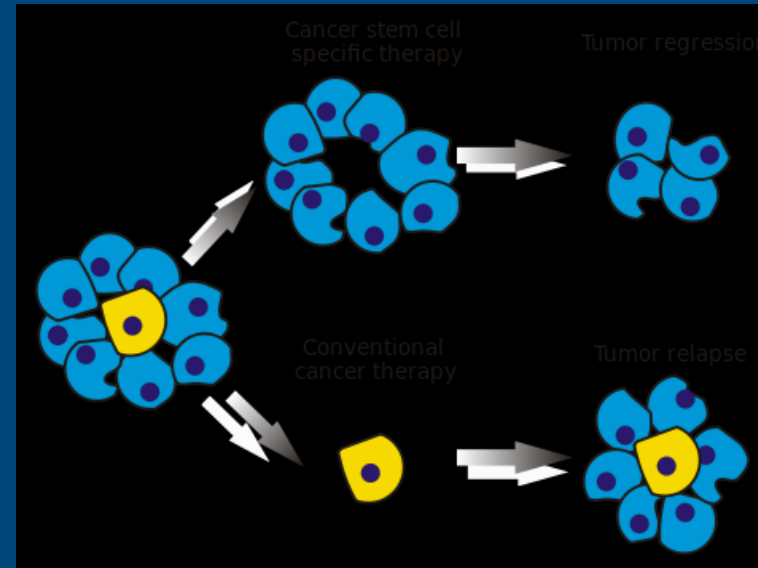
Het woord "kanker" is afgeleid van het Latijnse woord "cancer", dat kankergezwel" betekende. Deze naam is waarschijnlijk bedacht door Hippocrates rond 400 voor Christus. Hij gebruikte "cancer" als leenvertaling voor het Griekse woord 'karkínos', dat oorspronkelijk "krab" betekende.^[2] Een tumor deed hem denken aan een in het zand ingegraven krab, die ook bestond uit een hard centrum met zachte uitlopers (poten). Hippocrates gebruikte de term nog als paraplubegrip voor elk mogelijk gezwel,^[2] maar tegenwoordig wordt het woord alleen gebruikt om ziektes aan te duiden waar sprake is van een ongeremde celdeling.

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

Cancer stem cells

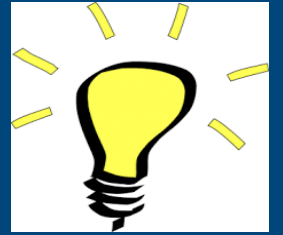
Cancer stem cells (CSCs) are cancer cells (found within tumors or hematological cancers) that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. CSCs are therefore tumorigenic (tumor-forming), perhaps in contrast to other non-tumorigenic cancer cells.^[1] CSCs may generate tumors through the stem cell processes of self-renewal and differentiation into multiple cell types. Such cells are hypothesized to persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors. Therefore, development of specific therapies targeted at CSCs holds hope for improvement of survival and quality of life of cancer patients, especially for patients with metastatic disease.

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



College 4

Biotechnologie.



DNA/RNA-technologie

=> Gentherapie/mRNA therapie

Afweersysteem

=> Immunotherapie

Stamcellen

=> Stamceltherapie

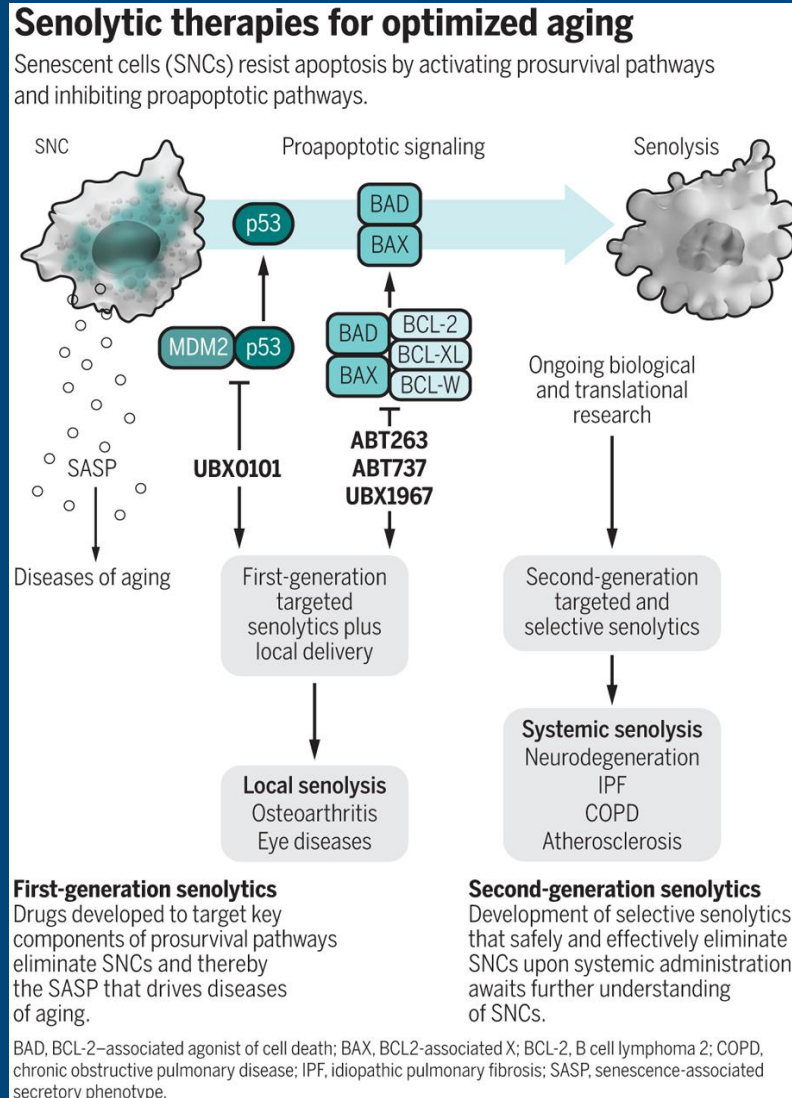
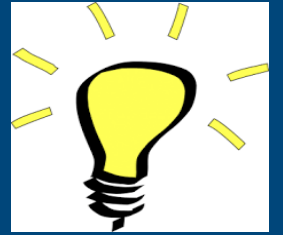
Cybernetica

=> Verbeteren (integratie technologie en biologie)

Synthetic biology

=> Wat is leven?

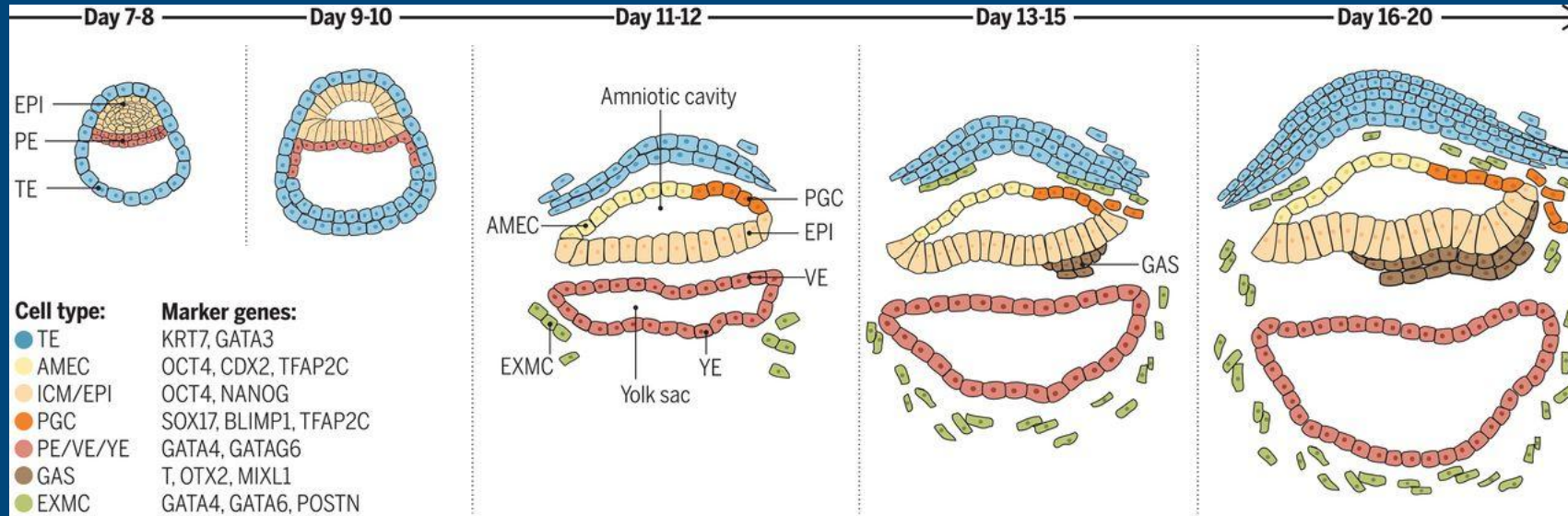
Senolytic therapies for healthy longevity



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 aging-associated 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>

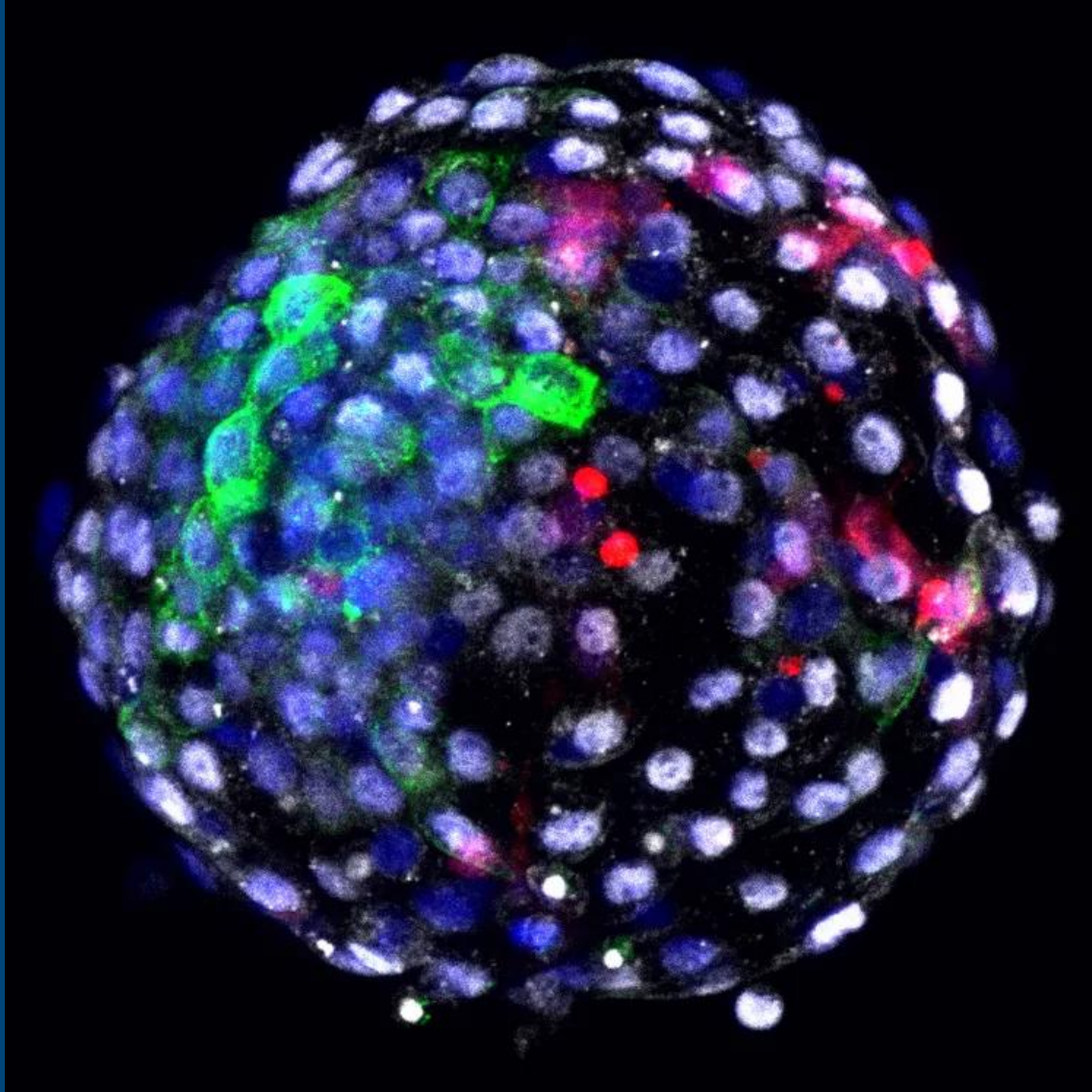
Monkey embryos cultured in vitro recapitulate primate postimplantation embryogenesis in vivo. => culture beyond 14 days



- 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>

Hybrid embryo.

First monkey embryos containing human cells.

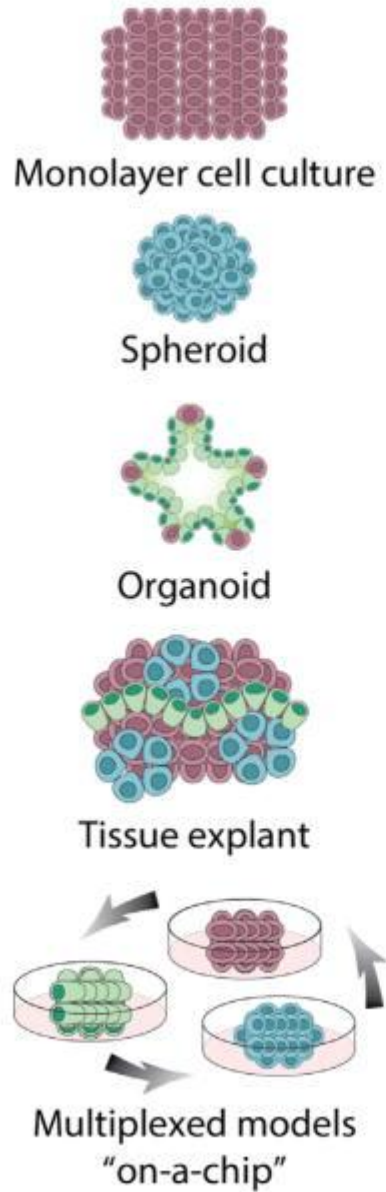


Toepassingen om onderzoek te verbeteren leiden tot methoden die **ethische grenzen** raken.

En ethiek veranderen?



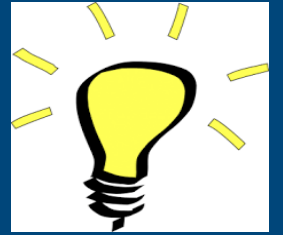
Model systems in life sciences



Organization of the body

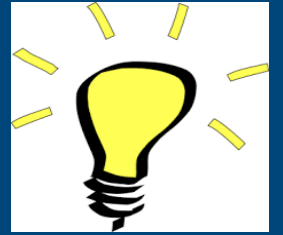


Tissue-engineering kan op elk niveau

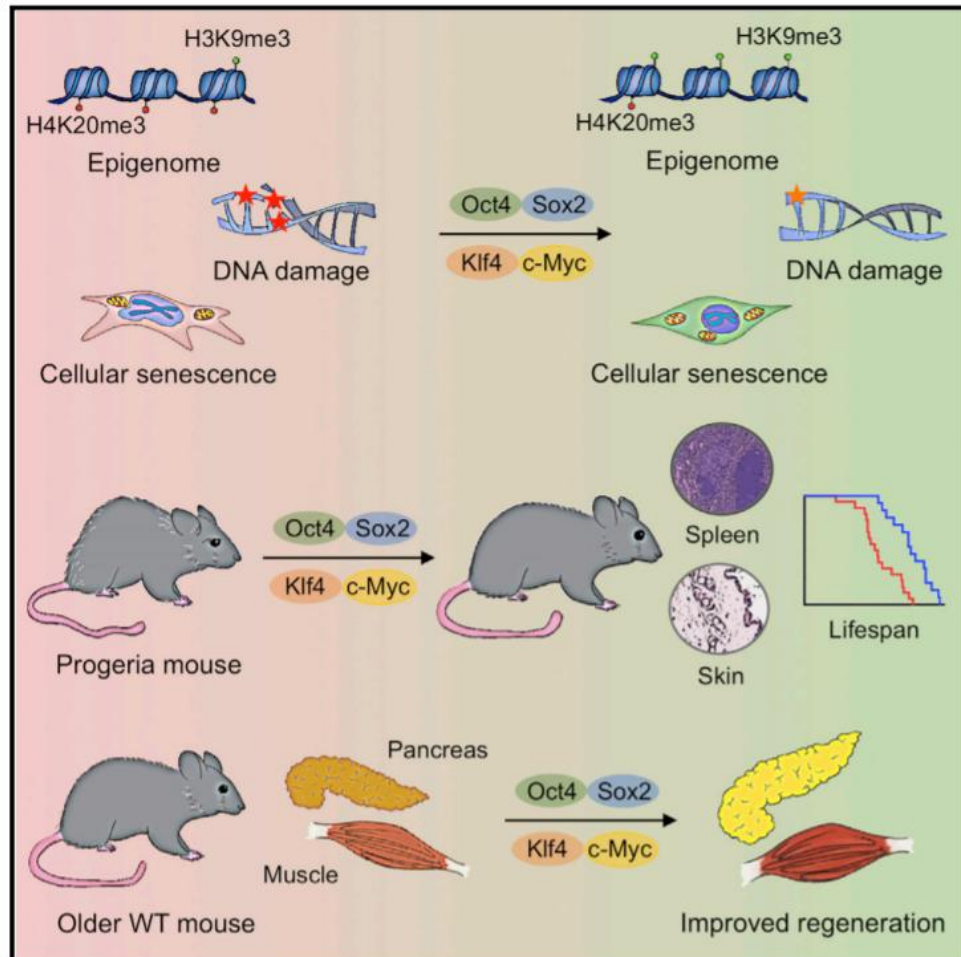


<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4728053/>

In Vivo Amelioration of Age-Associated Hallmarks by **Partial** Reprogramming



Graphical Abstract



Authors

Alejandro Ocampo, Pradeep Reddy,
Paloma Martinez-Redondo, ...,
Isabel Guillen, Pedro Guillen,
Juan Carlos Izpisua Belmonte

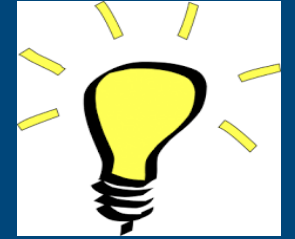
Correspondence

belmonte@salk.edu

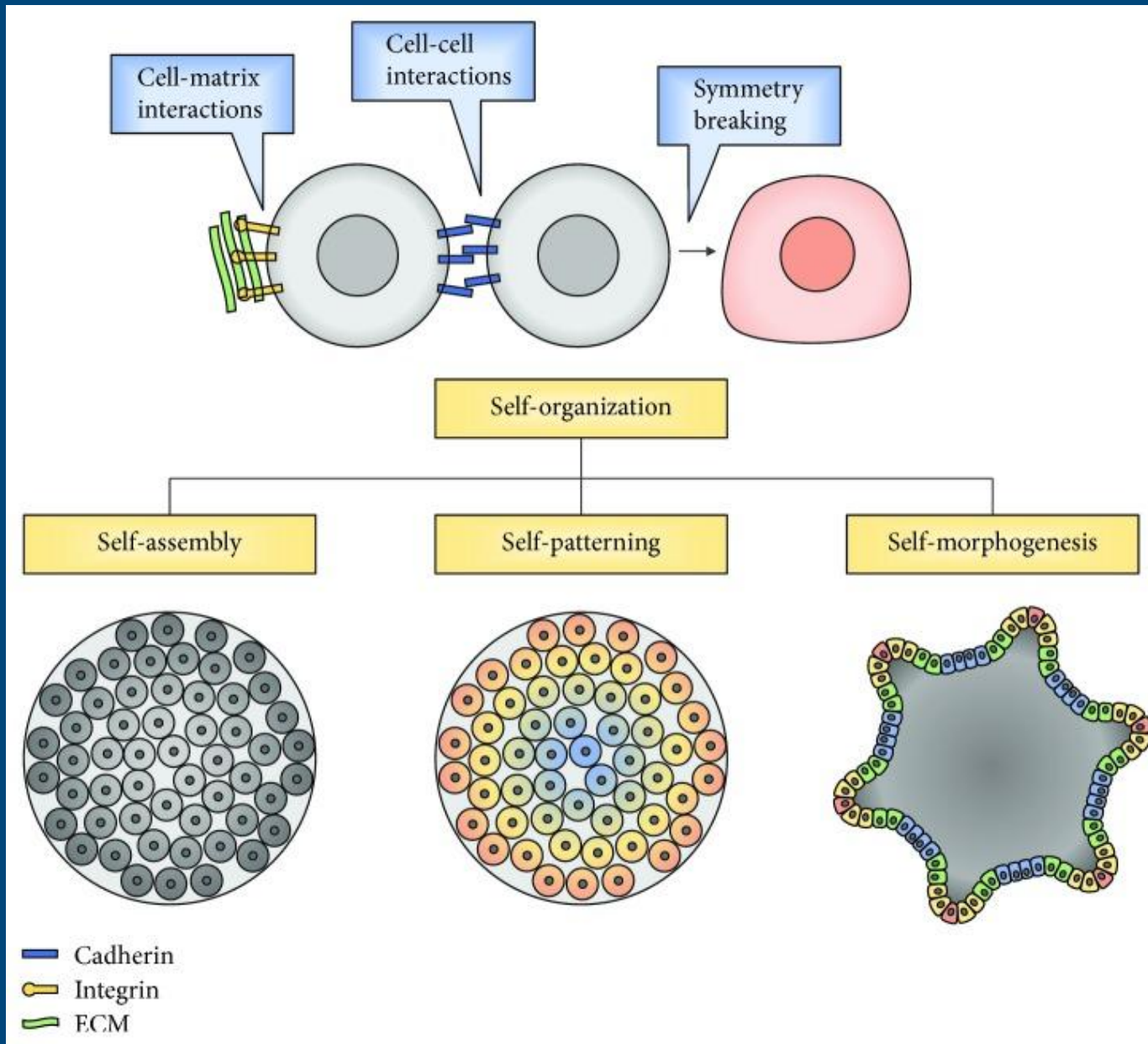
In Brief

Cellular reprogramming by transient expression of Yamanaka factors ameliorates age-associated symptoms, prolongs lifespan in progeroid mice, and improves tissue homeostasis in older mice.

Organoids and self-organisation



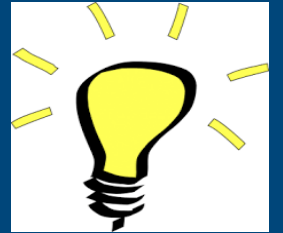
=> Life is self organizing



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6501244/>
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6784492/>

Leven is..

- Een informatie systeem
- Manipuleerbaar met informatietechnologie
- Individuele processen kunnen ook buiten een levend systeem plaatsvinden
- Modulair
- Self-organizing



College 4

Biotechnologie.



DNA/RNA-technologie

=> Gentherapie/mRNA therapie

Afweersysteem

=> Immunotherapie

Stamcellen

=> Stamceltherapie

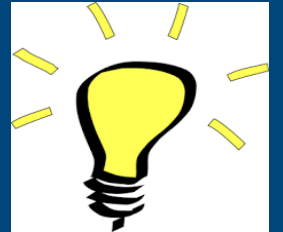
Cybernetica

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=> Wat is leven?

Celbio 3: De zenuwcel

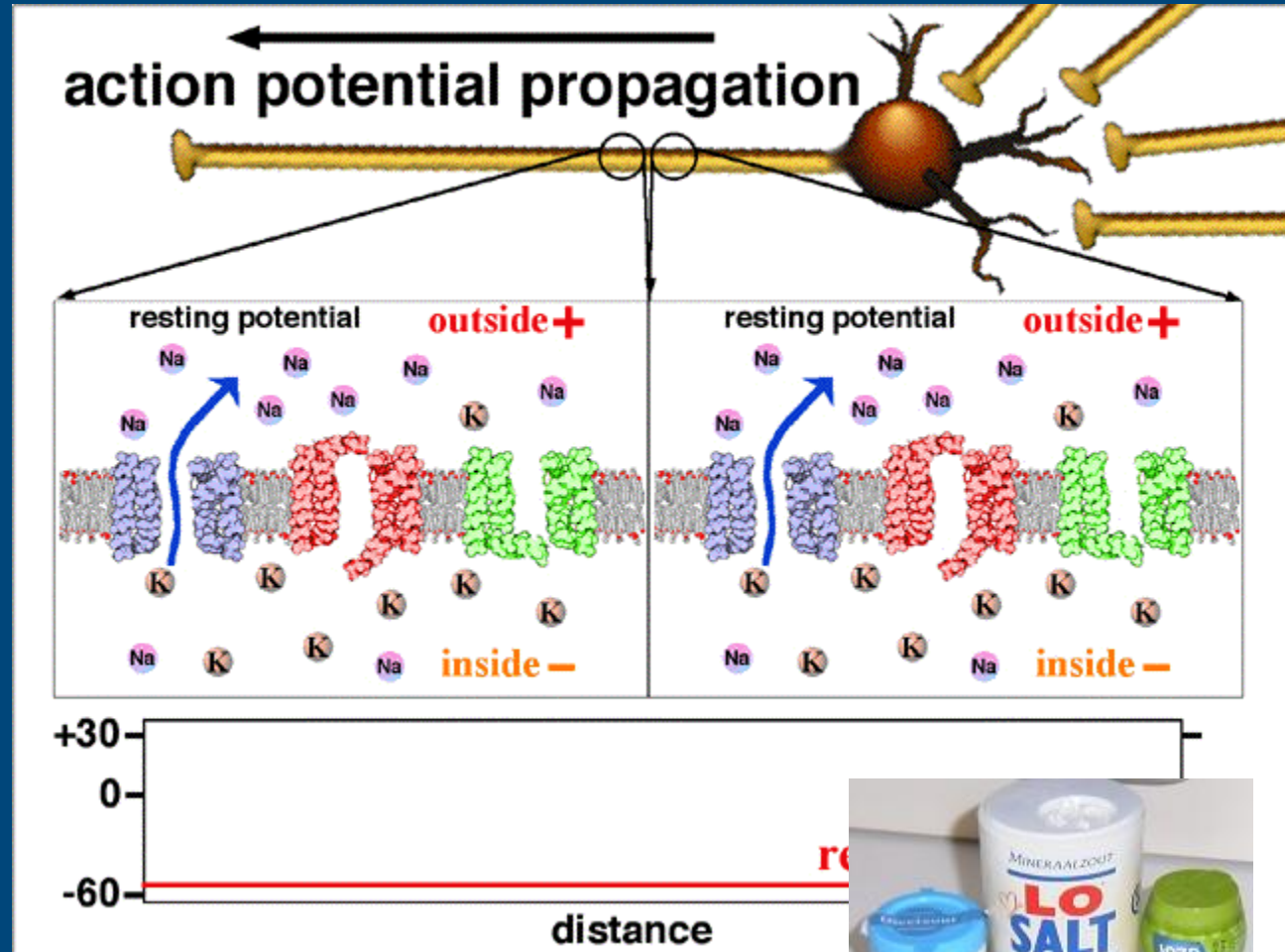


Gemiddelde zenuwcel vuurt ongeveer 10x per seconde, (x86miljard).

Meeste neuronen vuren continue, ook al “denk” je nergens aan!

Maar vooral het patroon van vuren (actiepotentialen) is belangrijk.

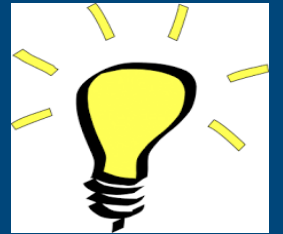
Lokale depolarisatie leidt tot depolarisatie verderop via “Voltage gated **ion channels**” (=> stuwt zichzelf voort)



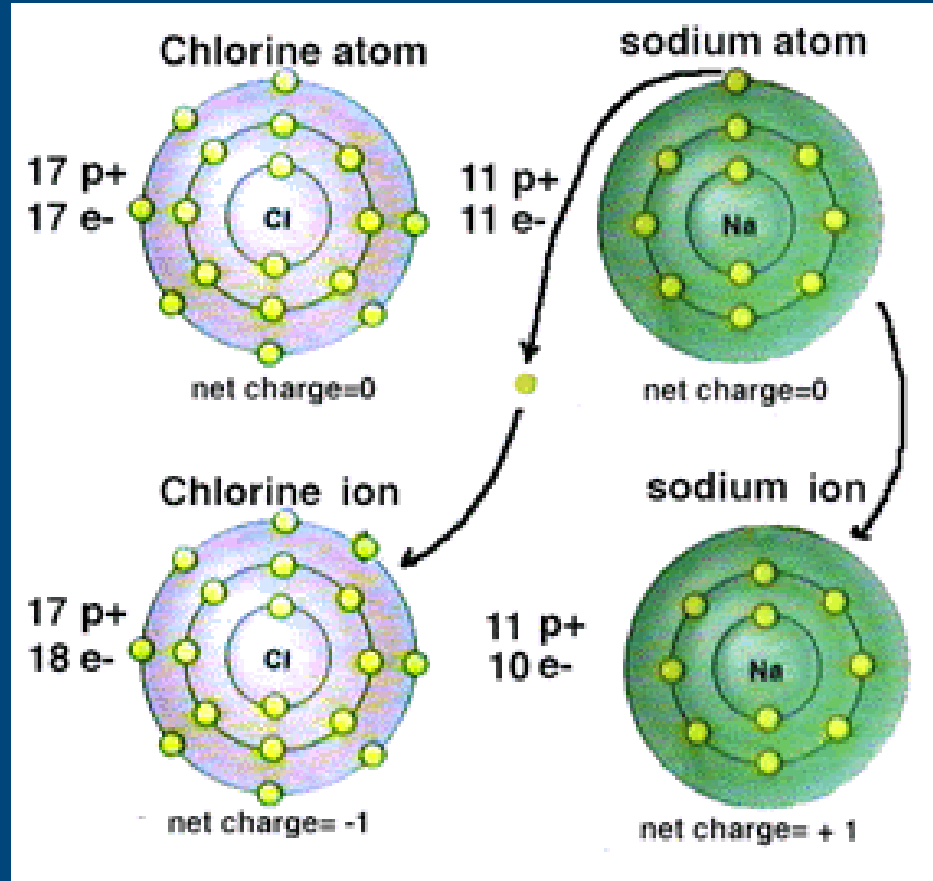
Elektriciteit op basis van ionen, zoals K⁺

Celbio:

Ionen

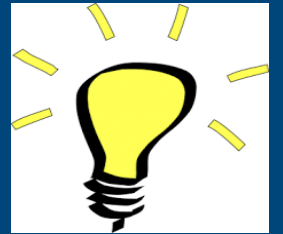


- Chloor heeft 1 elektron te weinig en Natrium 1 elektron teveel, in de buitenste schil
- Komen het liefst voor als Cl^- en Na^+ => ion => **netto lading**
- En bij elkaar is alles OK => (keuken)zout
- Er zijn ook 2- en 3- voudige ionen



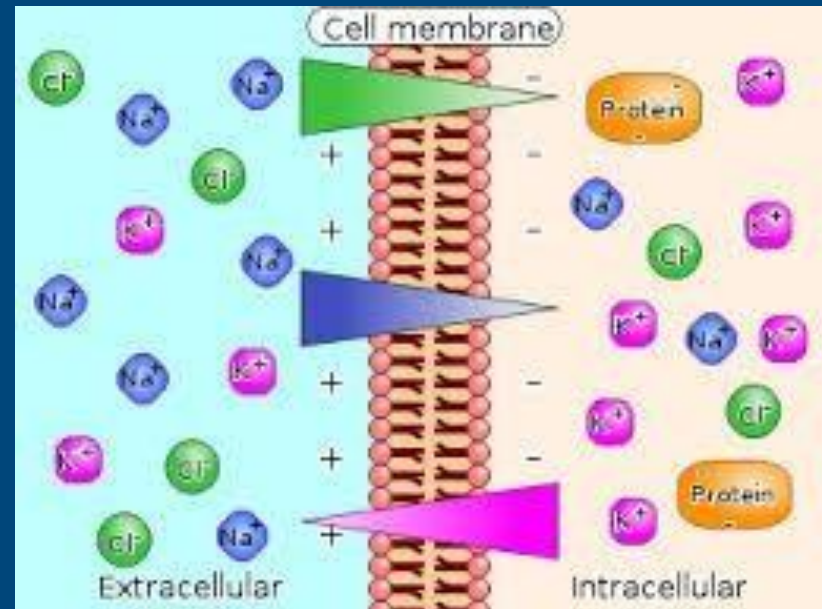
Celbio:

Celmembraan en ionen



- All cells are **polarized**, which means the concentrations of charged atoms, called ions, of the fluid inside them is different from the fluid outside them. It is this difference in ion concentrations that creates a difference in charge (or voltage) across membrane. This difference – called a *membrane potential* - **allows work to be performed**.
- Stromende lading is elektriciteit
=> net als apparaat met elektronen

http://www.youtube.com/watch?feature=player_embedded&v=2YZJt_Bw3eo



The largest contributions usually come from sodium (Na^+) and chloride (Cl^-) ions which have high concentrations in the extracellular region, and potassium (K^+) ions, which have high concentrations in the intracellular region.

Biotechnologie: Precision electronics in the brain

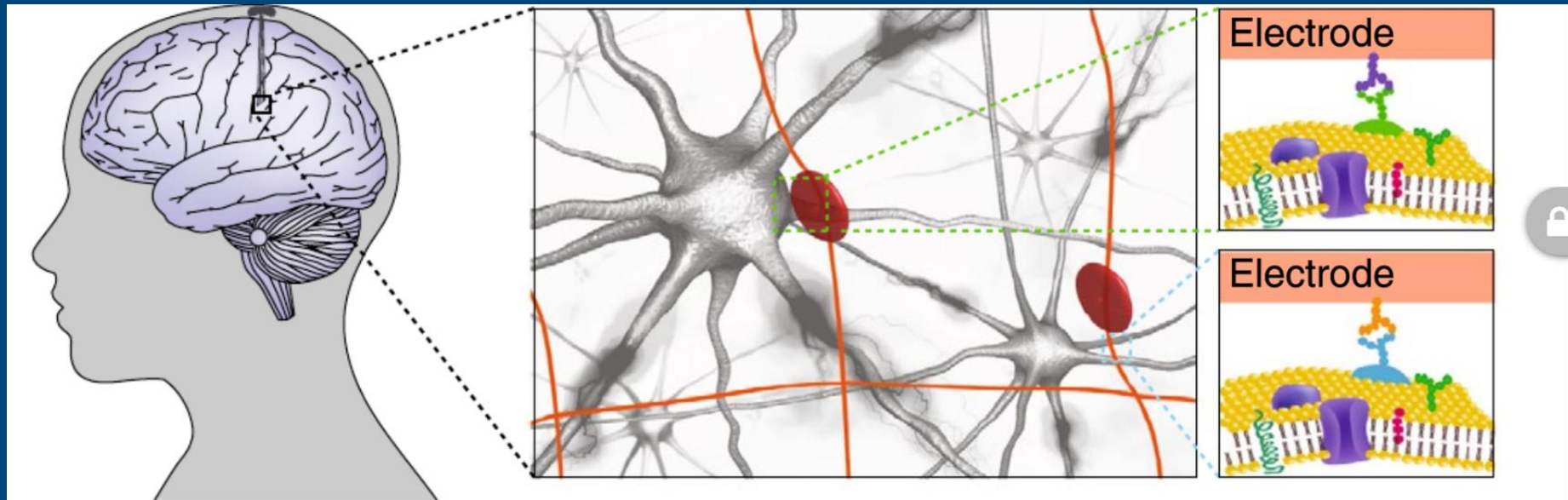
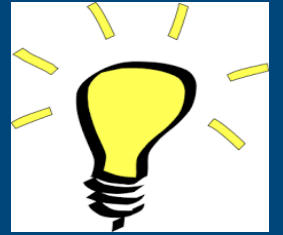
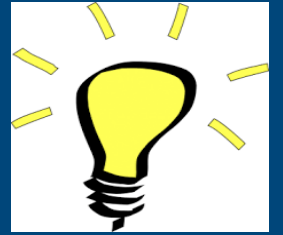


Fig. 3 | Schematic representation of syringe-injectable mesh electronic implant in a human brain. Mesh electronics directly address the structural, mechanical and topological mismatch between probe and host tissue.

<https://www.nature.com/articles/s41587-019-0234-8.epdf>

Using thought to control artificial limbs



Woman with Quadriplegia Feeds Herself Using Mind-Controlled Robot Arm | UPMC

Leerproces, voor
computer en mens.

=> Het was makkelijker
om de hersenen te laten
leren dan een machine..

<https://www.youtube.com/watch?v=76lIQtE8oDY>

<https://youtu.be/76lIQtE8oDY?t=392>

<https://www.youtube.com/watch?v=ogBX18maUiM>

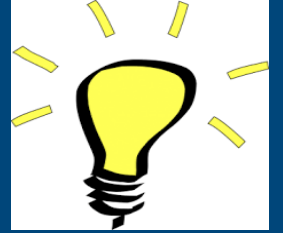
[be.com/watch?v=ogBX18maUiM](https://www.youtube.com/watch?v=ogBX18maUiM)

Mind-reading devices are revealing the brain's secrets



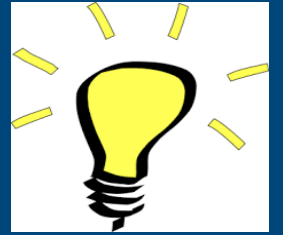
- **Implants and other technologies that decode neural activity can restore people's abilities to move and speak — and help researchers to understand how the brain works.**

Neuralink



- <https://neuralink.com/>
- ‘We weten he-le-maal niets’ van Neuralink, het hersenimplantaat van Elon Musk
- Al sinds januari zou een patiënt een hersenimplantaat hebben van Elon Musks bedrijf Neuralink. Maar hij brengt geen enkel detail naar buiten.
- 28 februari 2024

Cybernetica

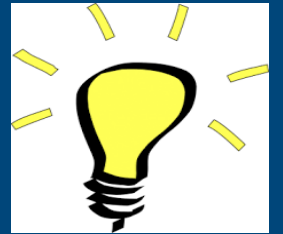


=> Verbinden biologie en technologie

- Bril (al 700 jaar)
- Pacemaker (al 70 jaar)
- Kunstarm
- Telefoon
- AI ?
- Cyborg ?

=> niets nieuws?

We are already cyborgs



- Telefoon

Elon Musk

"People don't realize — we are already a cyborg because we are so well integrated with our phones and our computers. The phone is almost like an extension of yourself. **If you forget your phone, it's like a missing limb.**

=> Co-evolutie met onze technologie!

=> Outsourcing geheugen

NB Vuur: How cooking made us human



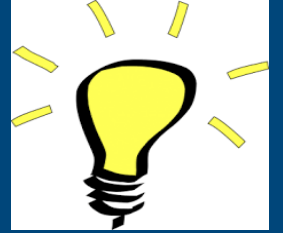
Exoskeleton boots **improve on evolution**

Unpowered mechanical design lowers the energetic costs of walking.

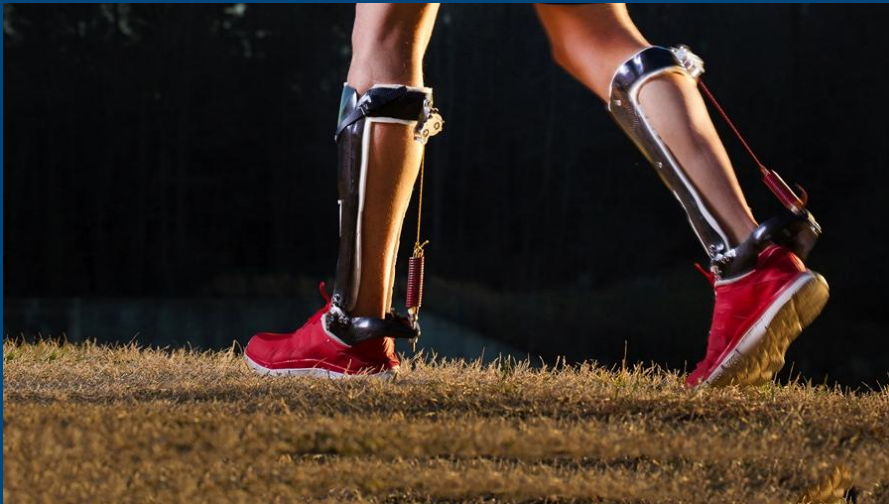


Low tech

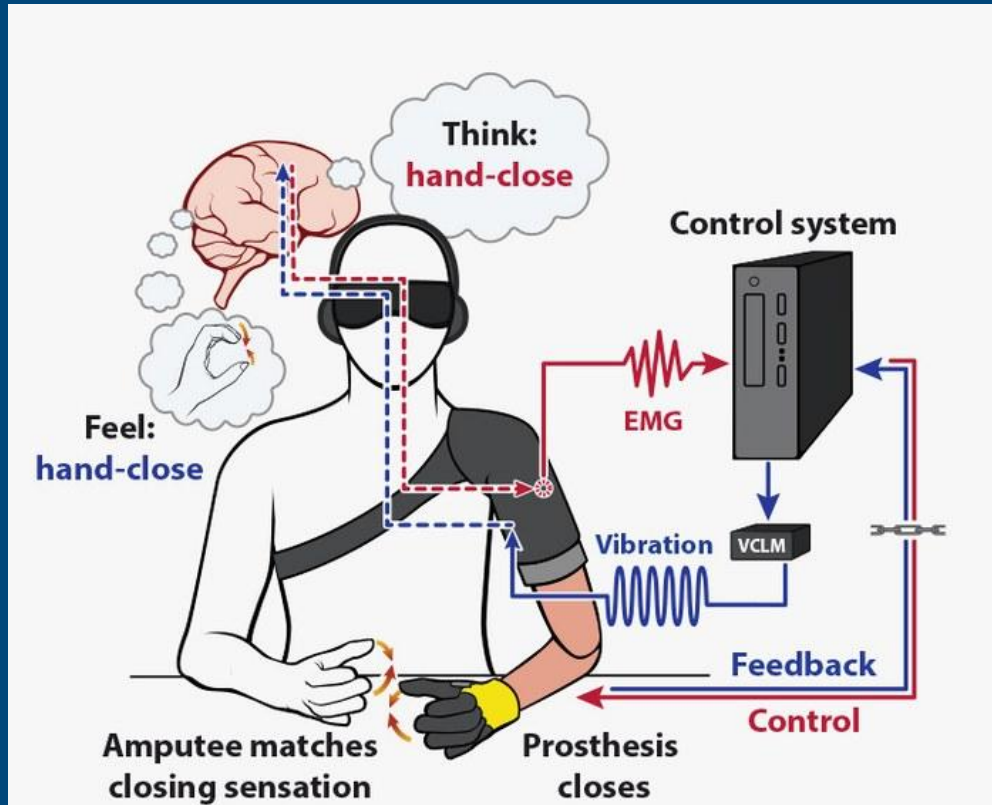
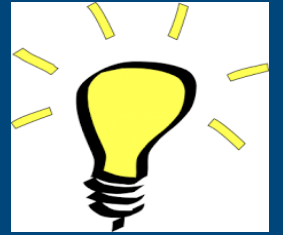
Exoskeleton to ensure an active old age



October 14, 2015
Aalborg University
Researchers are creating portable robot skeletons for the elderly so they can continue to be active longer. **Think of it as a tool**, not as a robot, says researcher.



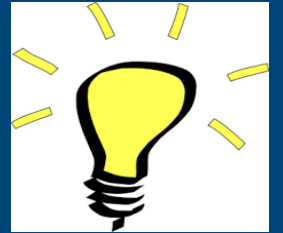
RESTORING FEELING TO LOST LIMBS



<https://www.wired.com/story/researchers-restore-feeling-to-lost-limbskinda/>

- Neural interface that mimics **kinesthetic feedback** via a prosthesis, restoring the sense in test subjects with upper limb amputations
- The method hinges on an extraordinary phenomenon that neurophysiologists call vibration-induced kinesthetic illusions: Vibrating a tendon at a frequency between 70 and 115 Hz makes you feel like its associated joint is moving.
- These **illusions**, they're incredibly powerful," Marasco says. "They can override your sense of what's real."

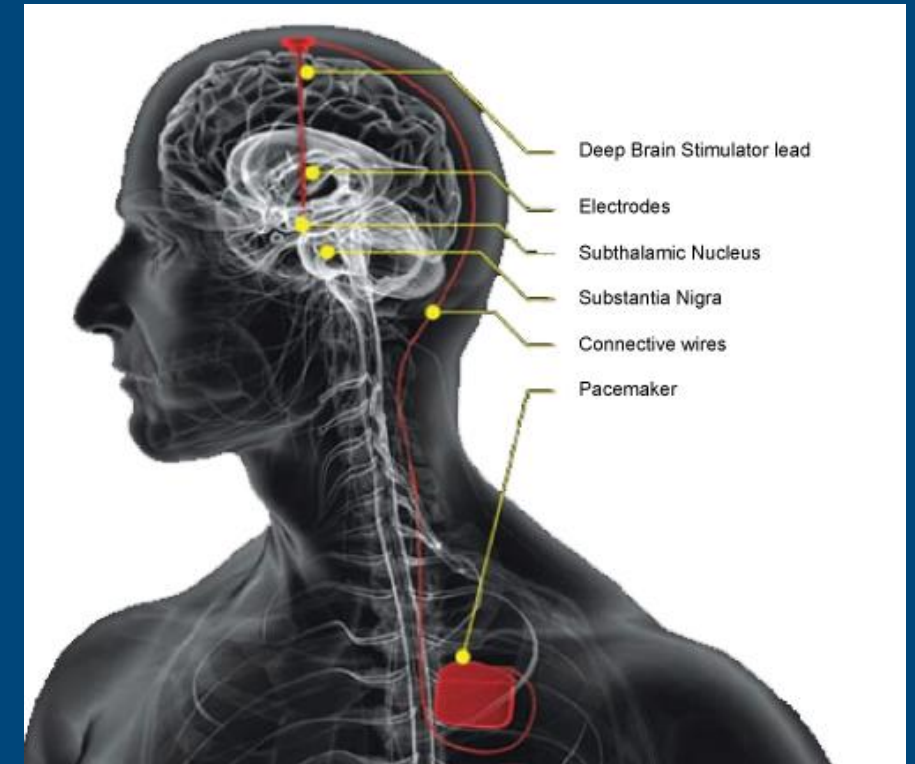
Beïnvloeden van hersenactiviteit



- **Deep brain stimulation (DBS)** is a neurosurgical procedure involving the placement of a medical device called a neurostimulator (sometimes referred to as a "brain pacemaker"), which sends electrical impulses, through implanted electrodes, to specific targets in the brain (brain nuclei) for the treatment of movement disorders, including Parkinson's disease, essential tremor, dystonia,^[1] and other conditions such as obsessive-compulsive disorder and epilepsy. While its underlying principles and mechanisms are not fully understood, DBS directly changes brain activity in a controlled manner.^{[2][3]}

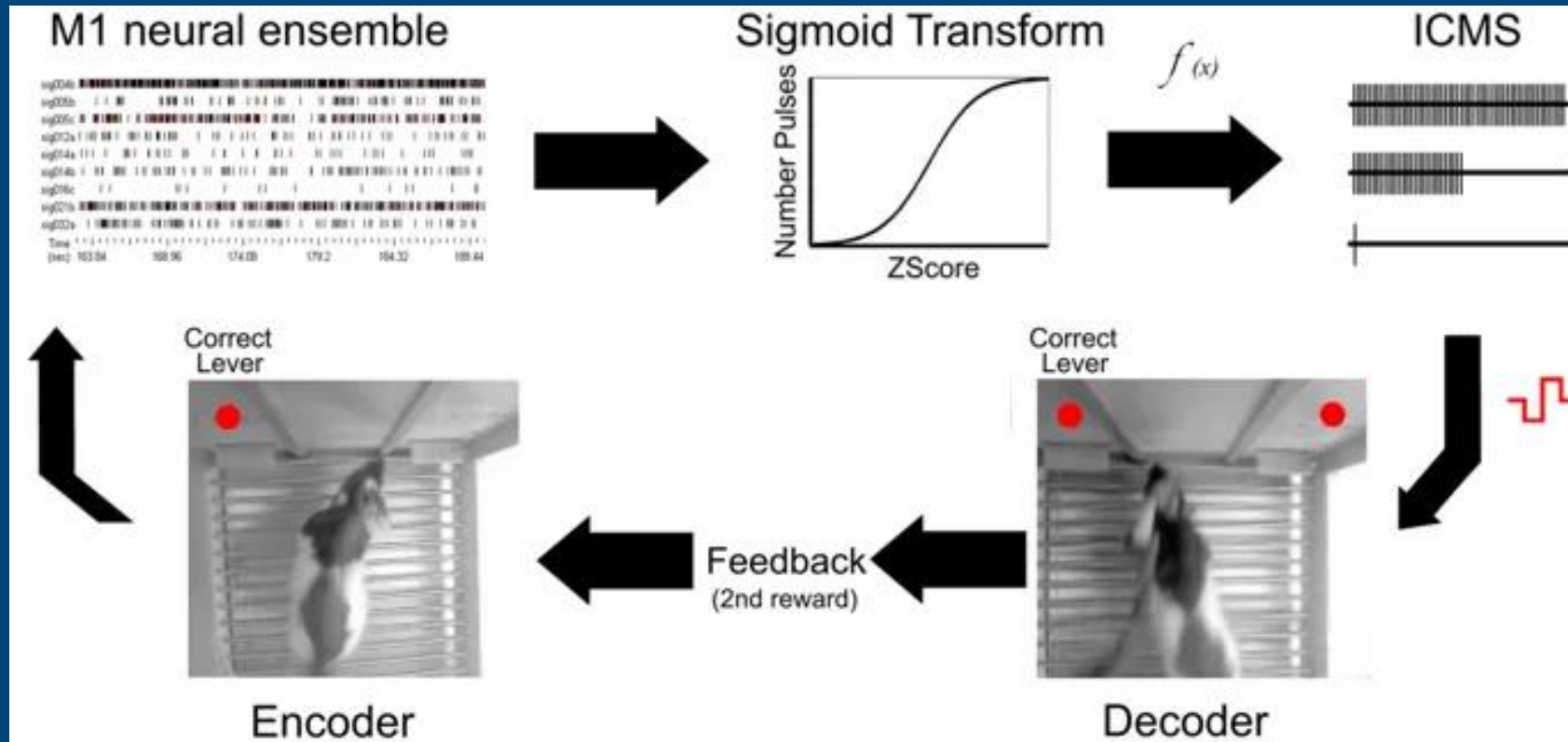
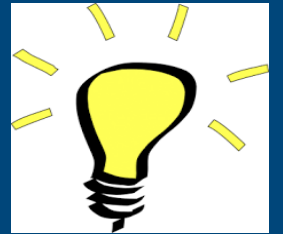
- Vgl met pacemaker voor het hart

=> communicatie = 2 kanten op



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

Biotechnologie: Gedachte transplantatie

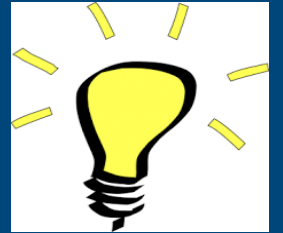


Ook hogere
hersenfuncties zijn
informatie

=> A Brain-to-Brain
Interface for Real-Time
Sharing of
Sensorimotor
Information

<http://www.nature.com/articles/srep01319>
<https://youtu.be/nNuntbrwXsM>

Uploaden



- Heel veel data
- Dynamisch (tijdsdimensie => 4D)

⇒ big tech

⇒ onsterfelijkheid

⇒ Kloon => nieuw individu?

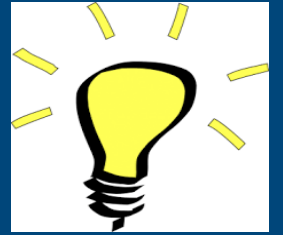
Ja, zodra die kloon zijn eigen ervaringen heeft

⇒ Avatar!

⇒ Plutarchus. Ben jij nog dezelfde persoon

⇒ Dezelfde Input => andere output => dus ander persoon

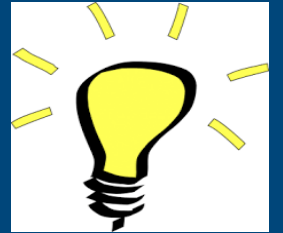
Interface kunst en echt weefsel => Biologie is informatie



Een interface zet **informatie** van het ene systeem om in begrijpelijke en herkenbare informatie van een ander systeem

Door deze kunstmatige alveesklier is Annekes leven een stuk aangenamer

NOS, 050324



- Anneke heeft diabetes, maar sinds ze gebruikmaakt van een kunstmatige alveesklier voelt ze zich stukken beter. Ze heeft meer energie en rust: "Alsof je af en toe vakantie hebt van chronisch ziek zijn."

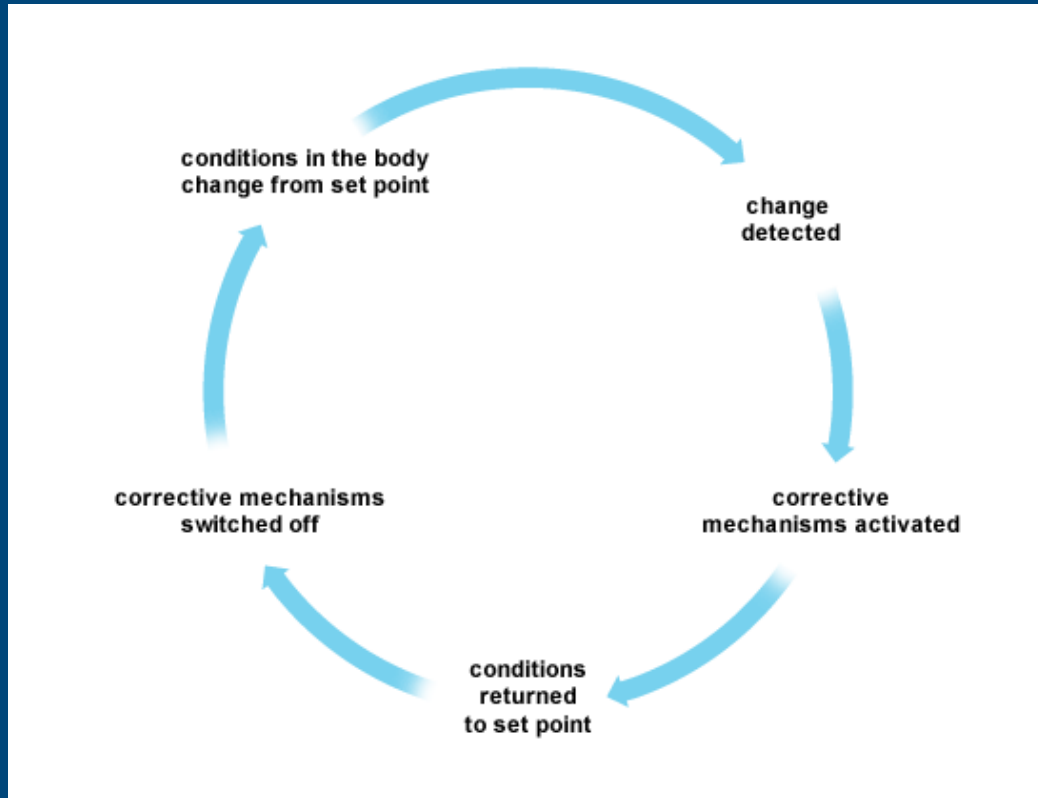
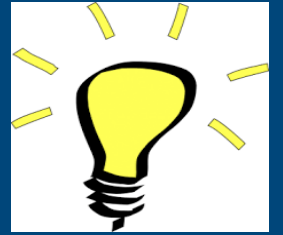
=> verbeterde interface

=> minder zelf doen, betere kwaliteit behandeling



- <https://nos.nl/video/2511531-door-deze-kunstmatige-alveesklier-is-annekes-leven-een-stuk-aangenamer>

Celbio 4: Feedback is continuous



For example: Biological clock, or Nerve cell firing, where input generates output, which generates input, which generates output...

Analogie is een stad:

Beetje centrale aansturing maar eigenlijk gevolg van activiteit van individuele onderdelen.

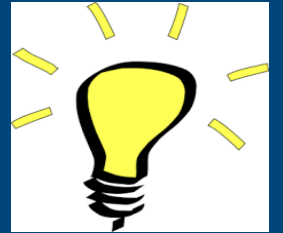
Bottom-up ipv top-down (vgl spons)

En, er is altijd iets dat het evenwicht verstoord (al is het maar entropie), dus er is continue correctie

Behoud van ordening mbv feedback (kost energie).
Proces is metastabiel, maar bestaat al 4 miljard jaar

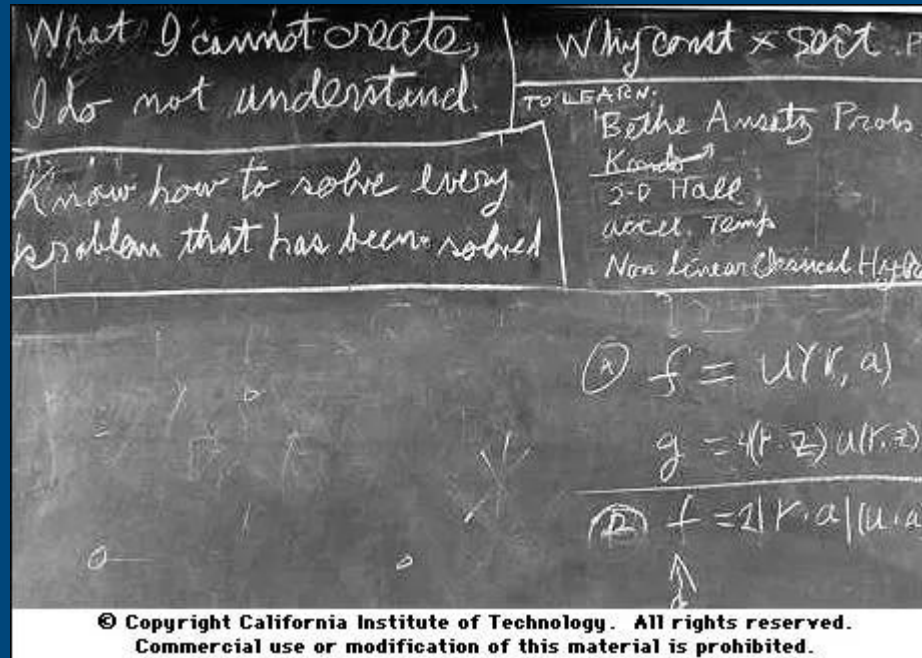
https://www.youtube.com/watch?v=AZUeKoD_3y0

HOW TO BUILD A SELF-CONSCIOUS MACHINE



Leven en bewustzijn zijn niet
alleen meer filosofisch
⇒ Spannende tijden

What I cannot create,
I do not understand.
(Richard Feynman)



- <https://www.wired.com/story/how-to-build-a-self-conscious-ai-machine/>
- <http://www.nature.com/nature/journal/v550/n7676/full/nature24270.html>

1 The accelerating pace of change ...



2 ... and exponential growth in computing power ...

Computer technology, shown here climbing dramatically by powers of 10, is now progressing more each hour than it did in its entire first 90 years

COMPUTER RANKINGS

By calculations per second per \$1,000



Analytical engine
Never fully built, Charles Babbage's invention was designed to solve computational and logical problems



Colossus
The electronic computer, with 1,500 vacuum tubes, helped the British crack German codes during WW II



UNIVAC I
The first commercially marketed computer, used to tabulate the U.S. Census, occupied 943 cu. ft.

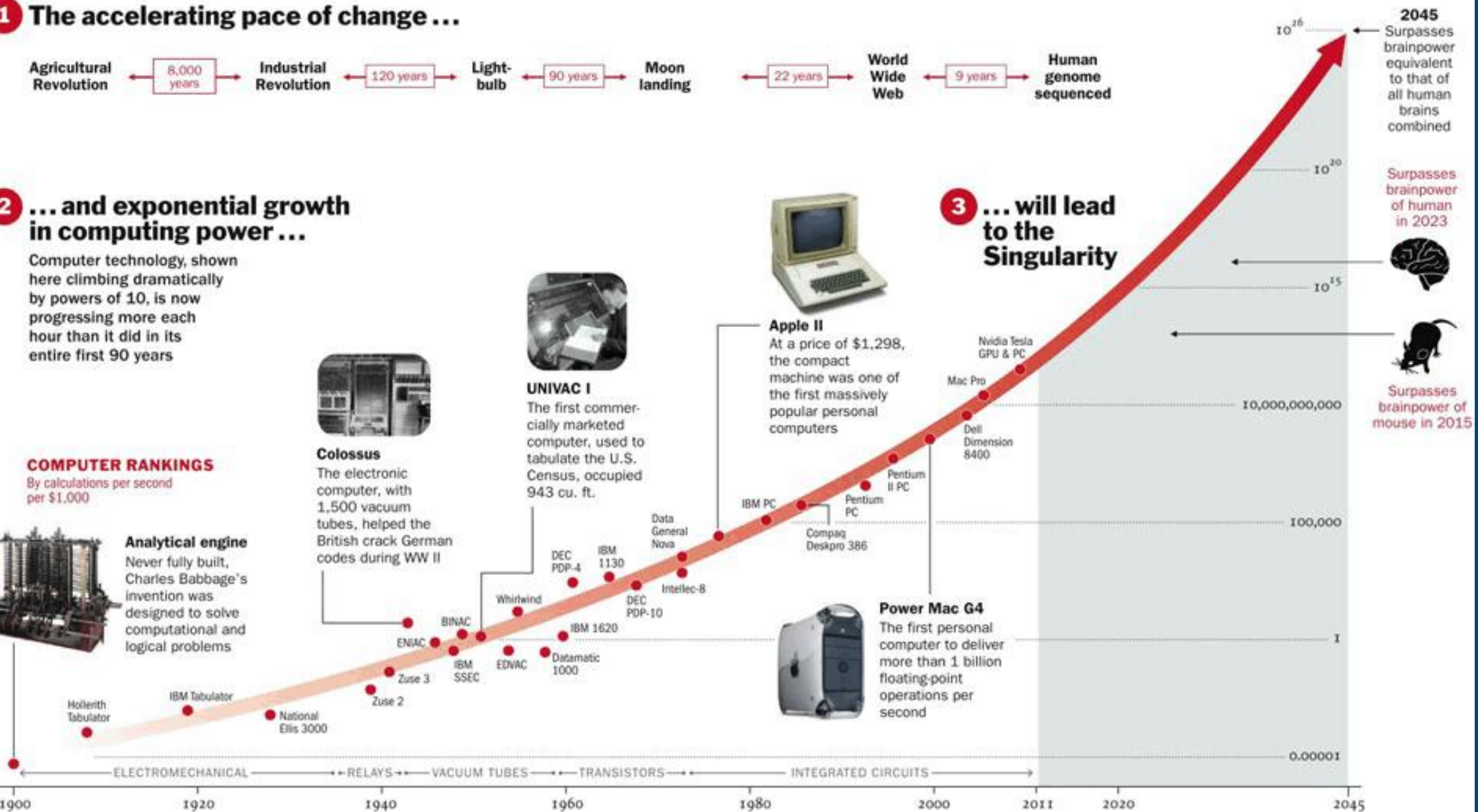


Apple II
At a price of \$1,298, the compact machine was one of the first massively popular personal computers

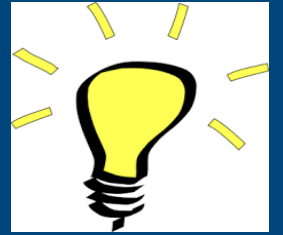


Power Mac G4
The first personal computer to deliver more than 1 billion floating-point operations per second

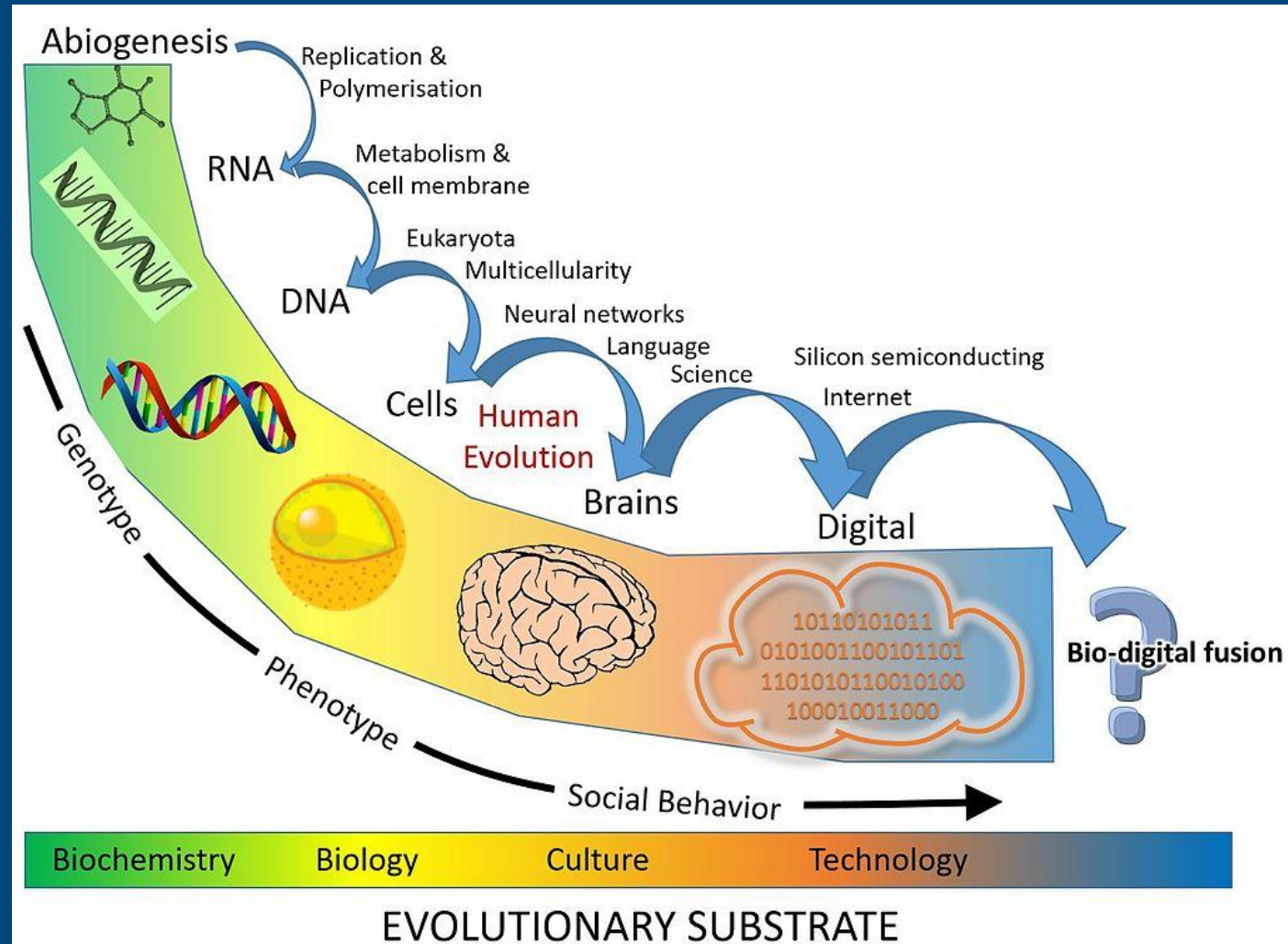
3 ... will lead to the Singularity



Evolution of Information



- https://en.wikipedia.org/wiki/Technological_singularity



based on: Gillings, M. R., Hilbert, M., & Kemp, D. J. (2016). Information in the Biosphere: Biological and Digital Worlds. *Trends in Ecology & Evolution*, 31(3), 180–189. <http://escholarship.org/uc/item/38f4b791>

Biotechnologie: Leven (intelligentie/bewustzijn) namaken, en dan **verbeteren**

Kunstmatige intelligentie (AI):

Het is al gelukt om slimmer te zijn dan sommige mensen (cambridge analytica, facebook)

Wat gaat AI ons vertellen over onszelf?

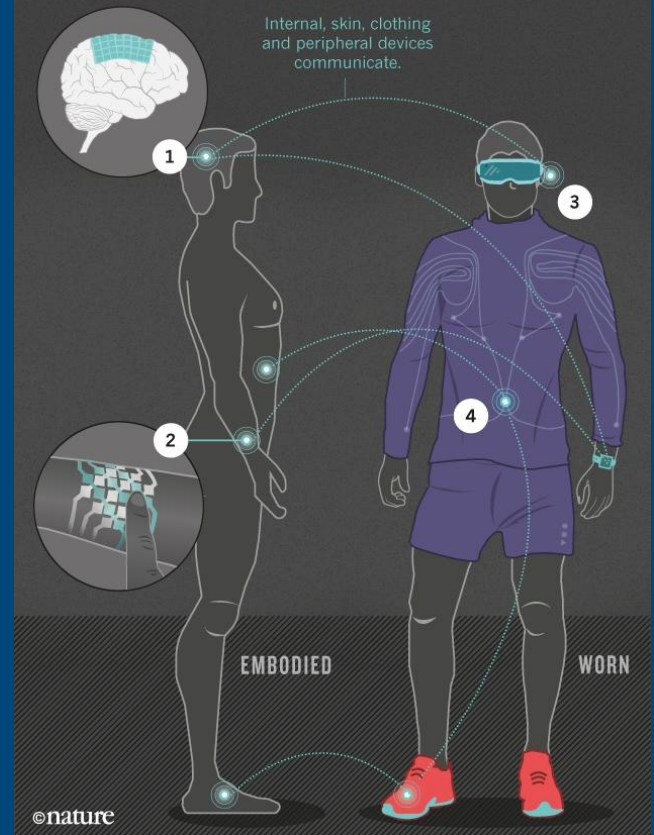
Is intelligentie gekoppeld aan bewustzijn?

Wat is goed, en wat slecht. En wie bepaalt dat

SUPERHUMAN POWERS

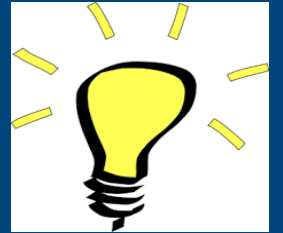
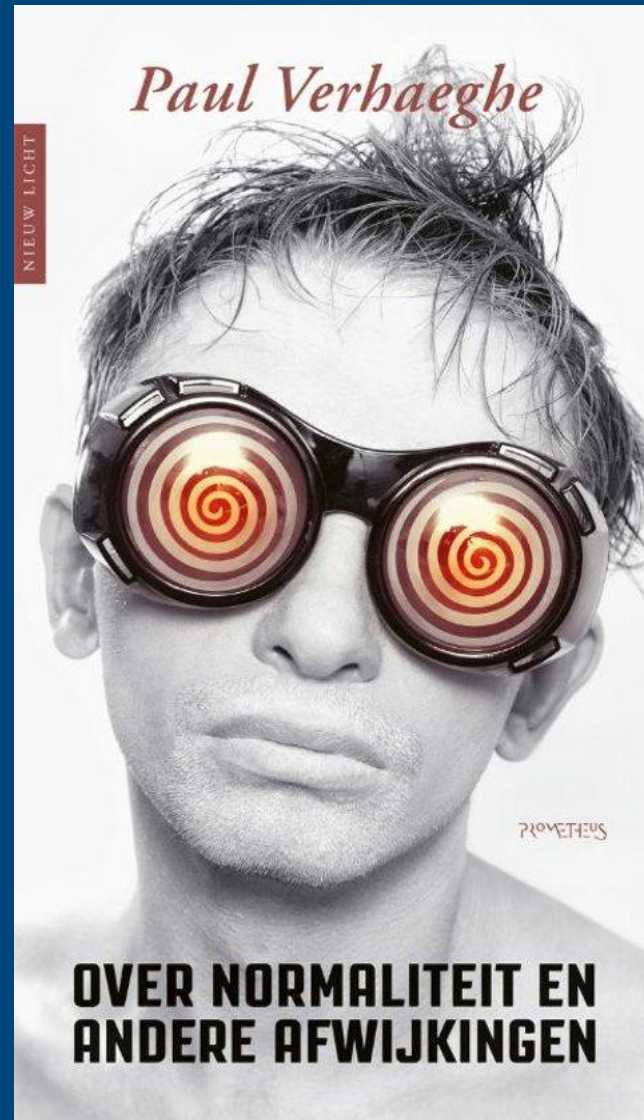
Electronics that can stretch (elastronics), from circuits and batteries to sensors and screens, will extend our senses and abilities. Devices within our clothes and accessories, attached to our skin and implanted in our bodies will establish a new technology platform — the bodyNET. It will allow us to interact with digitally networked objects and individuals using our bodies, and perceive physical and biological signals that were once invisible.

- 1 IMPLANTS**
Monitor brain activity for therapy, or to control devices; blood glucose levels to manage insulin doses; or antibody levels to trigger treatment for severe allergic reactions, for example.
- 2 SKIN DEVICES**
Track biometrics such as temperature, heart rate and muscle activity. Also provide touch controls, displays and tactile feedback.
- 3 PERIPHERALS**
Include virtual- and augmented-reality glasses; smart athletic shoes that prevent injury; and other next-generation wearables that source, display and act on data from networked devices.
- 4 SMART CLOTHING HUB**
Hosts the bodyNET's central processing and power-management system, including energy harvesting, storage and distribution.

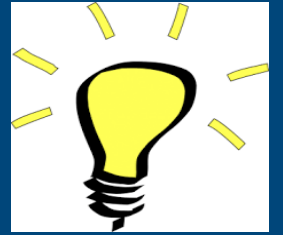



Wat is normaal ?

- Auteur: Paul Verhaeghe
- Uitgever: Prometheus
- Nederlands
- 9789044643220
- november 2019



Normaal is variabel

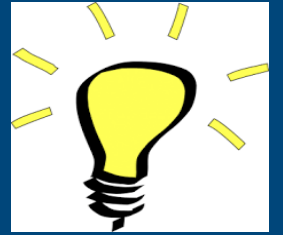


- Beter 
=> nieuwe normaal
- Normaal
- Slechter

NB Slechter dan normaal repareren is OK. Van normaal naar beter is vaak niet OK

Toch streven we allemaal naar beter (Instagram)?

Technologie en biologie



- “Verbetering” van de mens (beperkt => normaal => verbeterd)

- Lens-implantaat

=> Aandoening (staar)

=> Militair

=> Iedereen?

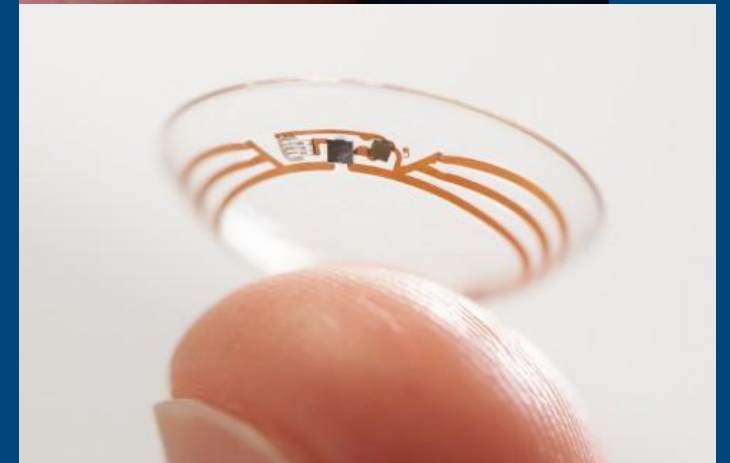
- Exoskelet

http://www.ted.com/talks/eythor_bender_demos_human_exoskeletons

- Outsourcing (geheugen) => telefoon! => verdwijnen interface

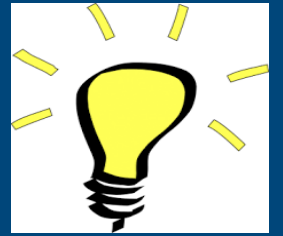
• <https://www.youtube.com/watch?v=ogBX18maUiM>

- Enhanced reality, Virtual reality



Julian Savulescu

- A professor of practical ethics at the University of Oxford, Savulescu thinks deeply about the ethics of the biological enhancement of the human race.
- **As a species, we have a moral obligation to enhance ourselves biologically.**
- **Humans have a lot of limitations.** We have limitations in terms of aging, we have cognitive limitations, various physical limitations, and of course moral limitations. When science offers us the opportunity to overcome these limitations, we should ask the ethical question: “should we?” In some cases we shouldn’t, but in many cases we have a moral obligation to overcome those limitations.
- One trivial example: about a billion IQ points are lost around the world each year because salt isn’t iodized. If you’re pregnant and have insufficient iodine, your fetus might lose 10 to 15 IQ points. You may still be “normal” — but it only costs 2-3¢ per person per year to iodize salt. We have an enormous moral obligation to do that because of the value of cognitive ability.
- We also have a moral obligation to overcome our moral limitations. People evolved to form groups of about 150. They care about their **tribal group**, and they tend to be violent to or derogate out-of-group members. They are altruistic to their friends and family, but much less so to other people. They free-ride. They think in the **near term**. All of these are essentially features built into our psychology.
- We’re far from perfect. We’ll never be perfect, but when science offers us the opportunity to understand those limitations and to build policies tailored towards them, or indeed to directly overcome them, we ought to at least do research into it.



<https://youtu.be/DhtlFTrJQJ4>

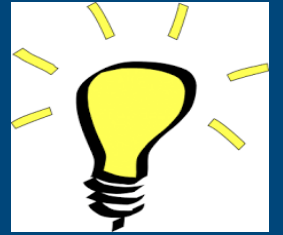
Rogue superintelligence and merging with machines: Inside the mind of OpenAI's chief scientist



- ARTIFICIAL INTELLIGENCE

- An exclusive conversation with Ilya Sutskever on his fears for the future of AI and why they've made him change the focus of his life's work.
- Sutskever tells me a lot of other things too. He thinks ChatGPT just might be conscious (if you squint). He thinks the world needs to wake up to the true power of the technology his company and others are racing to create. And he thinks some humans will one day choose to merge with machines.
- <https://www.technologyreview.com/2023/10/26/1082398/exclusive-ilya-sutskever-openais-chief-scientist-on-his-hopes-and-fears-for-the-future-of-ai/>

Meerdere vormen van bewustzijn, die samen een persoonlijkheid vormen?



Visueel (visuele trucjes, invullen van gezichtsveld)

Auditief (liedje in het hoofd, dat je niet perse leuk vind)

Verhalend/beschrijvend bewustzijn

linker/rechter hersenhelft

=> harari: we are individuals

Als er niet 1 ondeelbaar bewustzijn (ziel) is, wat betekent dit voor geloof?

Bewustzijn is een schil van feedback,
Samenleving is een nog hogere schil van feedback

Bewustzijn is fluide

A neural correlate of sensory consciousness in a corvid bird

<https://science.sciencemag.org/content/369/6511/1626>

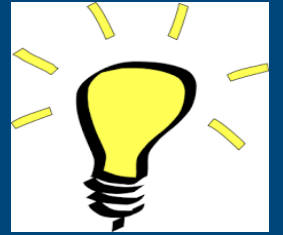


Subjective experiences that can be consciously accessed and reported are associated with the cerebral cortex. Whether sensory consciousness can also arise from differently organized brains that lack a layered cerebral cortex, such as the bird brain, remains unknown. We show that single-neuron responses 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.

The consciousness wars: can scientists ever agree on how the mind works?



- Nature 17 January 2024
- **There are dozens of theories of how the brain produces conscious experience, and a new type of study is testing some of them head-to-head.**



Nadelen van bewustzijn

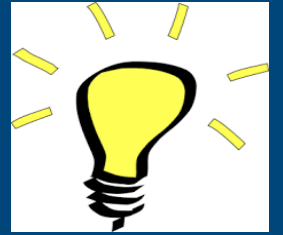
- Behoefte aan zingeving
- Besef van de dood
=> Evolutie doet niet aan moraal, dood gaan is essentieel.
- Illusie van sturing van bovenaf (vrije wil), terwijl vrijwel alles autonoom is. En bewustzijn is meestal juist achteraf.
- Wat we doen komt door genen, hormonen, ervaring die in onze informatieverwerkingsunit wordt verwerkt tot output.

⇒Swaab: Wij zijn ons brein

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

⇒Scheppend en vernietigend

Emerging properties Voorbij **reductionisme**



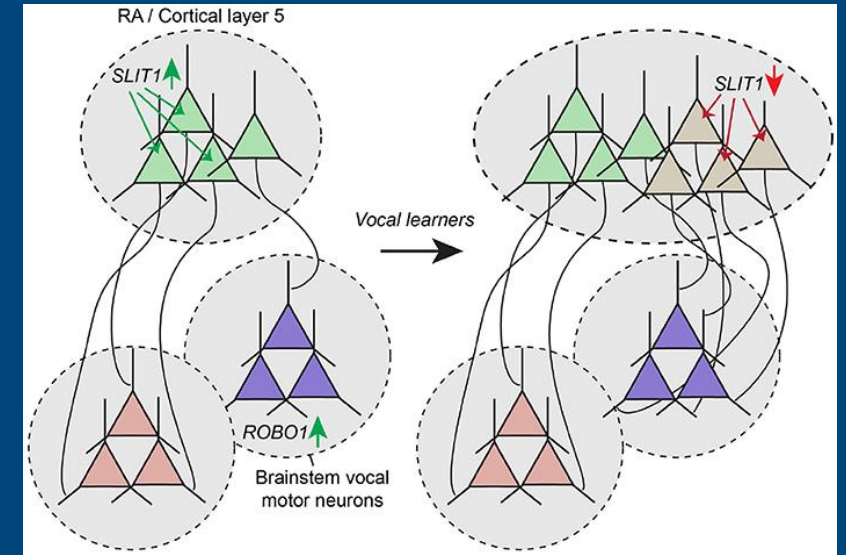
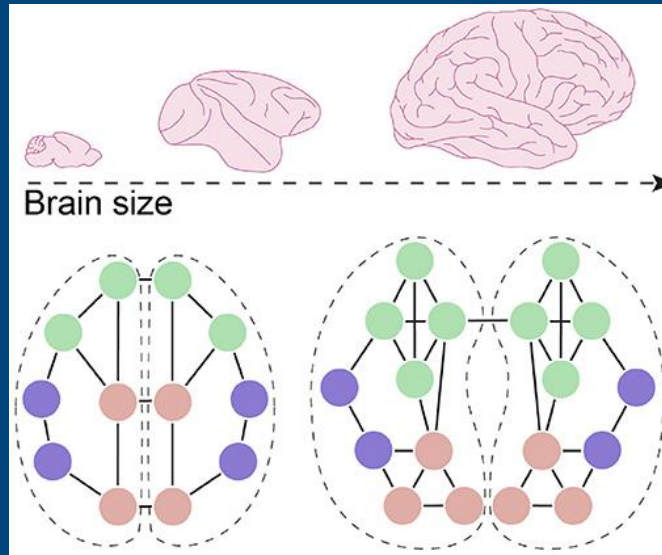
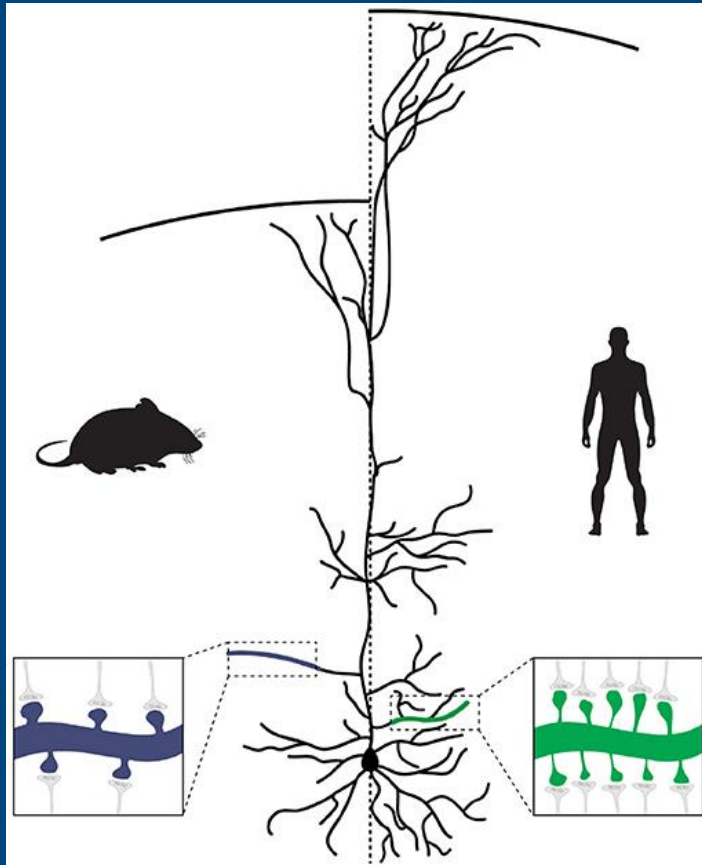
- http://www.npo.nl/de-volmaakte-mens/10-06-2015/VPWON_1231937



The human brain:

More connections

More flexible connections

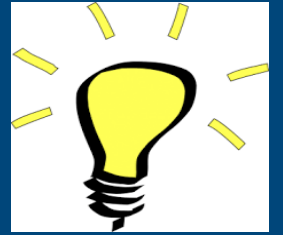


In human pyramidal neurons (PNs), a larger number of branch points leads to a more extensive and complex dendritic tree. Each branch also contains a larger number of synapses, resulting in an overall increase in the number of synapses made onto human PNs. In addition, because of the increased cortical thickness of the human brain, the apical dendrites of human PNs extend over a longer distance to reach layer I.

<https://www.frontiersin.org/articles/10.3389/fncir.2021.787164/full>

New genes, Synaptic pruning

Wat maakt de mens bijzonder? Is nog volop debat over, maar..



Complexe taken => kunnen dieren ook
Zelfbewustzijn => hebben kraaien al
Planning => kunnen chimpansees ook

Vooraf veel meer dan andere dieren (grotere hersenen)
Hierarchical thinking and abstractie (=> kurzweil)

En **flexibeler** (leren = nieuwsgierigheid),
Misschien wel de helft van ons gedrag is aangeleerd (nurture)

En taal (strottenhoofd !)
Geheugen begint ook bij taalontwikkeling

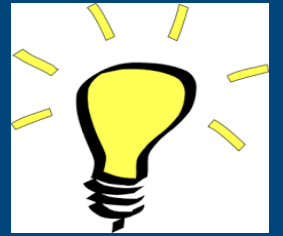
⇒ Informatieoverdracht (**the social brain**)

Social cognition encompasses all the information-processing mechanisms that underlie how people capture, process, store, and apply information about others to navigate social situations. It focuses on the importance of cognitive and emotional processes in our social interactions. The way we think about others plays a major role in how we think, feel, and interact with the world around us.

Strong covariation in size and developmental duration coupled with **flexible brains** allow organisms to adapt in variable social and ecological environments across the life span and in evolution.

The Social Brain

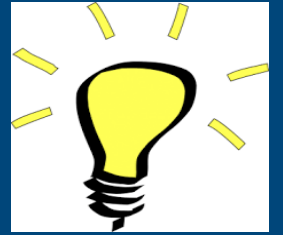
A Developmental Perspective | edited by Jean Decety



https://books.google.nl/books/about/The_Social_Brain.html

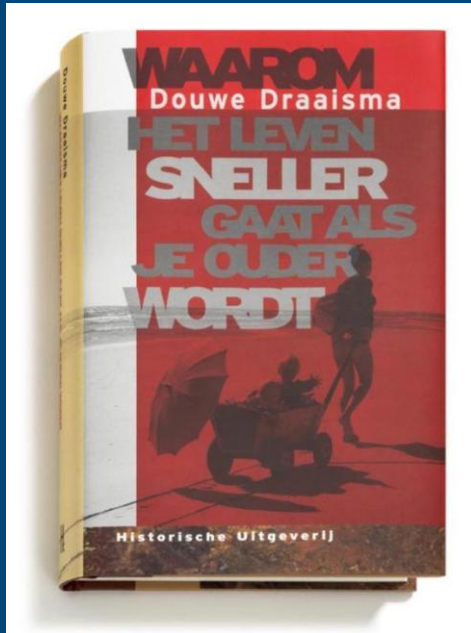
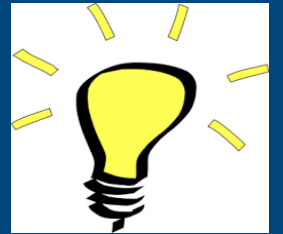
<https://www.sciencedirect.com/science/article/abs/pii/B978044538604000040>

Visuo-frontal interactions during social learning in freely moving macaques



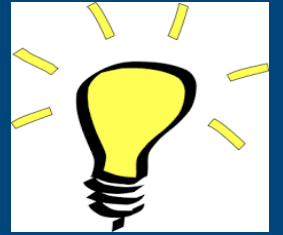
- Nature: 14 February 2024
- Social interactions represent a ubiquitous aspect of our everyday life that we acquire by interpreting and responding to visual cues from conspecifics¹. However, despite the general acceptance of this view, how visual information is used to guide the decision to cooperate is unknown. Here, we wirelessly recorded the spiking activity of populations of neurons in the visual and prefrontal cortex in conjunction with wireless recordings of oculomotor events while freely moving macaques engaged in social cooperation. As animals learned to cooperate, visual and executive areas refined the representation of social variables, such as the conspecific or reward, by distributing socially relevant information among neurons in each area. Decoding population activity showed that viewing social cues influences the decision to cooperate. **Learning social events increased coordinated spiking between visual and prefrontal cortical neurons, which was associated with improved accuracy of neural populations to encode social cues and the decision to cooperate.** These results indicate that the visual-frontal cortical network prioritizes relevant sensory information to facilitate learning social interactions while freely moving macaques interact in a naturalistic environment.

Douwe Draaisma, Rutger Kopland



- <https://douwedraaisma.nl/nl/books>
- https://nl.wikipedia.org/wiki/Rutger_Kopland

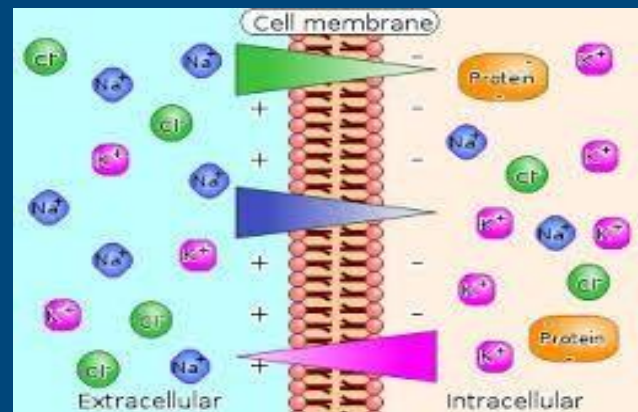
Biologie is elektrisch



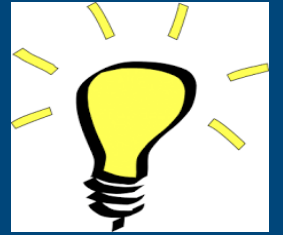
- Verschillende ionconcentraties => spannings-verschil => stroom => elektrisch veld
 - Veld strekt zich uit tot buiten het lichaam
- => EEG
- => Touchscreen



- “Life is the flow of charge”
- Integratie technologie en biologie op basis van elektriciteit !



Leven is..



- Een informatie systeem
 - Individuele processen kunnen ook buiten een levend systeem plaatsvinden
 - Modulair
 - Self-organizing
-
- Elektrisch
- => verbinding met technologie is eenvoudig

Evolutie

- Langzaam
- Slordig
- Moet functioneel zijn

=> Gevaar!

⇒ ethiek!

⇒ Permanente aanpassing (van de soort)

v

Gentechnologie

v

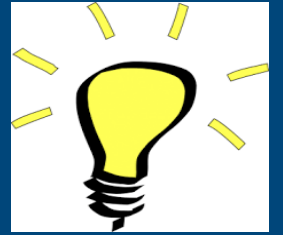
Snel

v

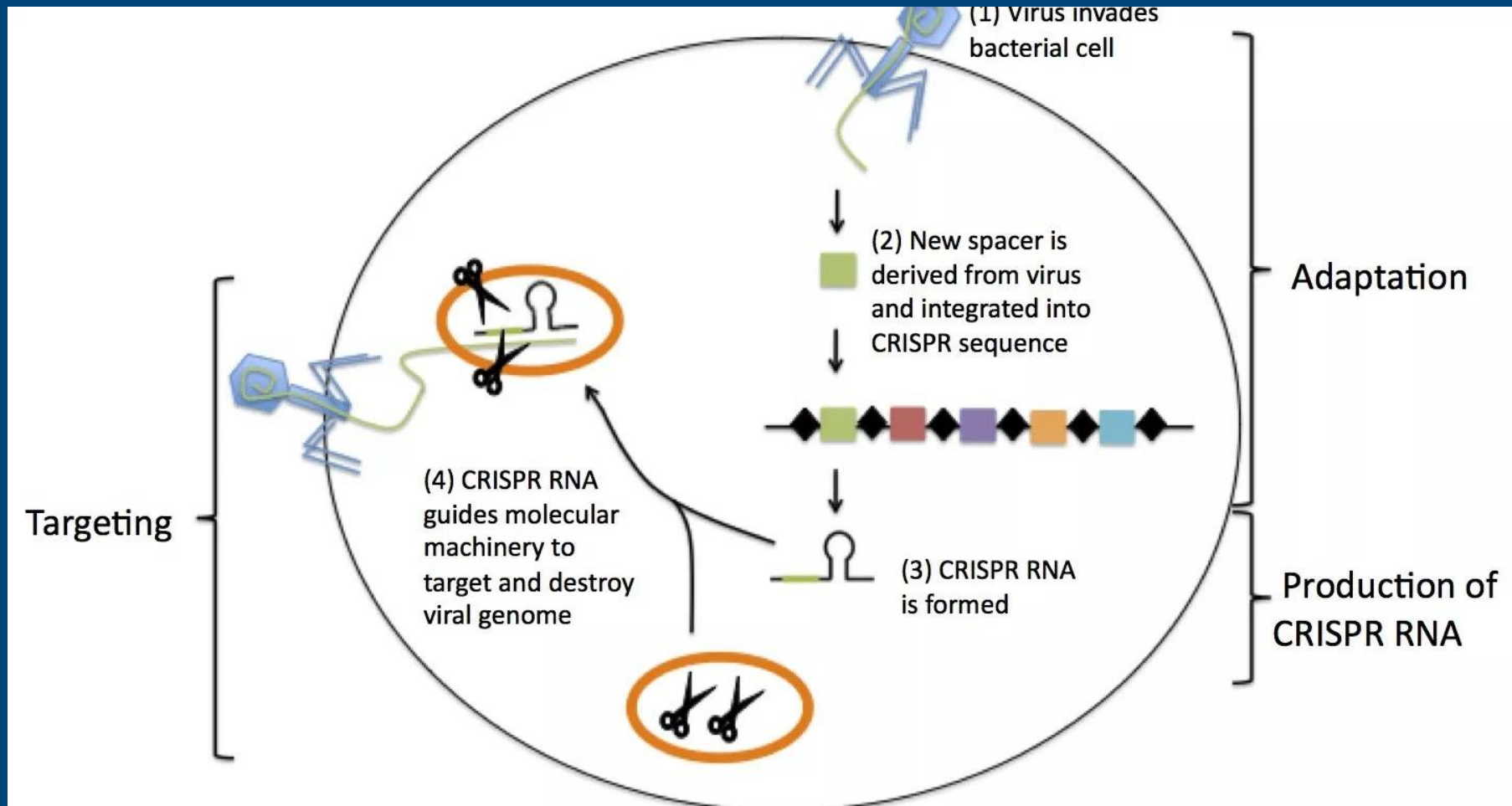
Precies

v

Kan alles zijn wat je wilt

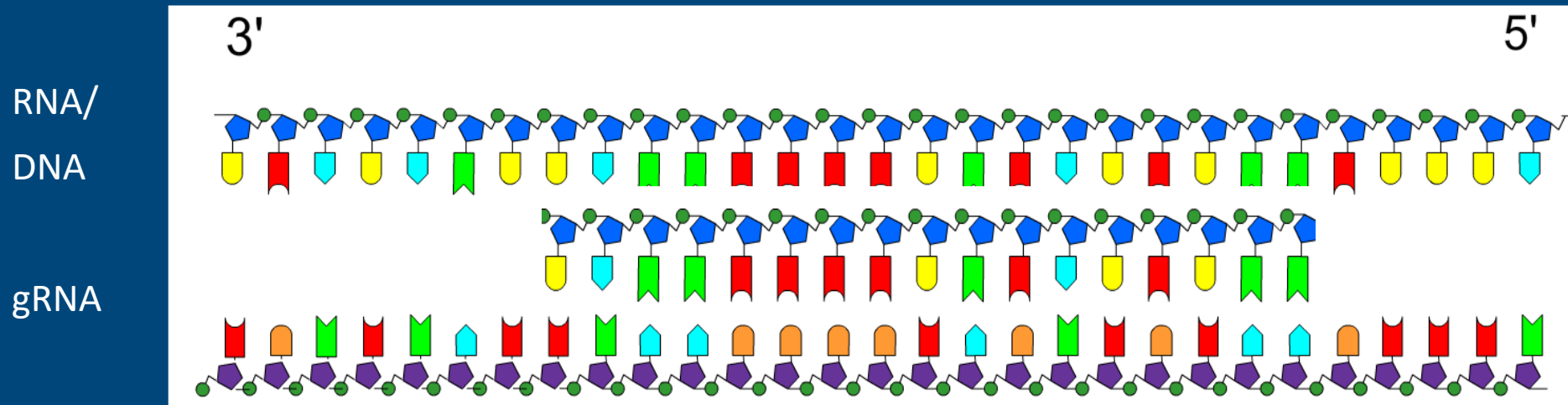
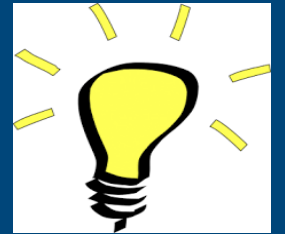
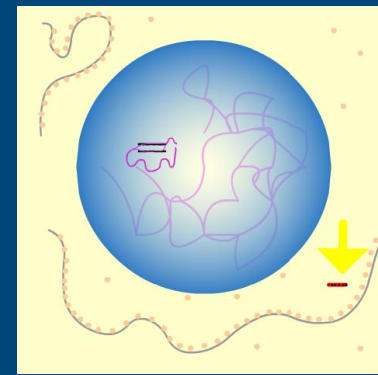


CRISPR, Intracellular bacterial defence against virus



- ⇒ specifiek, met memory !
- ⇒ Hoezo bacterien zijn simpel?

guideRNA/primer actie



Kans = $\frac{1}{4}$ voor 1^e nucleotide, en $\frac{1}{4}$ voor 2^e nucleotide (er zijn 4 verschillende)

Kans = $\frac{1}{4} \times \frac{1}{4} = \frac{1}{4^2} = 1$ op 16 voor 2 nucleotiden ($\frac{1}{4^n}$ voor n nucleotiden)

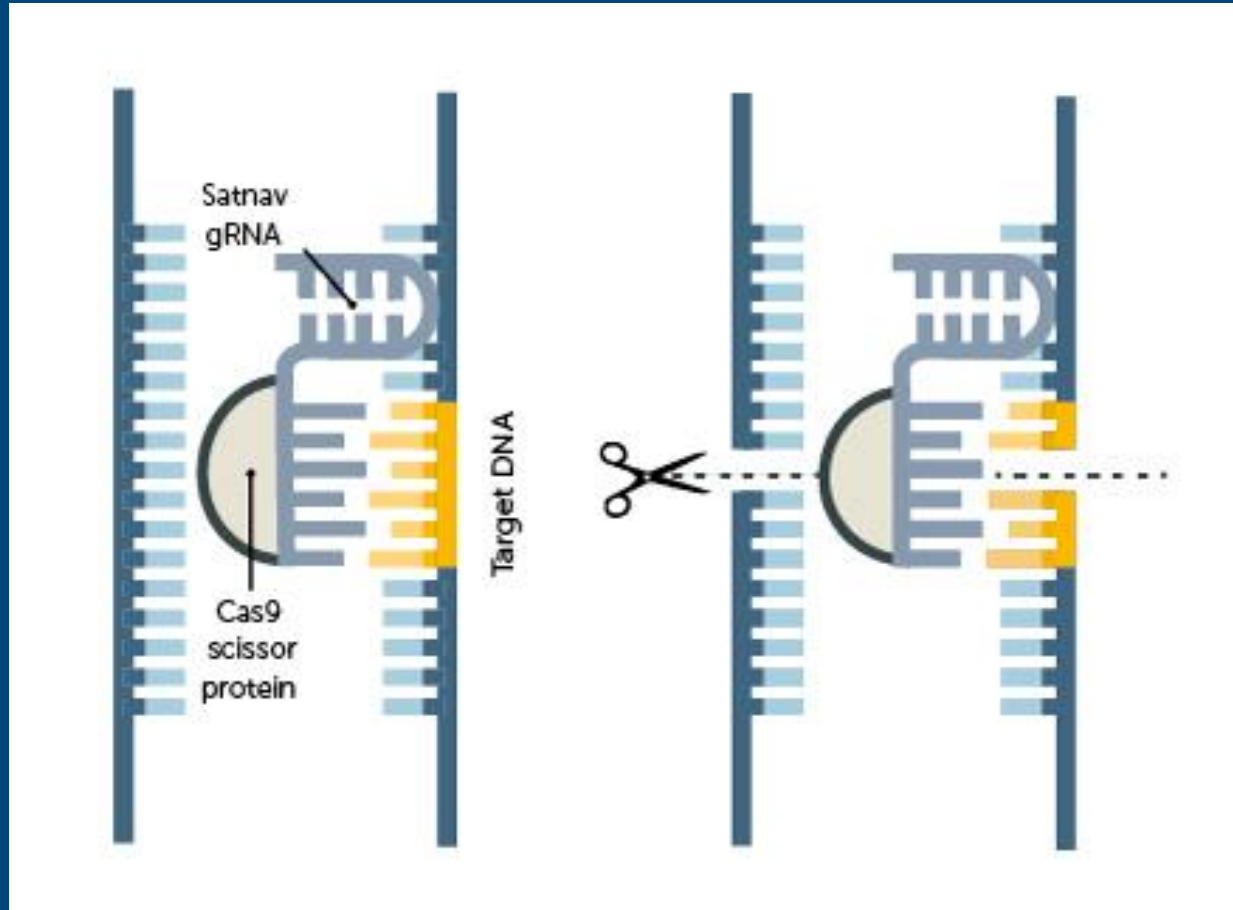
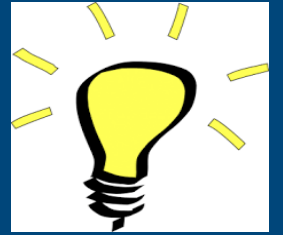
Kans = $\frac{1}{4^{20}}$ voor 20 nucleotiden = $\frac{1}{1000.000.000.000}$

Aantal nucleotiden in het genoom = 3.000.000.000

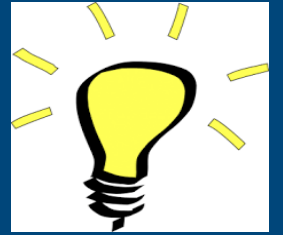
Klein stukje GuideRNA/primer zorgt al voor specifieke herkenning

=> in principe geen off-target effects

CRISPR targets (\Rightarrow SatNav), Cas cuts (\Rightarrow Scissor)



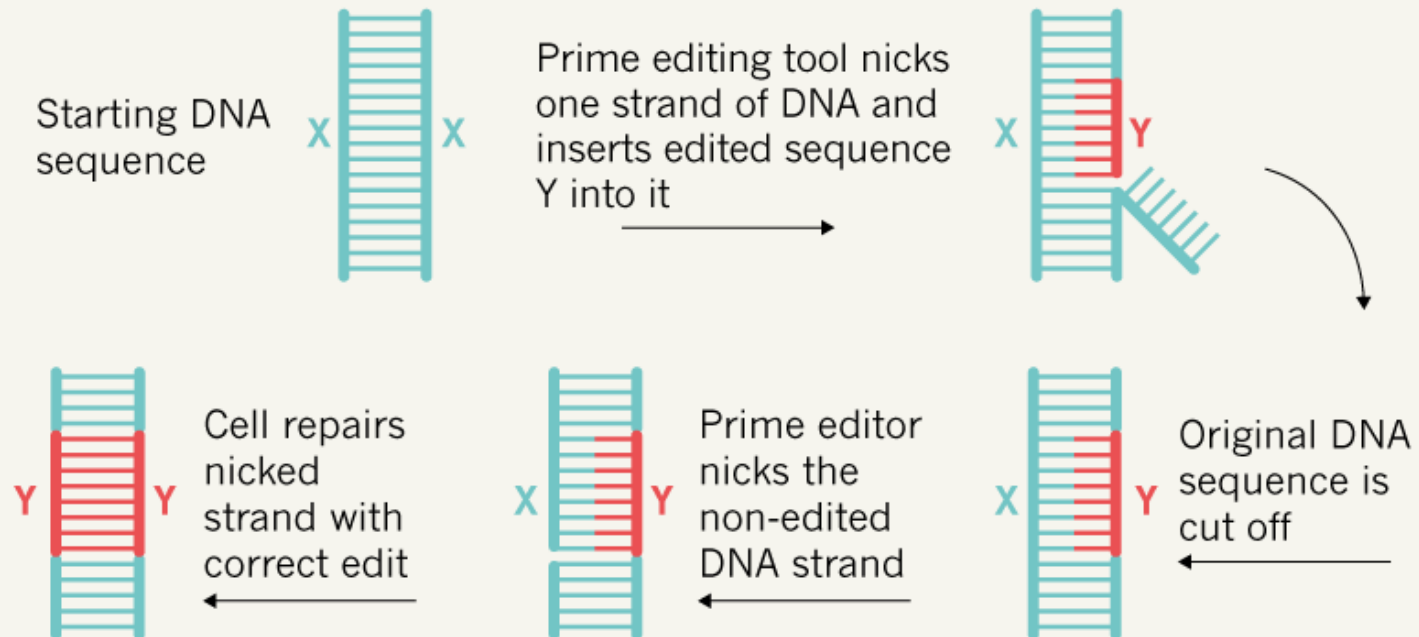
Super-precise new CRISPR tool allows more control over DNA changes



- CRISPR wordt in de toekomst nog beter, en verscheidener

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.



How CRISPR could yield the next blockbuster crop



- 09 January 2024
- **Scientists are attempting to rapidly domesticate wild plant species by editing specific genes,**

- 25 January 2024
- **CRISPR-edited crops break new ground in Africa**
- There are at least a dozen projects in the works, including one to make sorghum resistant to parasitic witchweed. Because in this case CRISPR–Cas9 is used to **mimic a natural mutation**, the crop can bypass some of the stringent regulations that many countries impose on plants modified with foreign DNA.