



# De impact van **CRISPR-Cas** op onze maatschappij

**Raymond H.J. Staals**

Associate Professor, Laboratory of Microbiology  
Wageningen University & Research

# Conflict of interest disclaimer

The logo for Scope Biosciences, featuring the word "scope" in a large, white, lowercase sans-serif font with a stylized 'o' that has a gap, and the word "biosciences" in a smaller, white, lowercase sans-serif font below it, all on a black background.

scope  
biosciences

Co-founder, scientific advisor and shareholder of **Scope Biosciences** (diagnostics)



Scientific advisor for **Novya Biotech**

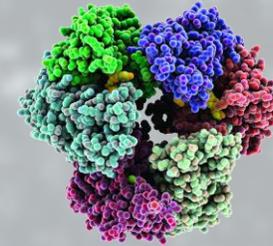


Inventor of several CRISPR-Cas-related **patents**/patent applications

# CV Raymond Staals (1979)

**2006-2011 : PhD student**

Department of Biomolecular Chemistry  
Radboud University Nijmegen



**Human RNA  
Exosome**

**2011-2014 : Research fellow**

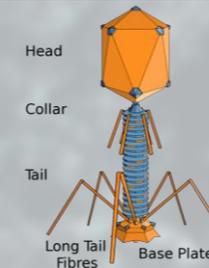
Laboratory of Microbiology  
Wageningen University & Research



**Type III  
CRISPR-Cas**

**2014-2017 : Postdoc / Principal investigator**

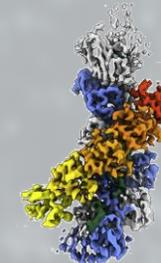
Department of Microbiology and Immunology  
Otago University (New Zealand)



**CRISPR-Cas &  
phage biology**

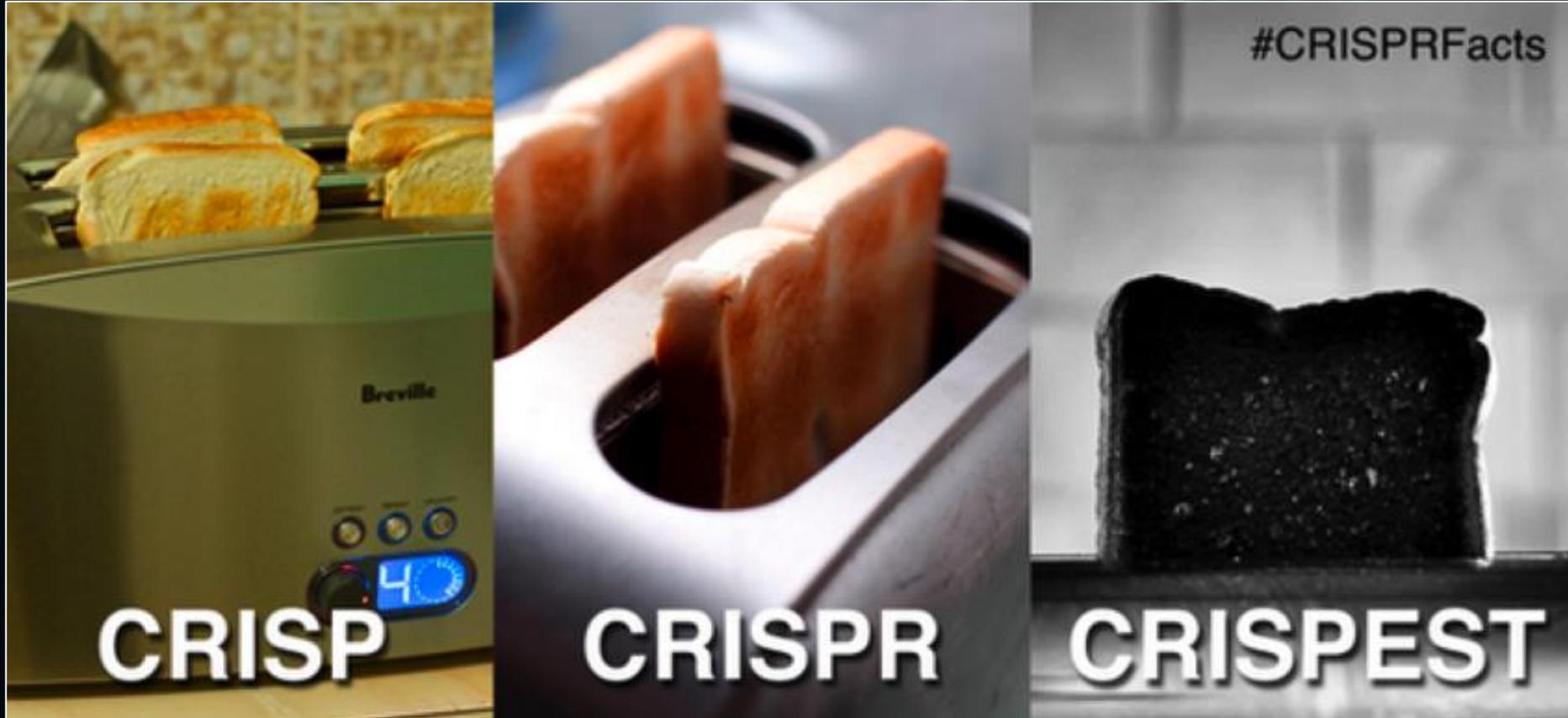
**2017-present : Associate Professor**

Laboratory of Microbiology  
Wageningen University & Research



**CRISPR-Cas &  
applications**

# CRISPR-Cas?



# CRISPR-Cas?



## 2020 Nobel Prize in Chemistry

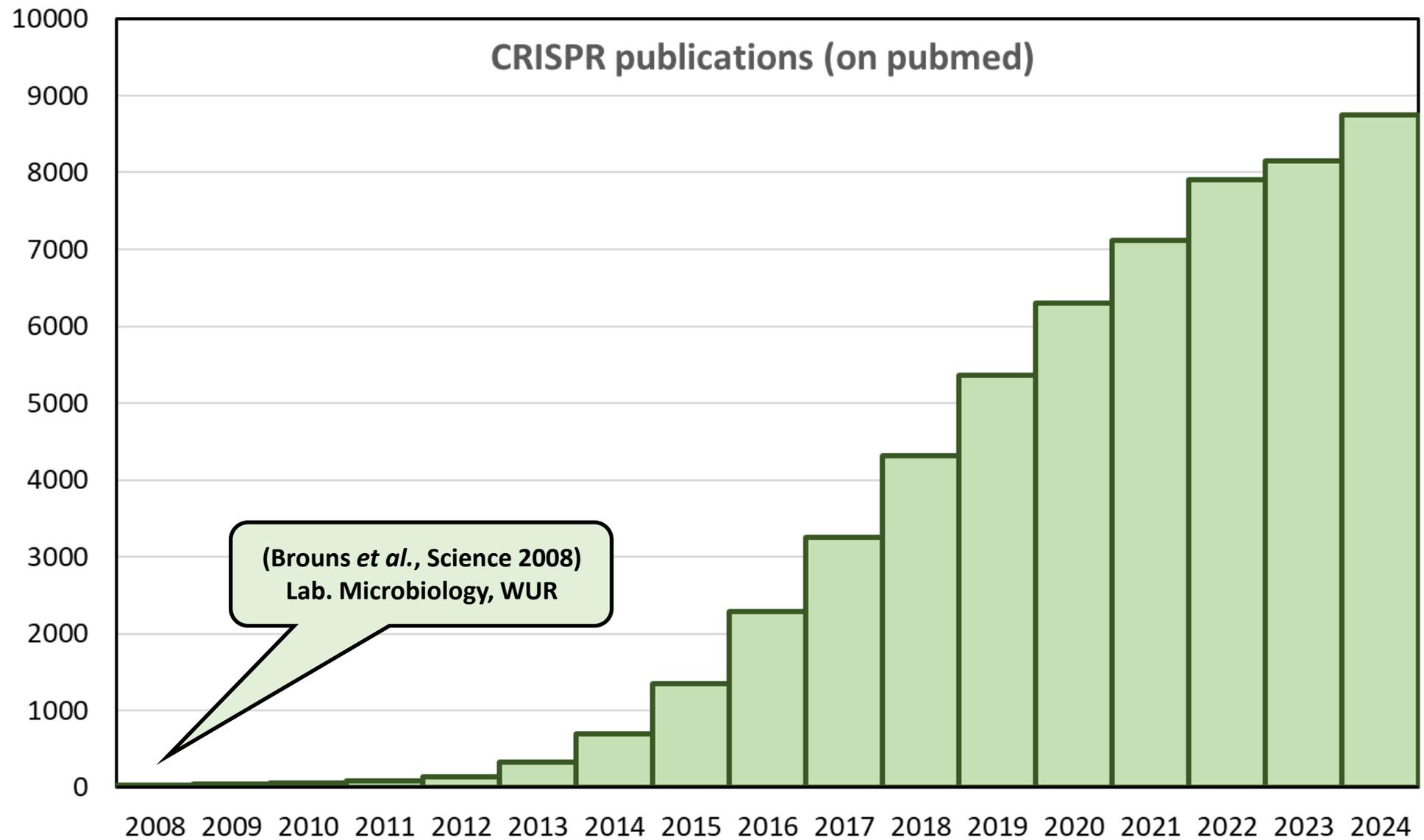


Jennifer  
Doudna

Emmanuelle  
Charpentier

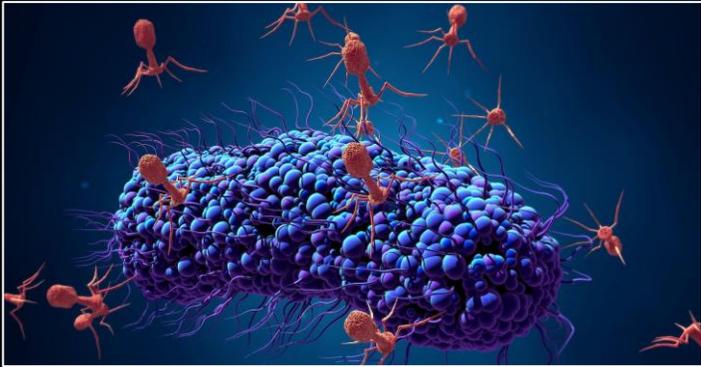


EVERYWHERE



**(Brouns *et al.*, Science 2008)  
Lab. Microbiology, WUR**

# Onderwerpen



Oorsprong CRISPR-Cas

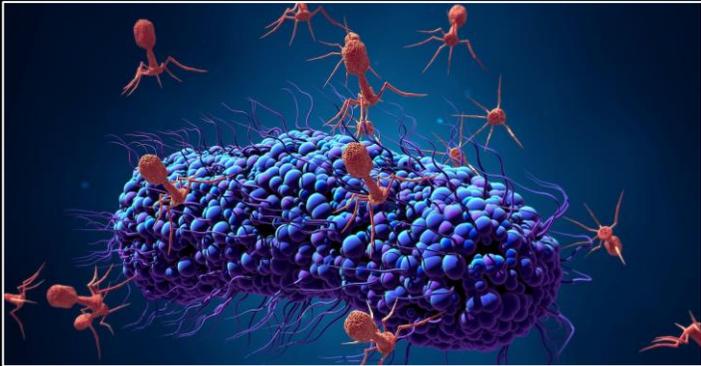


CRISPR-Cas als  
genetisch gereedschap



Impact op de maatschappij

# Onderwerpen



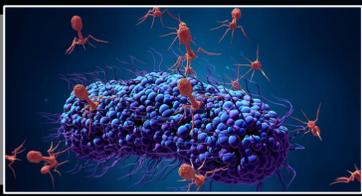
Oorsprong CRISPR-Cas



CRISPR-Cas als  
genetisch gereedschap



Impact op de maatschappij



# Oorsprong CRISPR-Cas

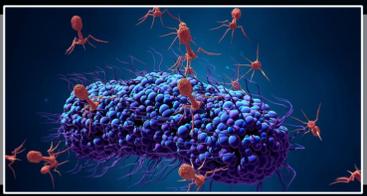


Dramatic impact of **viruses** on life...

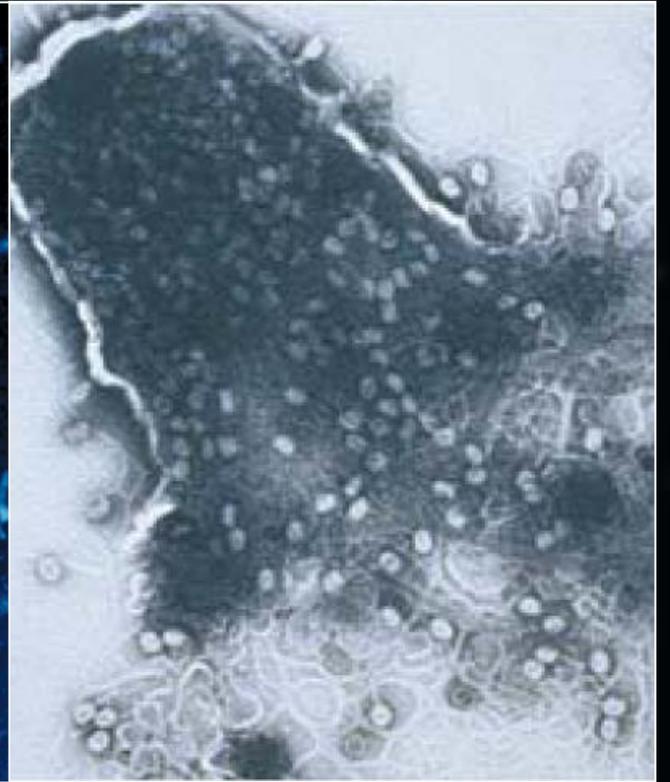
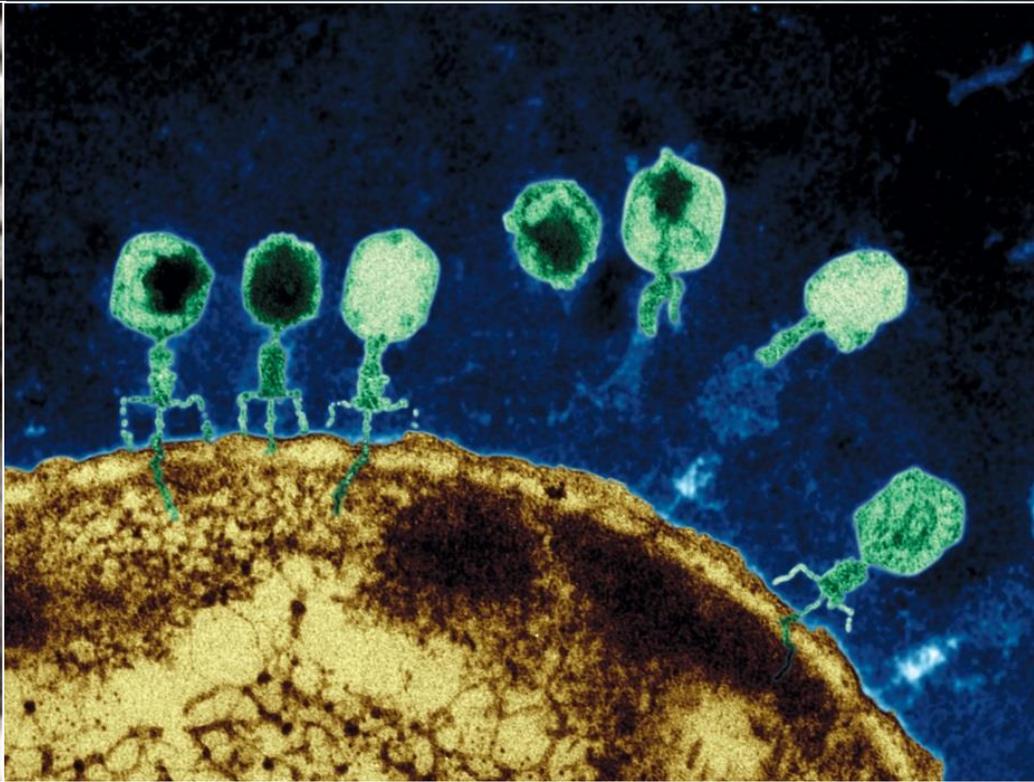
# COVID-19

Coronavirus Disease 2019

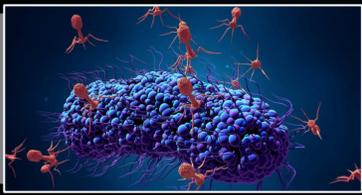




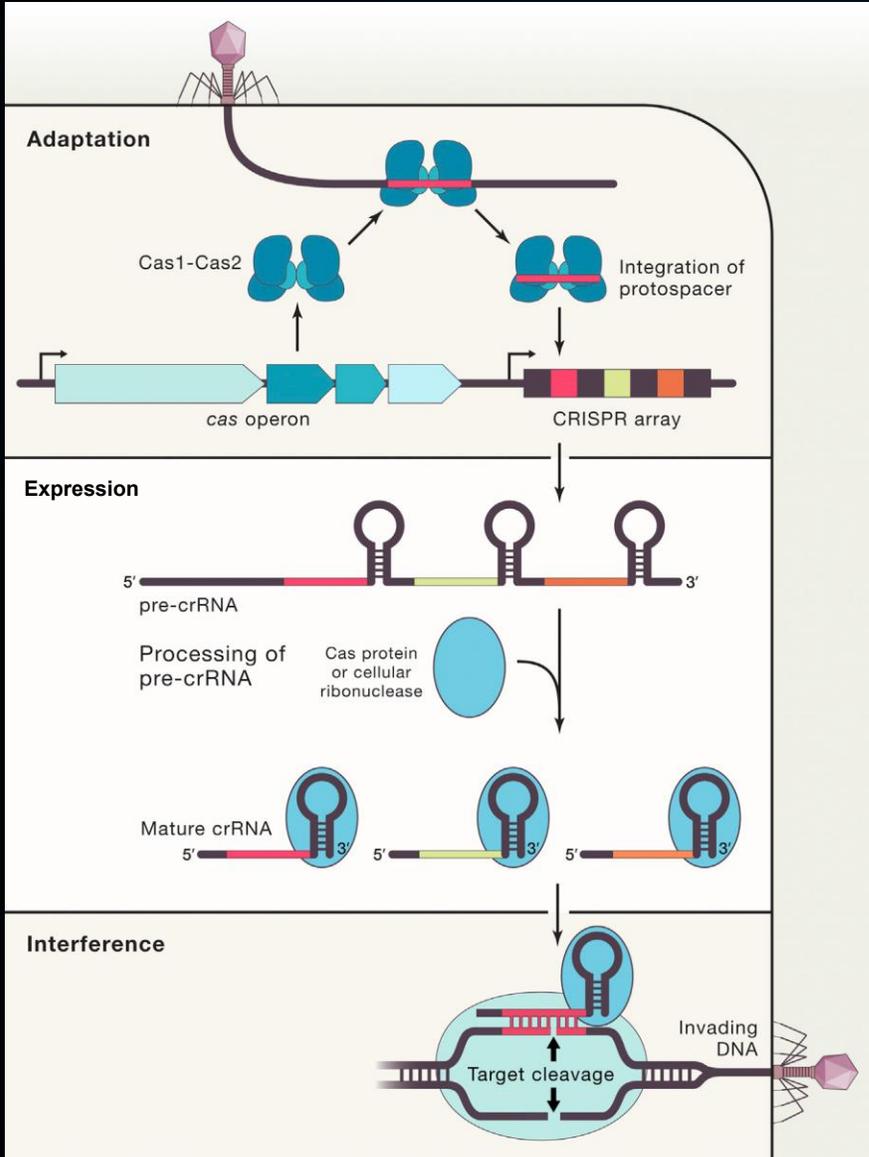
# Oorsprong CRISPR-Cas



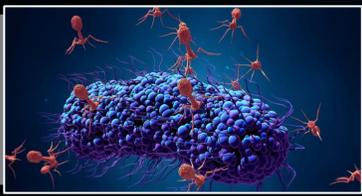
- $10^{24}$  infections/second!
- “If we line up all the viruses in the ocean, they would stretch across the diameter of the Milky Way galaxy one hundred times.” (Suttle 2007)



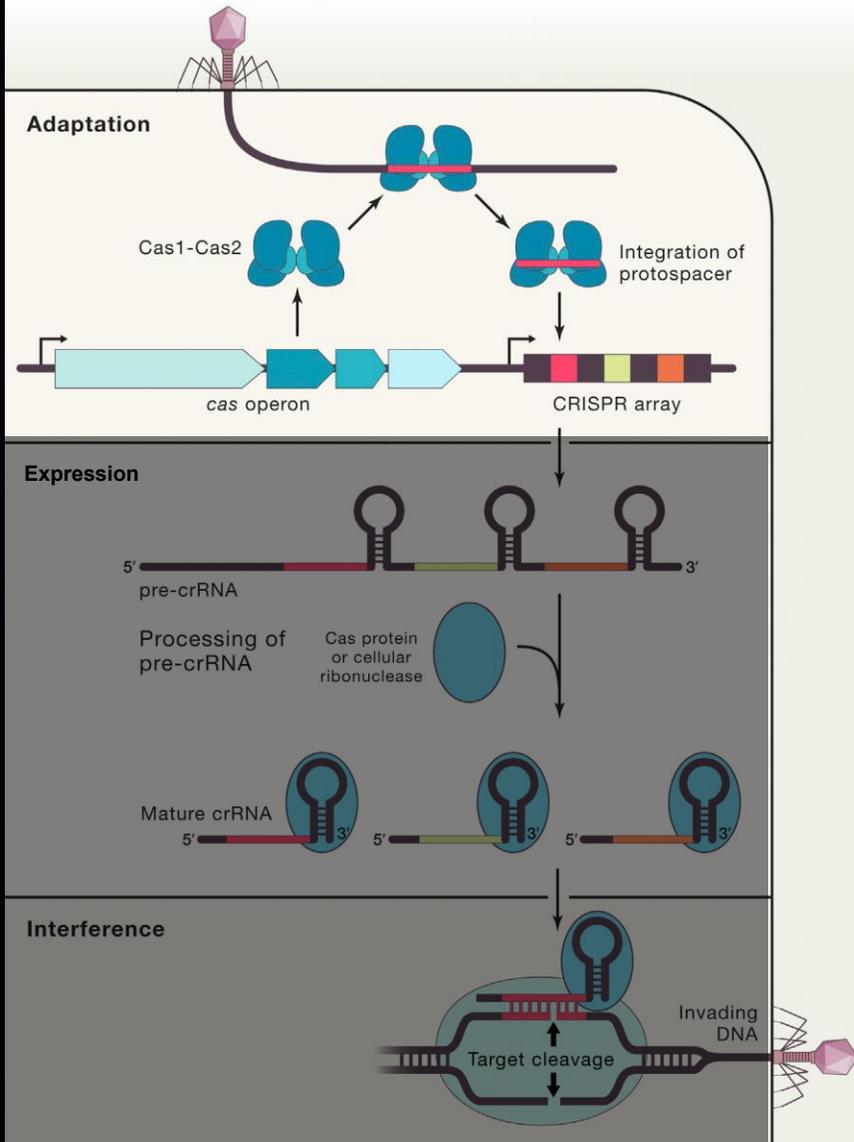
# Oorsprong CRISPR-Cas



Three stages of  
**CRISPR-Cas immunity**

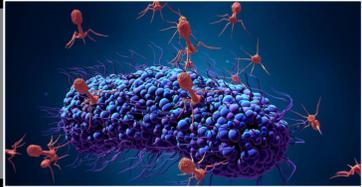


# Oorsprong CRISPR-Cas

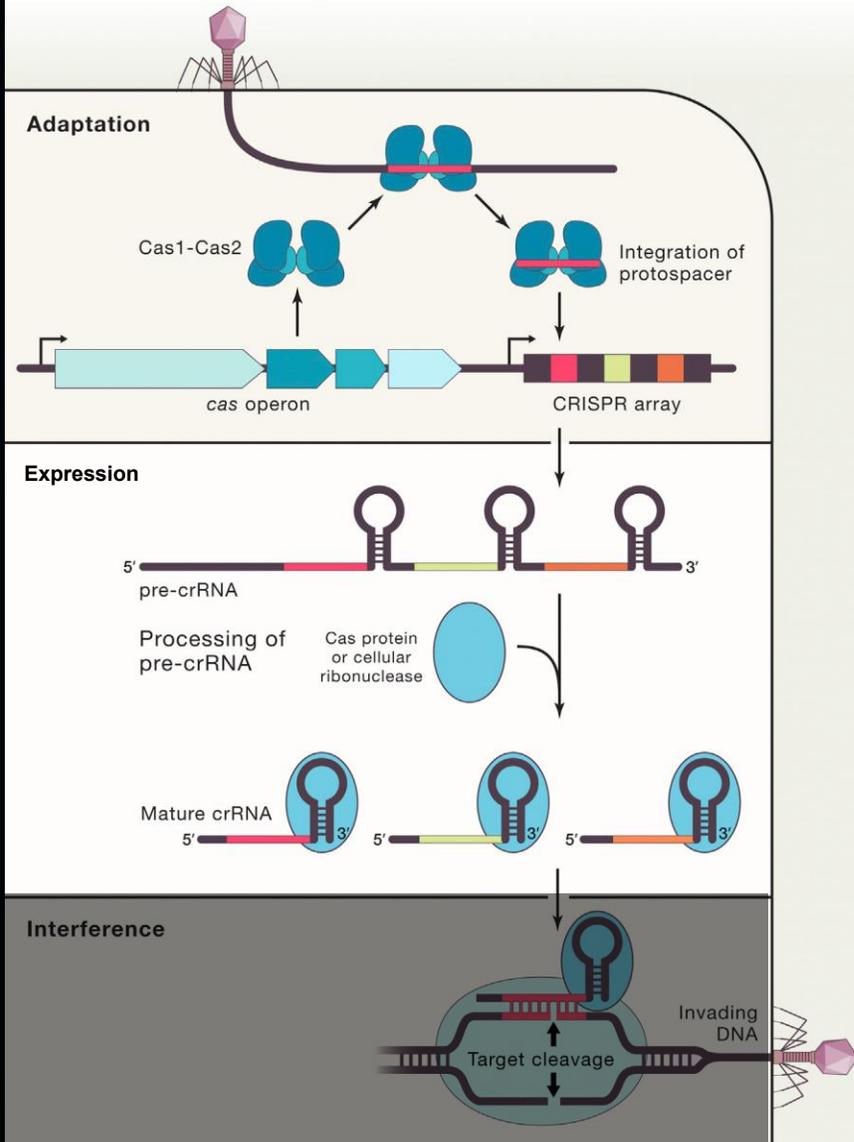


## 1. Adaptation

*Store short DNA sequence from virus into the CRISPR array*



# Oorsprong CRISPR-Cas

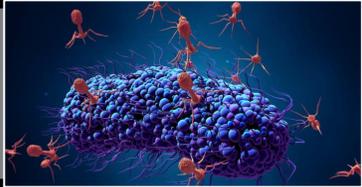


## 1. Adaptation

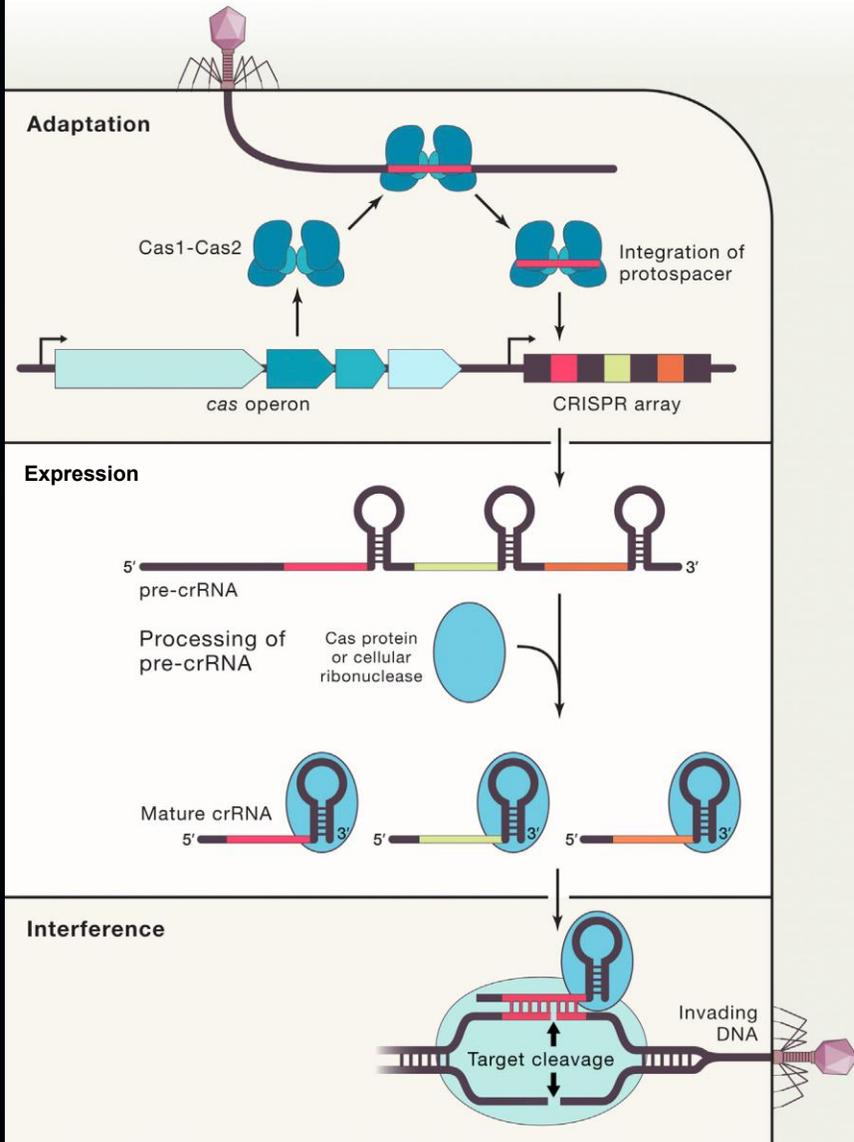
*Store short DNA sequence from virus into the CRISPR array*

## 2. Expression

*Cas genes and CRISPR RNA expression  
Formation of Cas-crRNA complex*



# Oorsprong CRISPR-Cas



## 1. Adaptation

*Store short DNA sequence from virus into the CRISPR array*

## 2. Expression

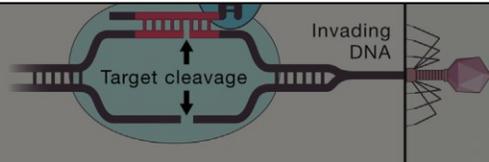
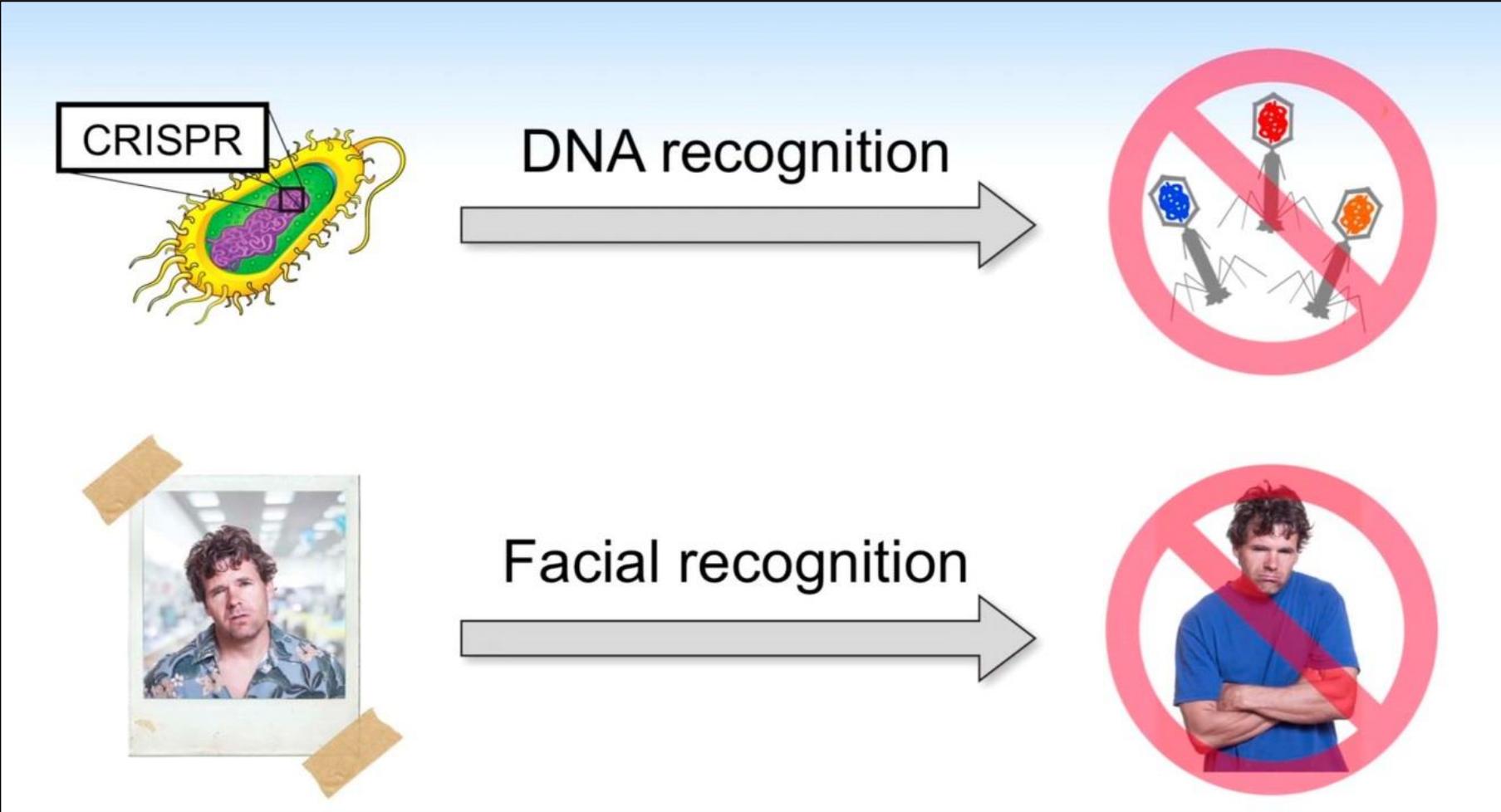
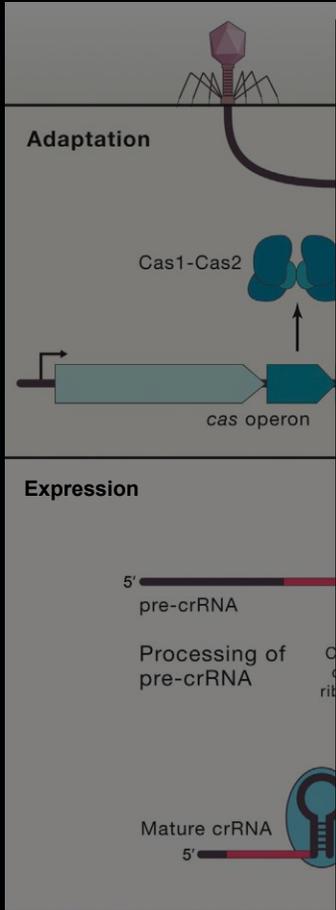
*Cas genes and CRISPR RNA expression  
Formation of Cas-crRNA complex*

## 3. Interference

*Cas-crRNA complex degrades virus*



# Oorsprong CRISPR-Cas

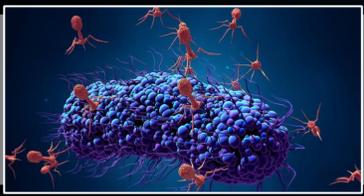


*Cas-crRNA complex degrades virus*

*n virus*

*pression*

*lex*



# Oorsprong CRISPR-Cas

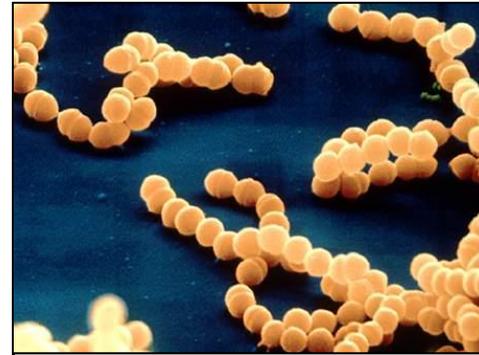


1. Bacteria

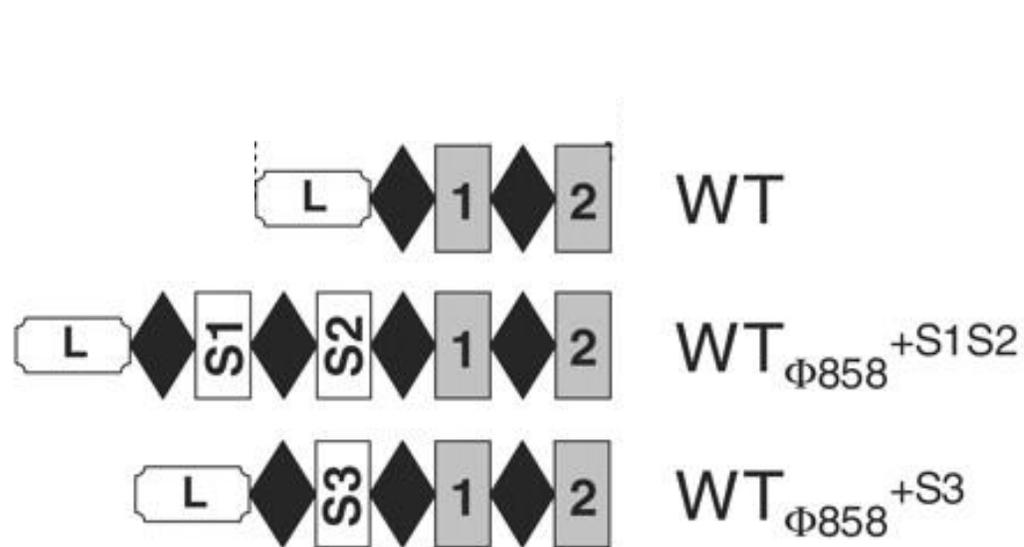
2. Bacteria + viruses

3. Bacteria (with CRISPR)  
+ viruses

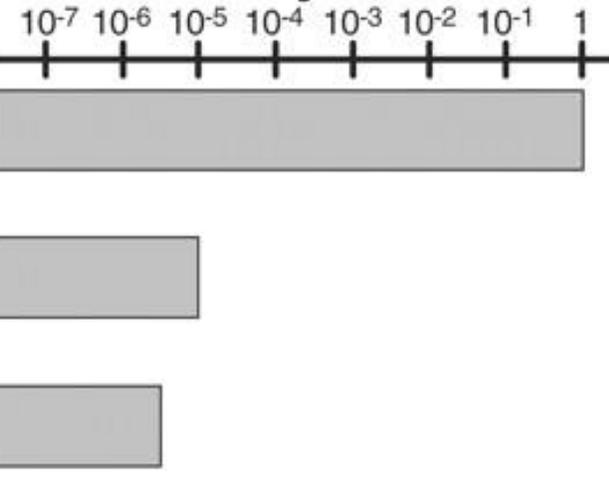
First application  
of CRISPR-Cas:  
**virus-resistant** bacterial  
production strains

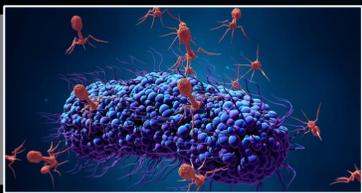


*Streptococcus  
thermophilus*

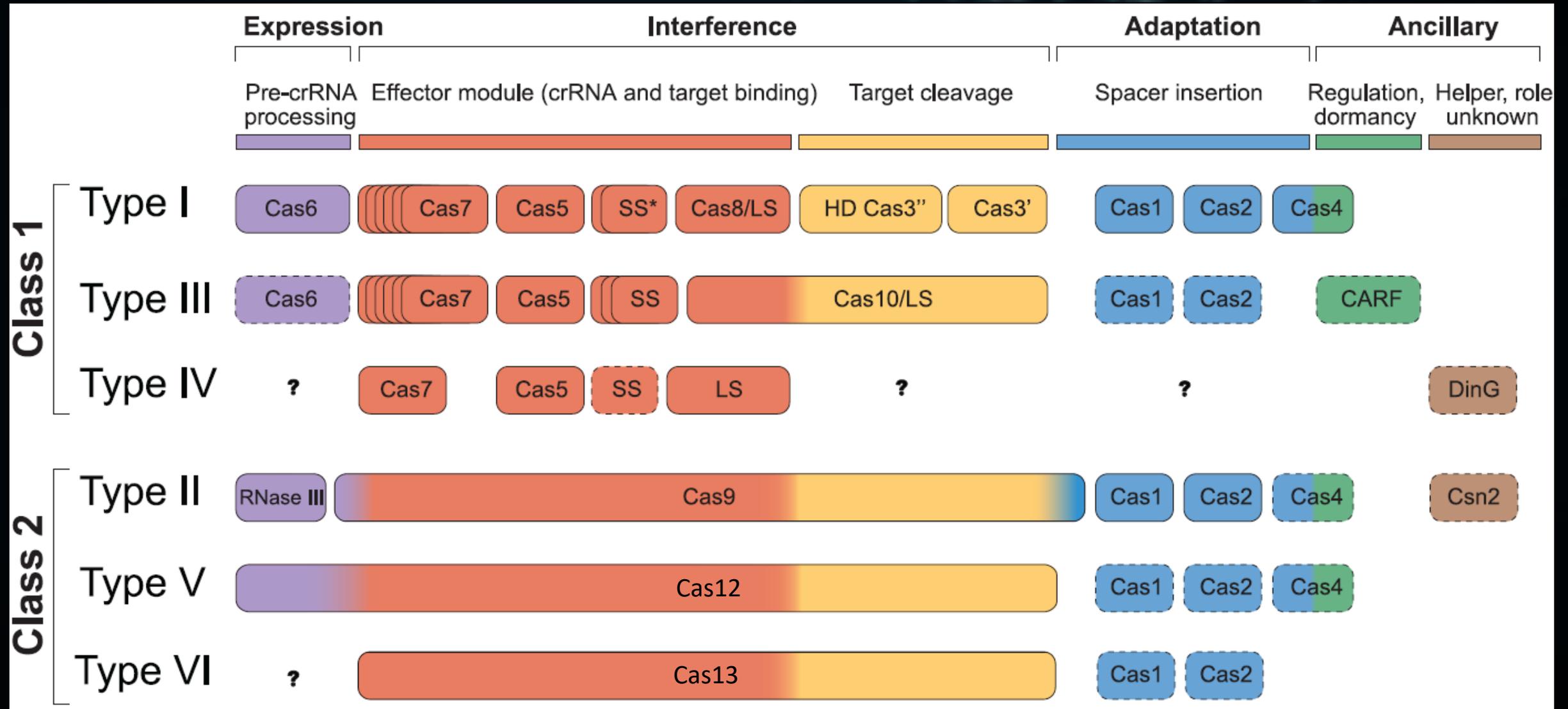


**Sensitivity to Φ858**





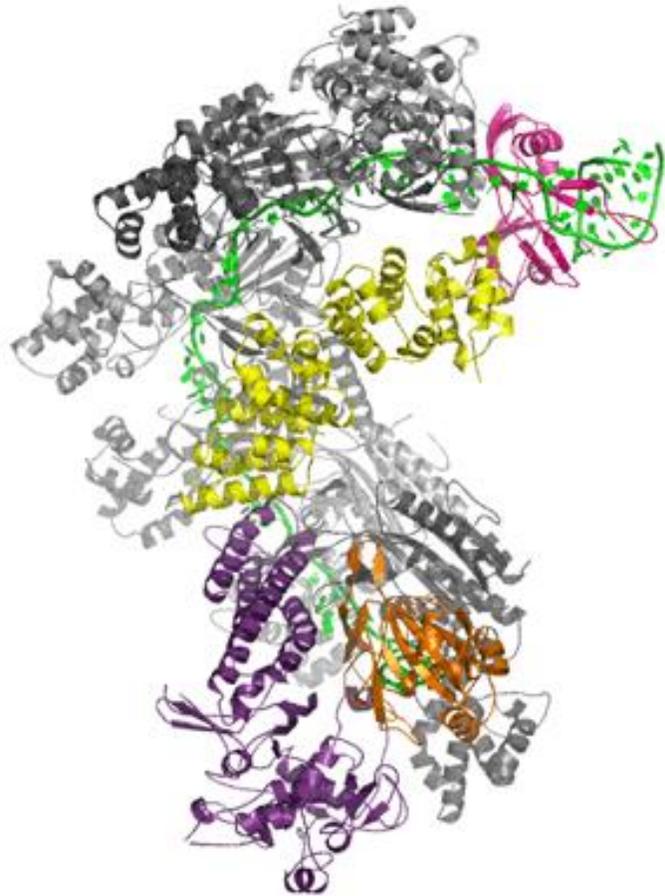
# Oorsprong CRISPR-Cas



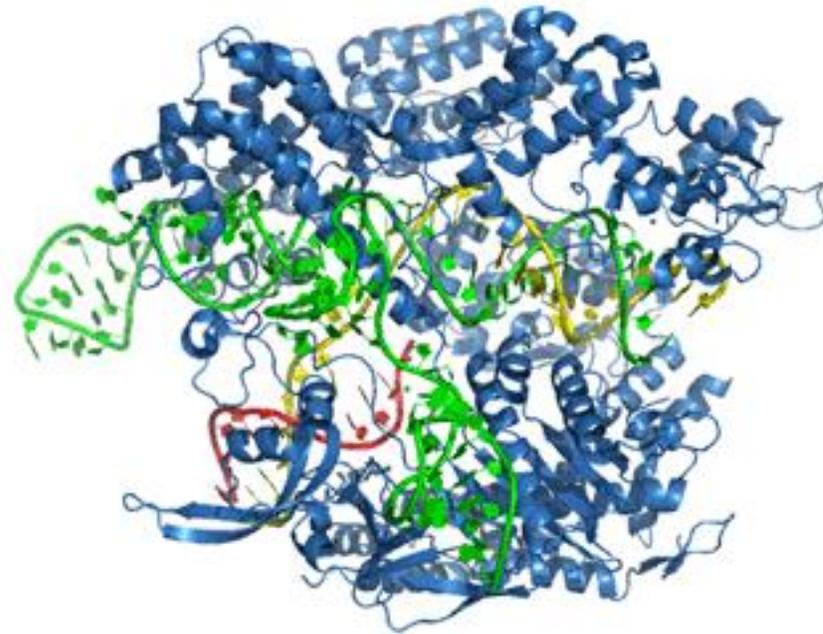


# Oorsprong CRISPR-Cas

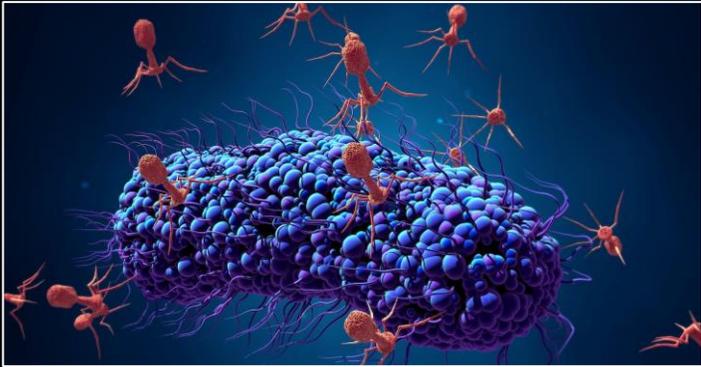
**Type I: Cascade**  
(multi-protein complex)



**Type II: Cas9**  
(single-protein complex)



# Onderwerpen



Oorsprong CRISPR-Cas



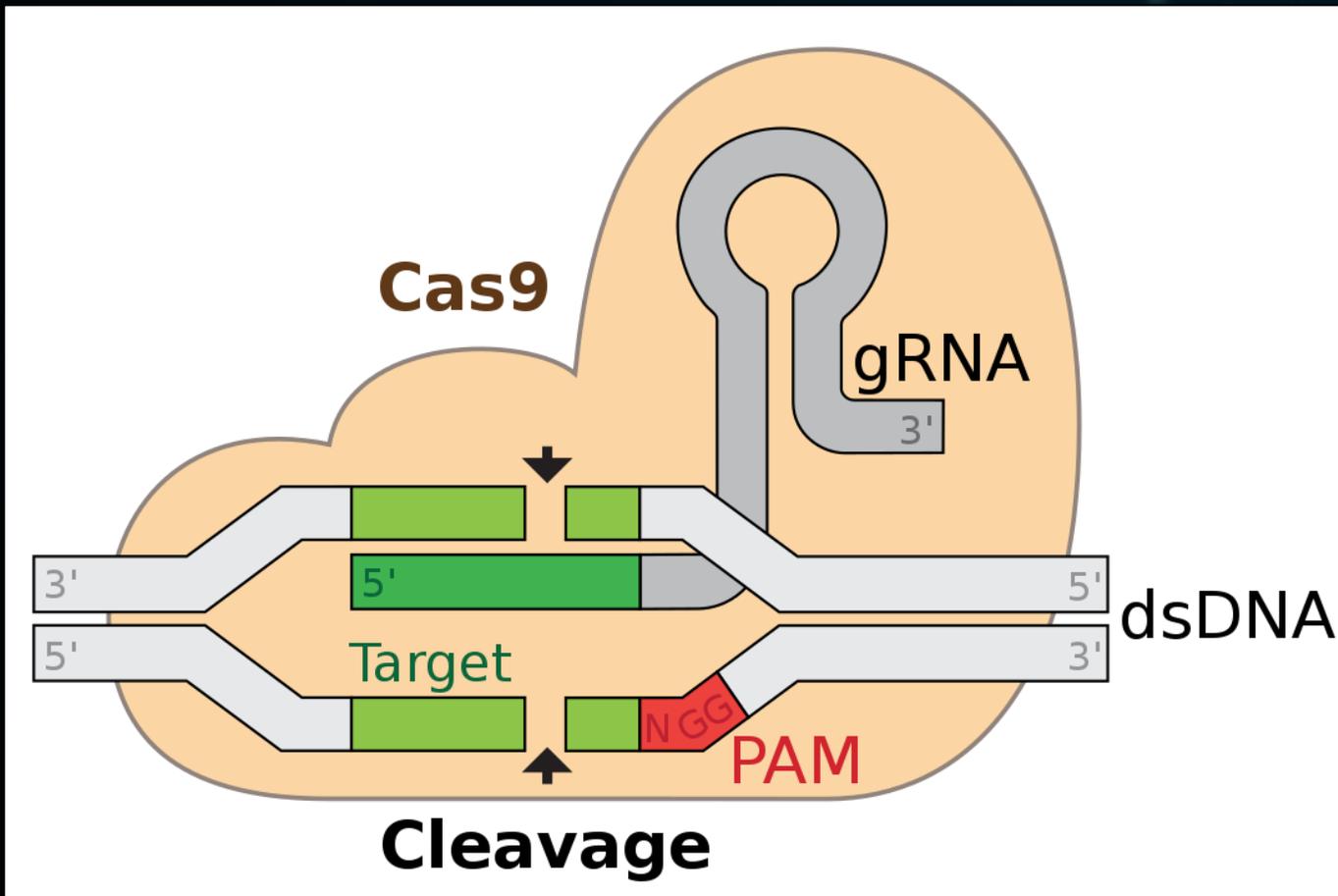
CRISPR-Cas als  
genetisch gereedschap



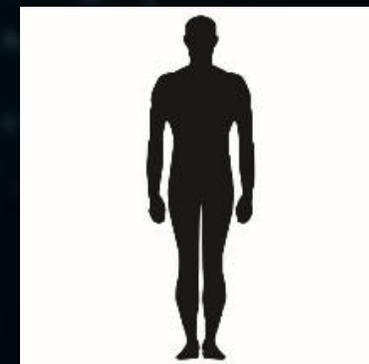
Impact op de maatschappij



# CRISPR-Cas als genetisch gereedschap



You can change the **gRNA** to any sequence of interest!



# CRISPR-Cas als genetisch gereedschap



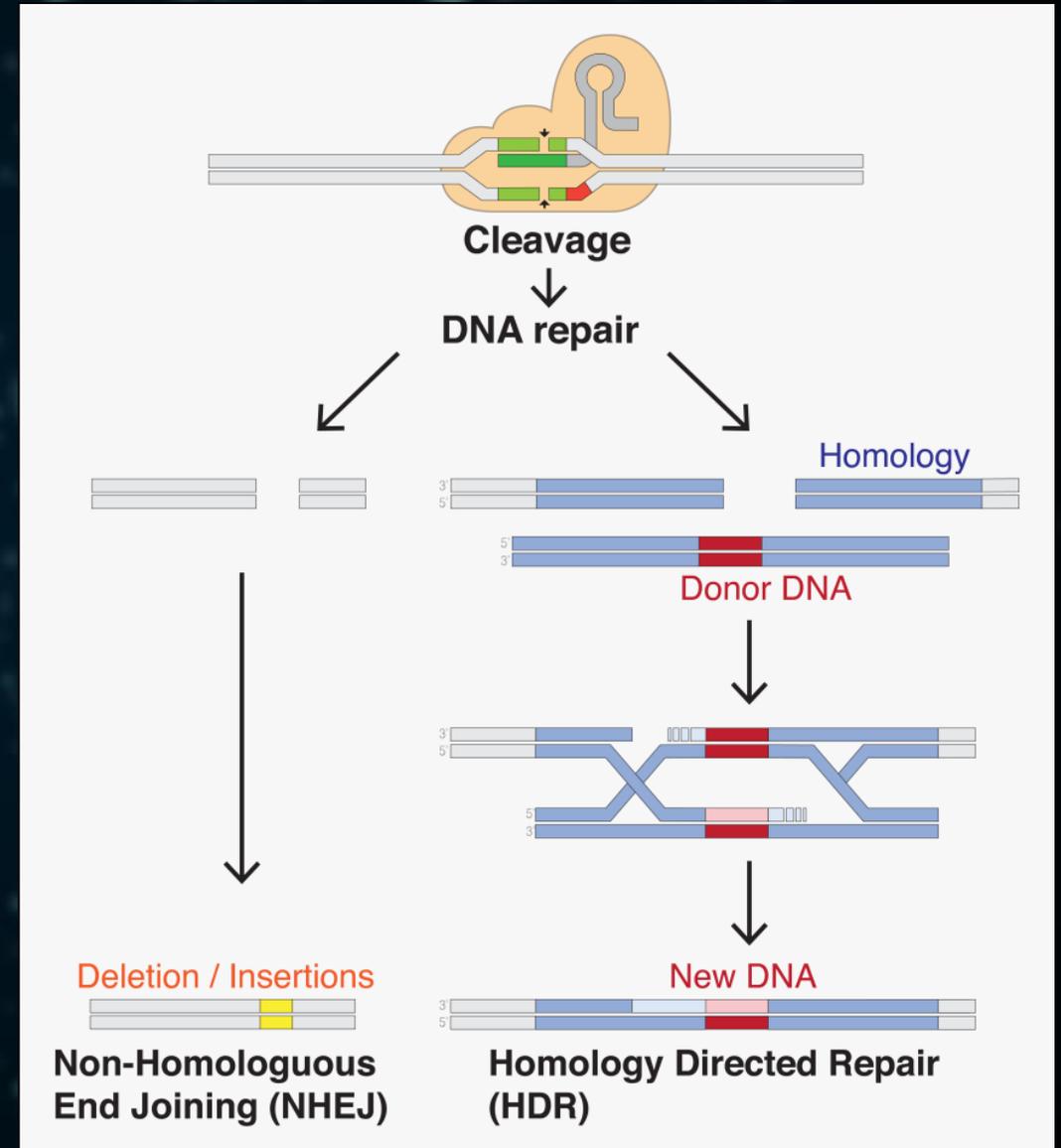
*How does cleaving  
DNA help with  
**editing** the DNA?*

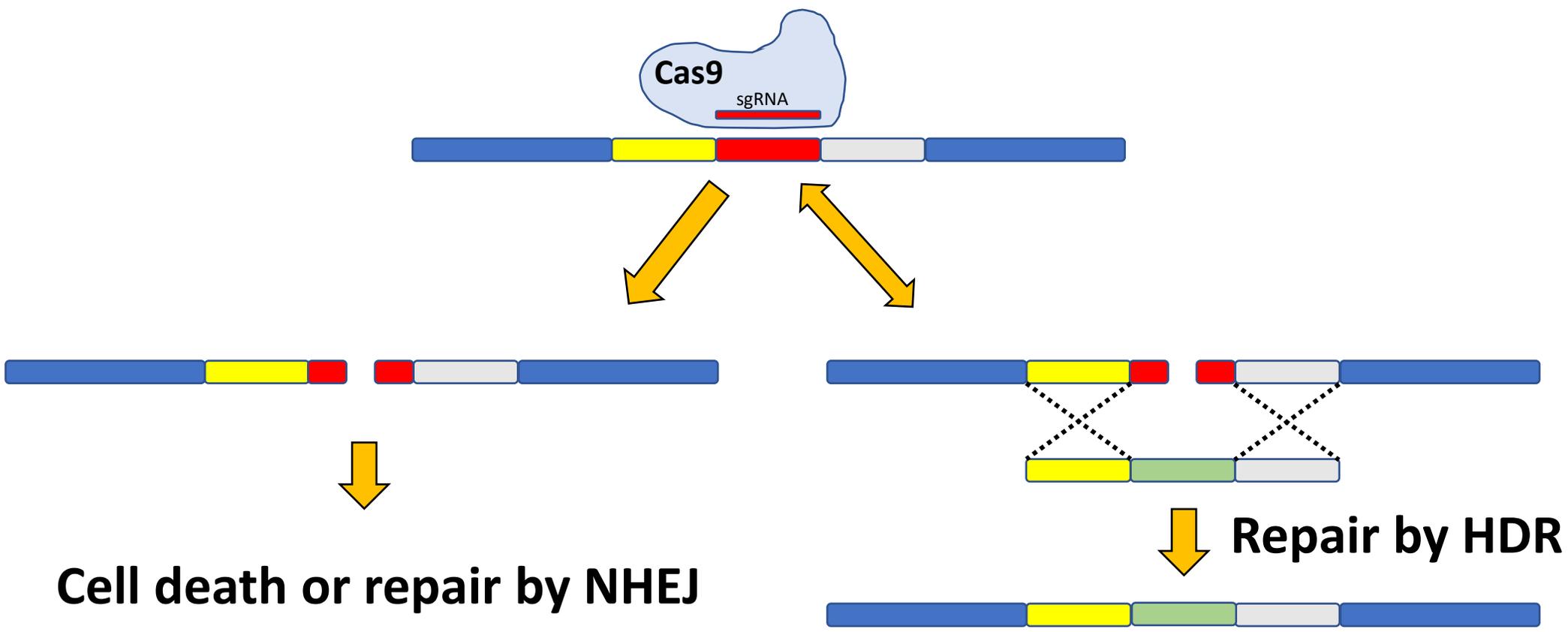




# CRISPR-Cas als genetisch gereedschap

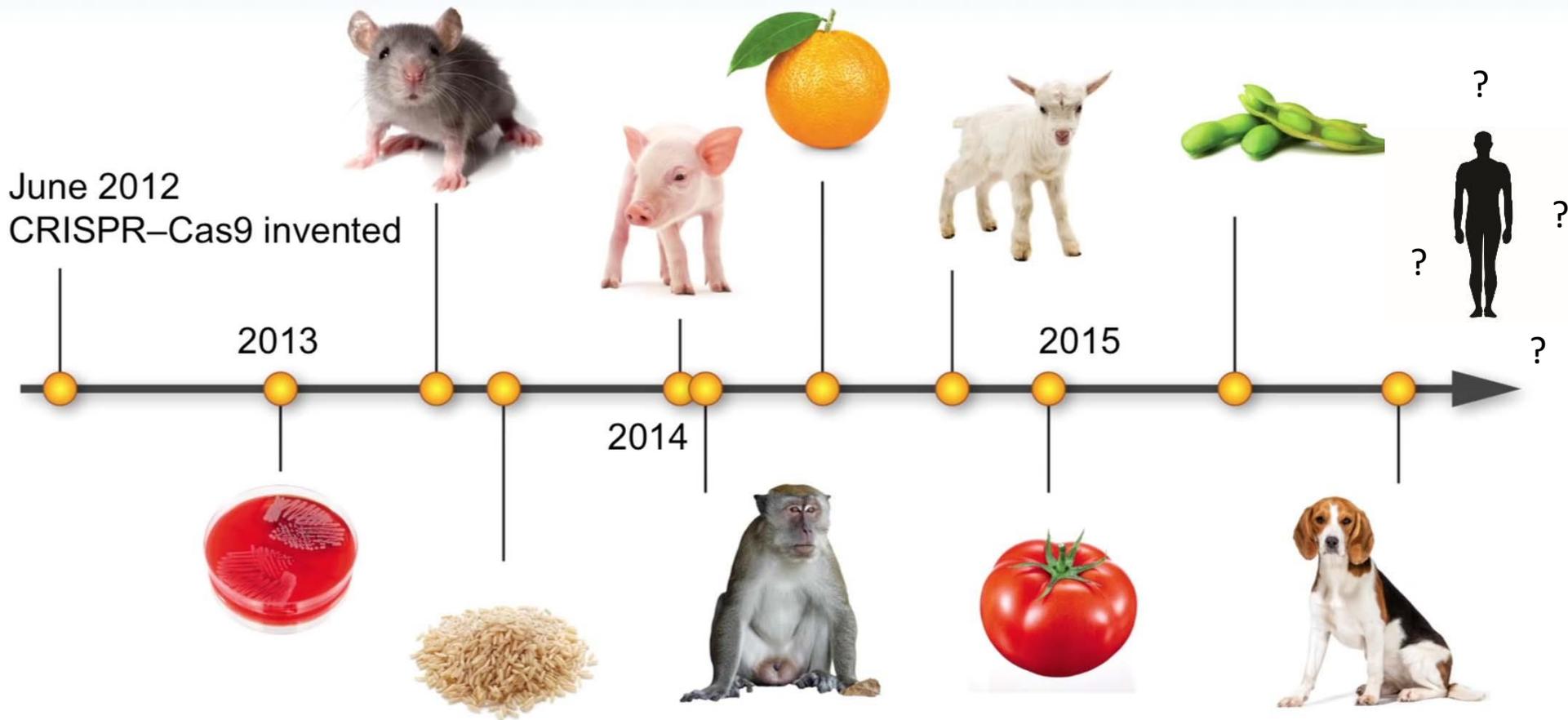
CRISPR-Cas  
counter-selects  
against the  
wild-type allele  
and stimulates  
DNA repair





# CRISPR-Cas als genetisch gereedschap

## CRISPR-edited cells, plants & animals





# CRISPR-Cas als genetisch gereedschap

Gene editing

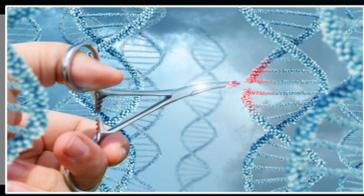
Epigenetics



(Source: Kurzgesagt)

Other...

Diagnostics



# CRISPR-Cas als genetisch gereedschap

Gene editing

Epigenetics

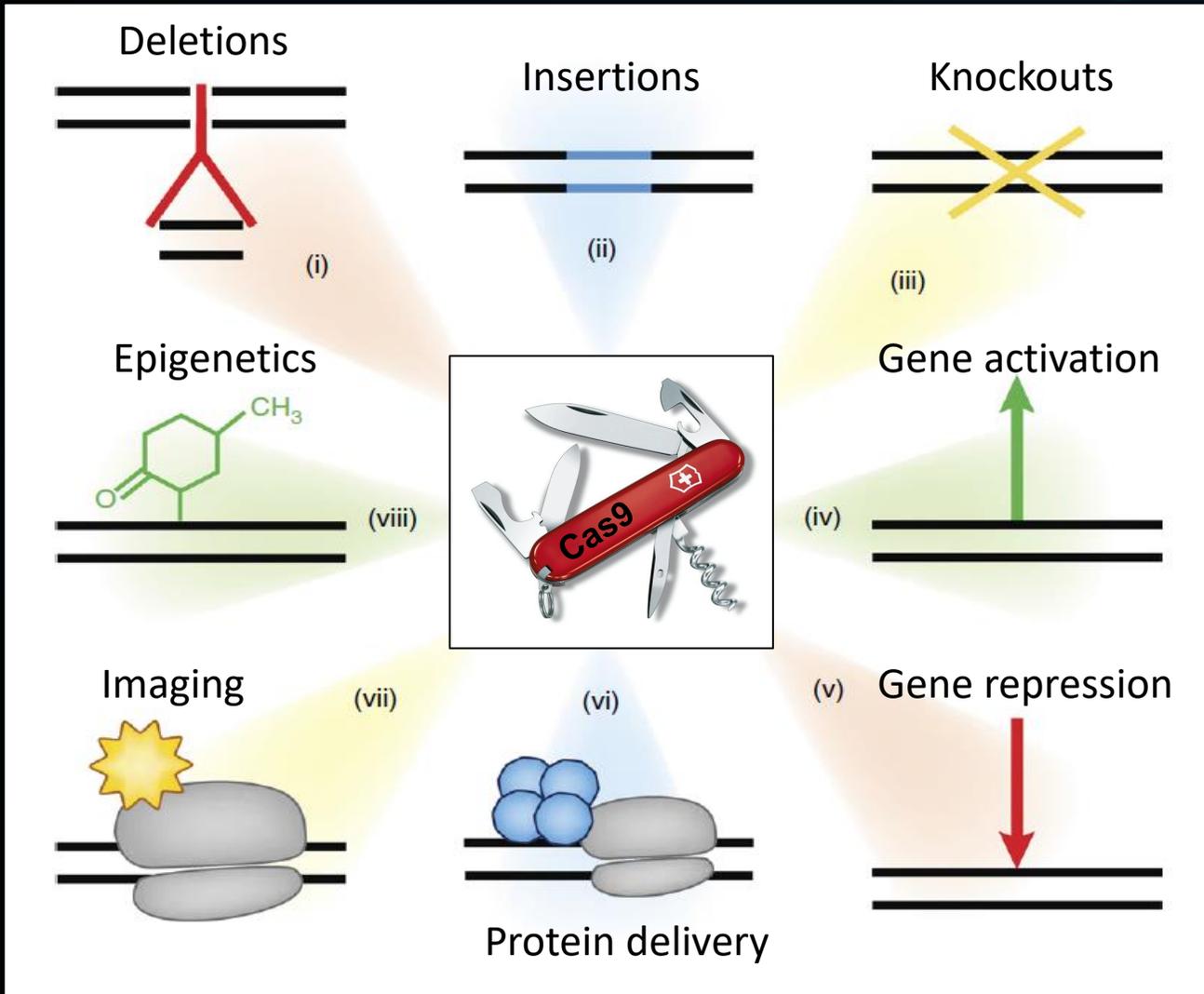


(Source: Kurzgesagt)

Other...

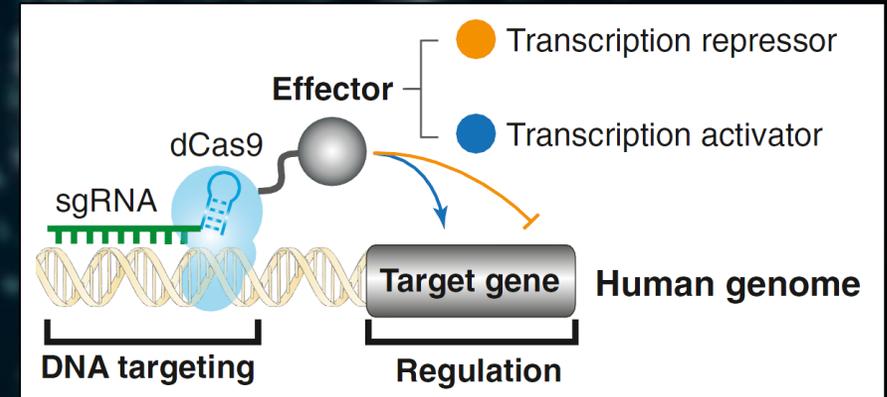
Diagnostics

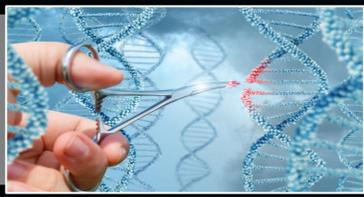
# CRISPR-Cas als genetisch gereedschap



(Barrangou & Doudna, Nat Biotechnol. 2016)

## Epigenetics





# CRISPR-Cas als genetisch gereedschap

Gene editing

Epigenetics



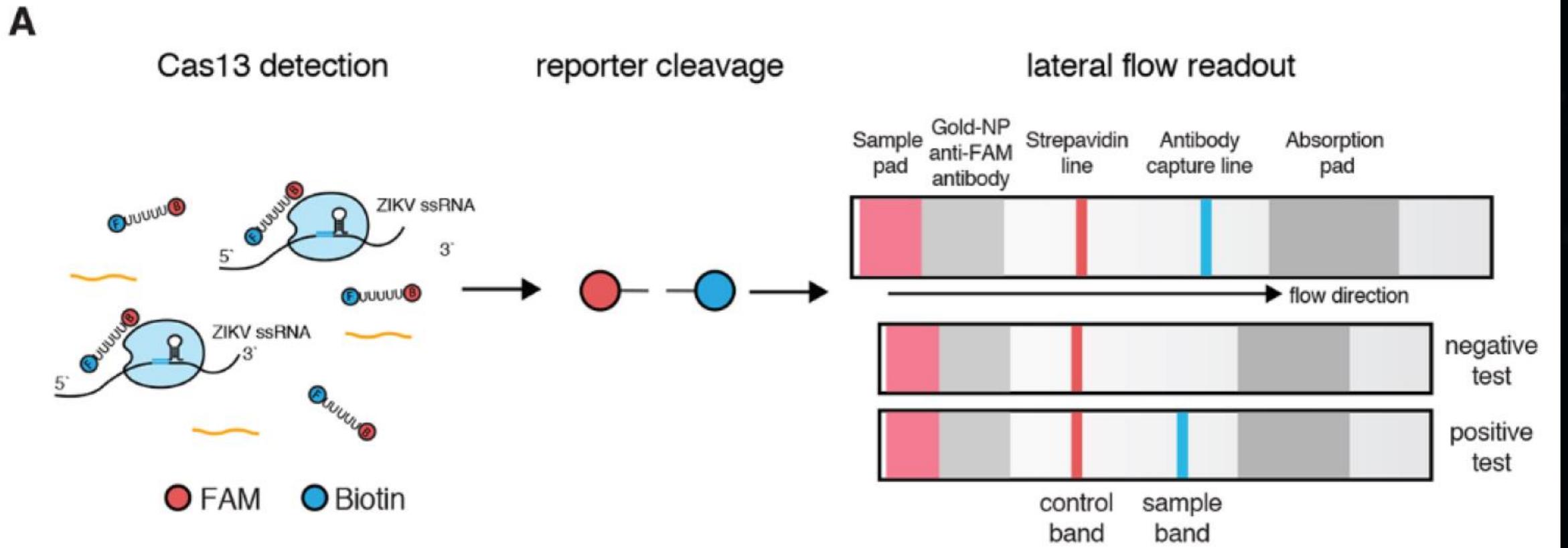
(Source: Kurzgesagt)

Other...

Diagnostics

# CRISPR-Cas als genetisch gereedschap

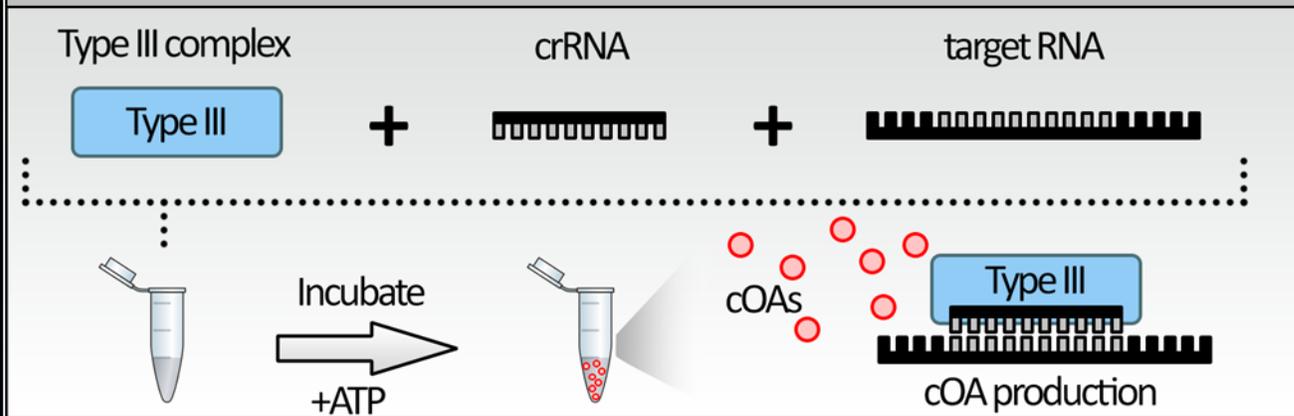
## Diagnostics





# CRISPR-Cas als genetisch gereedschap

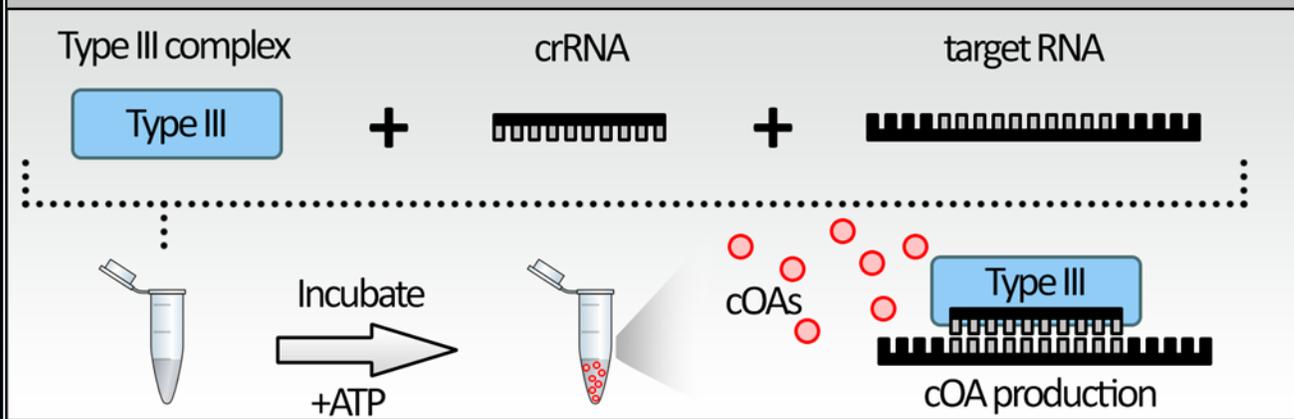
## 1. RNA detection by type III $\rightarrow$ cOA production



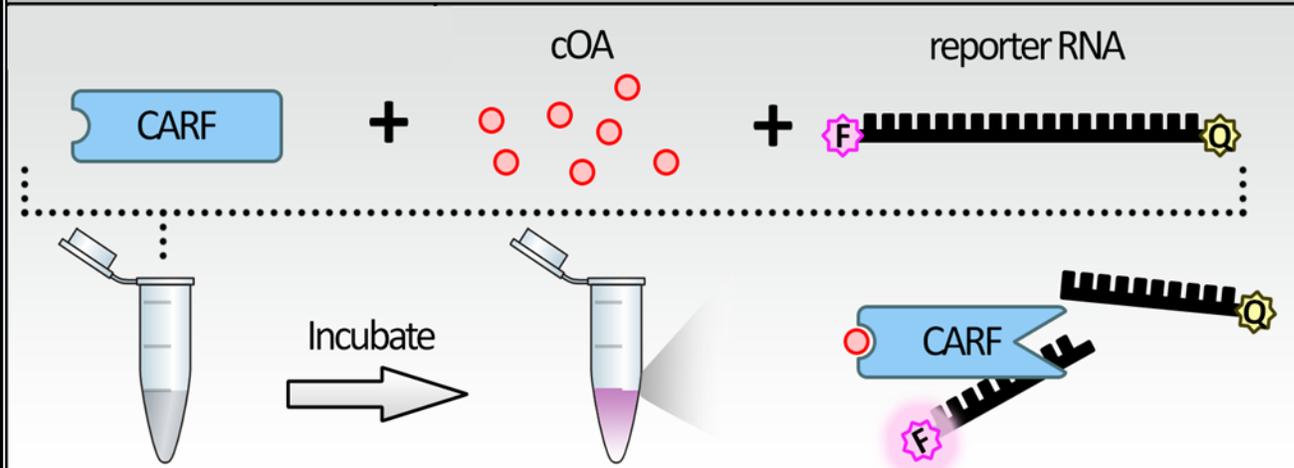
# CRISPR-Cas als genetisch gereedschap



## 1. RNA detection by type III → cOA production



## 2. CARF activation by cOAs → signal

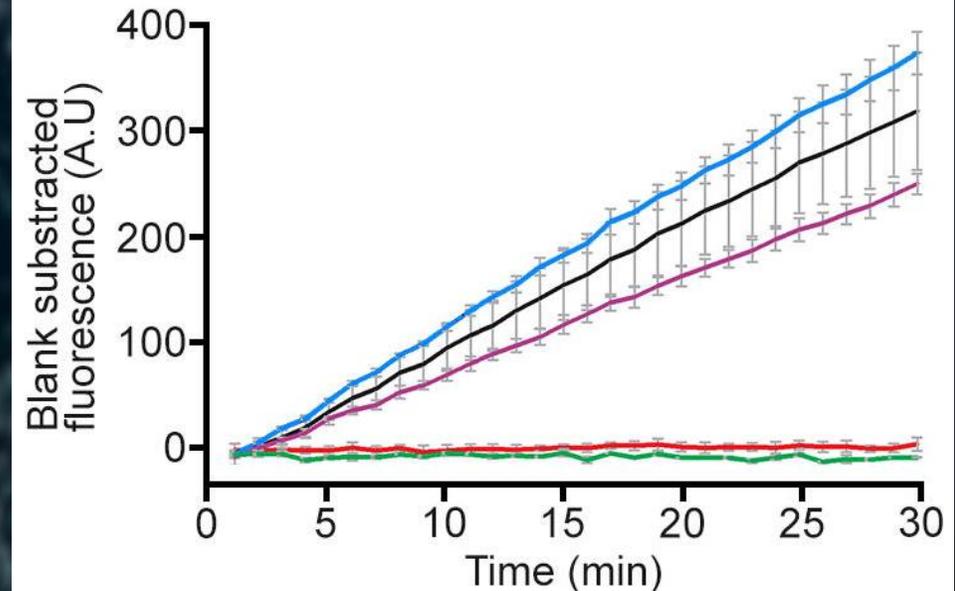


# SCOPE

biosciences

### SARS-CoV-2 E-gene 2-step SCOPE LOD

— 4 fM      — 40 aM      — 200 pM NT  
— 400 aM      — 4 aM



# CRISPR diagnostic company Scope Biosciences raises €1M funding in a partnership with GenDx

November 5, 2021



WAGENINGEN, 29<sup>th</sup> October 2021 – Diagnostic startup company Scope Biosciences B.V. has raised €1M funding from Utrecht based GenDx, specialized in Next Generation Sequencing (NGS) products for transplant diagnostics.



# CRISPR-Cas als genetisch gereedschap

Gene editing

Epigenetics



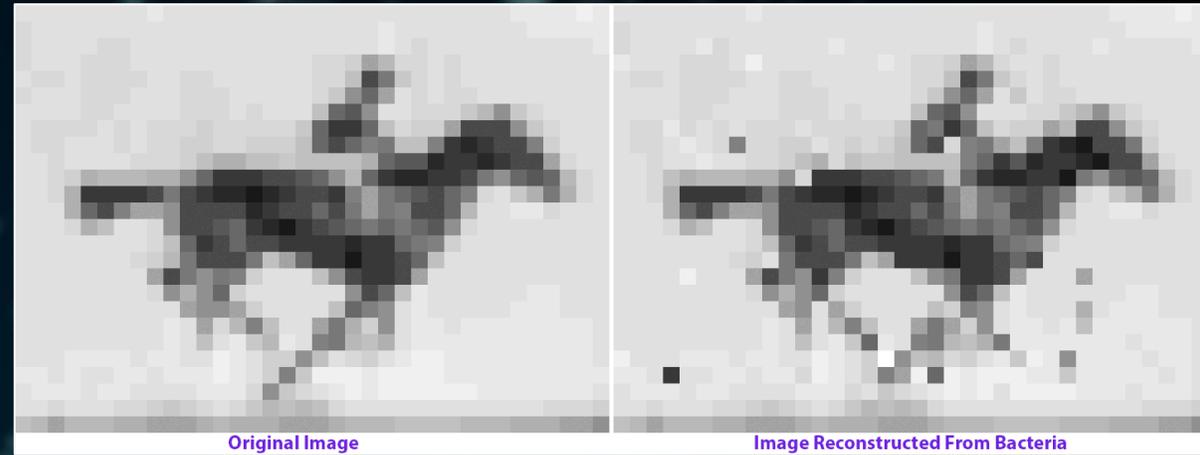
(Source: Kurzgesagt)

Other...

Diagnostics

# CRISPR-Cas als genetisch gereedschap

- Molecular recording
- Reviving extinct species
- 'Hybrid' species
- Gene drives (!)



(First movie recorded on a bacterial genome using CRISPR-Cas)



(Mammoth revival project - Colossal Biosciences)

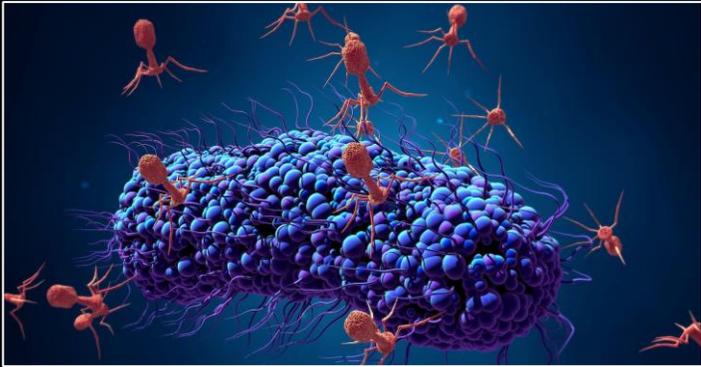


(Pyrenean ibex)



('Woolly Mouse' with mammoth-like traits)

# Onderwerpen



Oorsprong CRISPR-Cas



CRISPR-Cas als  
genetisch gereedschap



Impact op de maatschappij



# Impact op de maatschappij



Healthcare



Environment



Agriculture &  
food



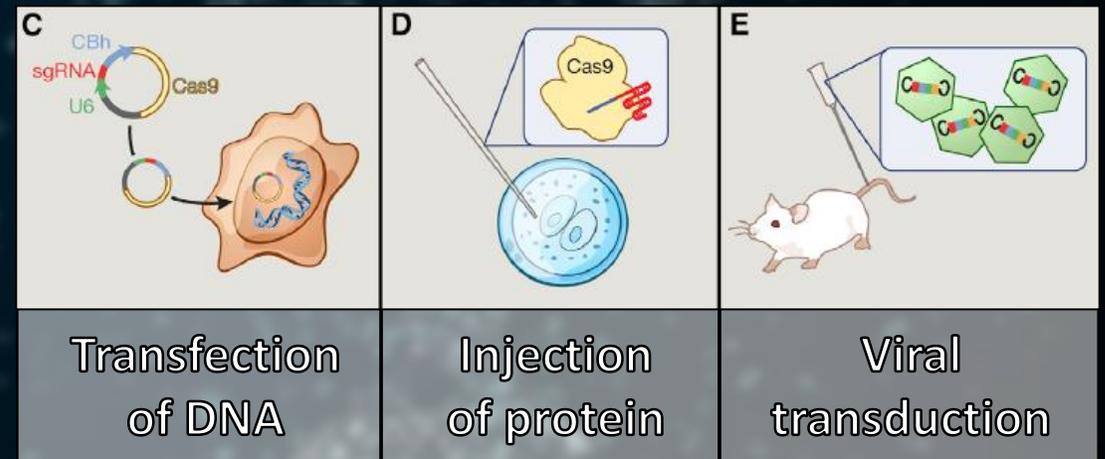
Ethics &  
legislation



# Healthcare

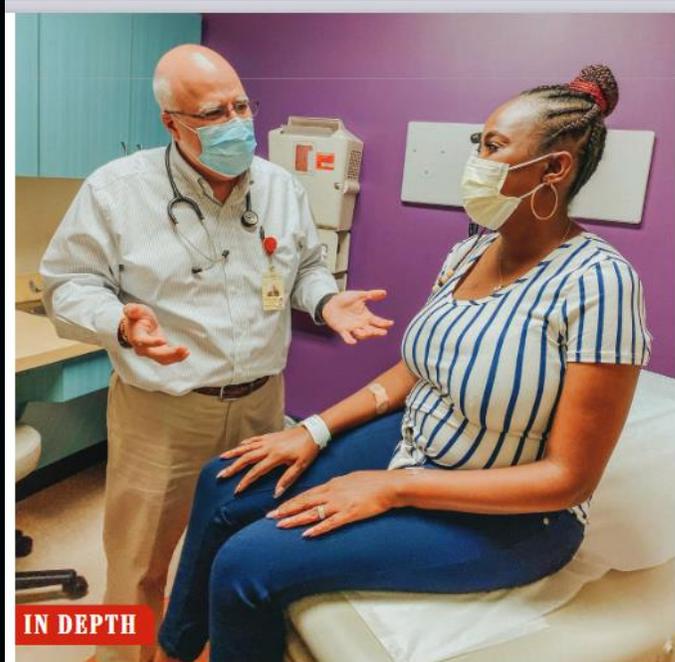
- ✓ Personalized medicine
- ✓ Germline editing
- ✓ Diagnostics
- × Delivery
- × Off-targeting
- × Ethics / legislation

## Delivery methods





# Healthcare



IN DEPTH

BIOMEDICINE

## Tweaking genes with CRISPR or viruses fixes blood disorders

People with sickle cell disease or beta-thalassemia could be freed of debilitating symptoms for a lifetime

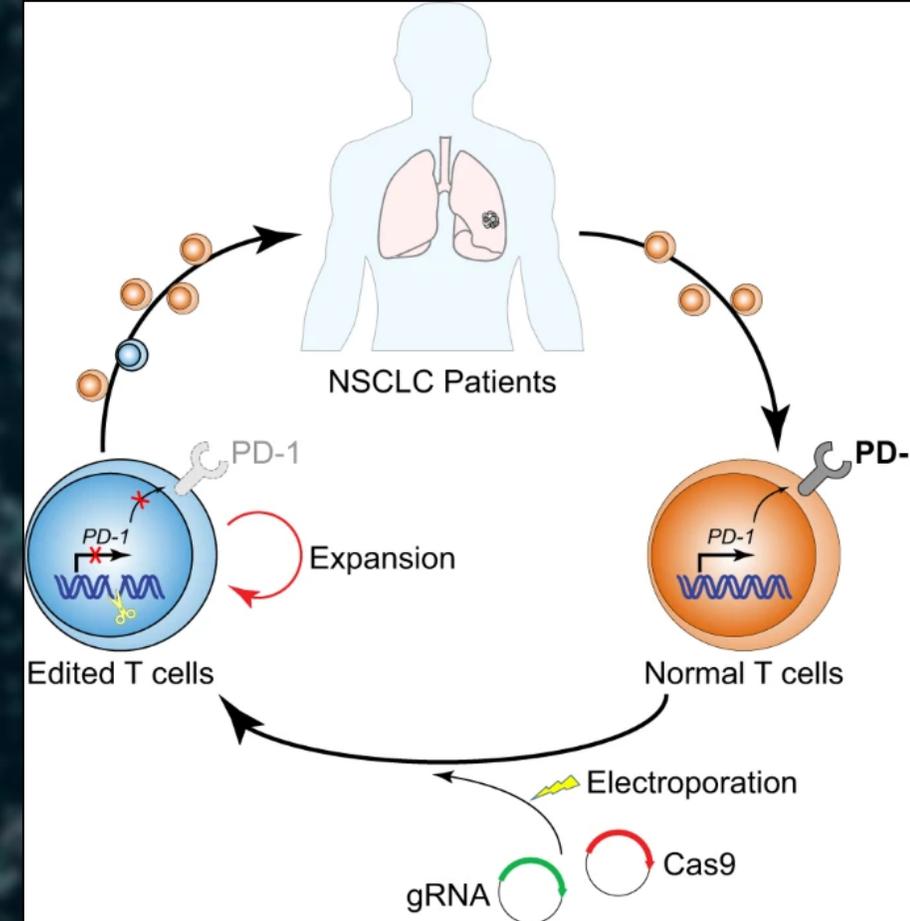
Dec 2020

## UK first to approve CRISPR treatment for diseases: what you need to know

The landmark decision could transform the treatment of sickle-cell disease and  $\beta$ -thalassaemia – but the technology is expensive.



Nov 2023





# Healthcare

Menu

Amsterdam UMC



Zoek

← Vandaag

🕒 24 mei 2022



## Eerste Nederlandse patiënt behandeld met CRISPR-Cas9-infuus

Innovatie

Patiëntenzorg

Zeldzame ziekten

Genen

De eerste behandeling met CRISPR-Cas9-infuus in Amsterdam UMC is een feit! Na vier uur aan het infuus kon de patiënt, die een ernstige vorm heeft van het hereditair angio-oedeem (HAE), nog dezelfde dag naar huis. Wereldwijd is hij de vijfde patiënt met HAE die deze nog experimentele behandeling mocht ondergaan. Internist en onderzoeksleider Danny Cohn volgde het proces vanaf Bonaire, waar hij tijdelijk is gedetacheerd.

Deel dit



Onderzoeksprofiel

[Danny M. Cohn](#)

Onderzoeksinstituut



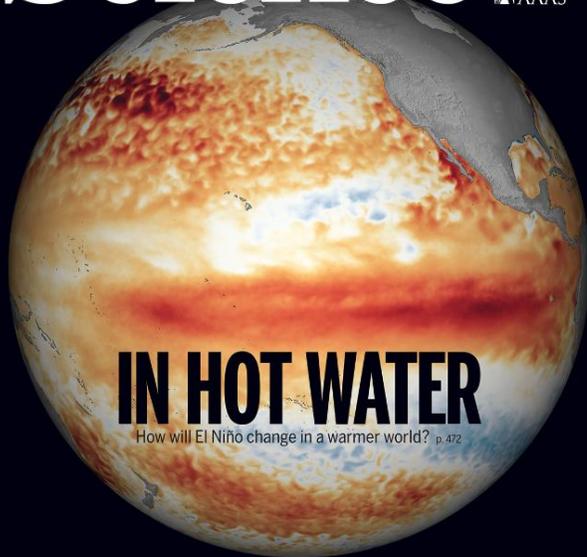
# Healthcare

Horbivore impacts don't depend on species origin pp. 478 & 531 | Polymer networks with reversibly tunable properties pp. 481 & 545 | Reconstructing histories of sign languages p. 519

# Science

\$15  
2 FEBRUARY 2024  
science.org

AAAS



## IN HOT WATER

How will El Niño change in a warmer world? p. 472

*“Type III-B CRISPR-Cas cascade of proteolytic cleavages”*  
(Steens *et al.*, Science 2024)

deVolkskrant

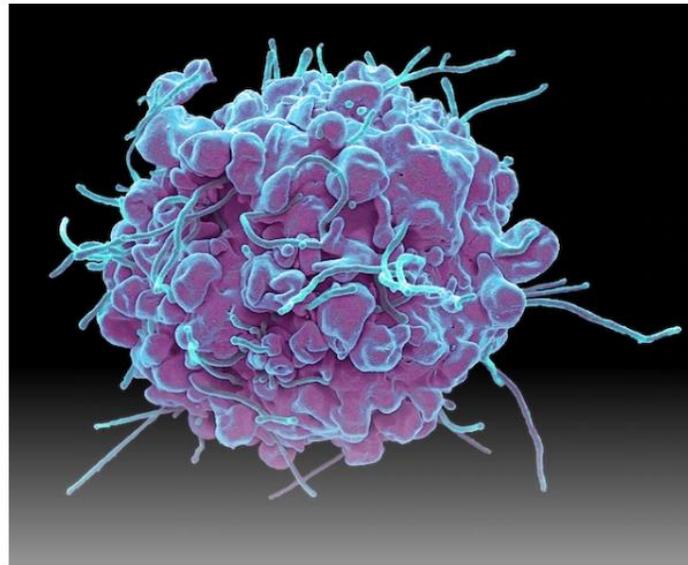
Topverhalen vandaag | Opinie | Cartoons | Cultuur & Media

NIEUWS

## Nieuwe stap crispr-cas: foute cellen tot zelfmoord drijven. Straks in tumoren?

Een obscure bacterie blijkt zichzelf aan stukken te knippen als hij een virusinfectie oploopt, ontdekten Wageningse wetenschappers. Bizar, diepzinnig en mogelijk met verstrekkende consequenties. ‘De natuur is soms prachtig.’

Maarten Keulemans 3 februari 2024, 05:00



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FEATURES

## Type III CRISPR-Cas launches ‘Destroyer of Worlds’ to save colony

Daniël Linzel | 12 februari 2024



Wageningen researchers describe in *Science* how type III CRISPR-Cas systems activate a cascade of reactions that causes an infected bacterium to die, but the rest of the colony to survive. ‘You could call it an altruistic act.’



# Agriculture & food

- ✓ Climate-resilient crops
- ✓ Higher yields, less pesticides
- ✓ Speed breeding
- ✓ Biotechnology / fermentation
- × GMO?
- × (European) legislations
- × Patents & malpractices



Bioreactor



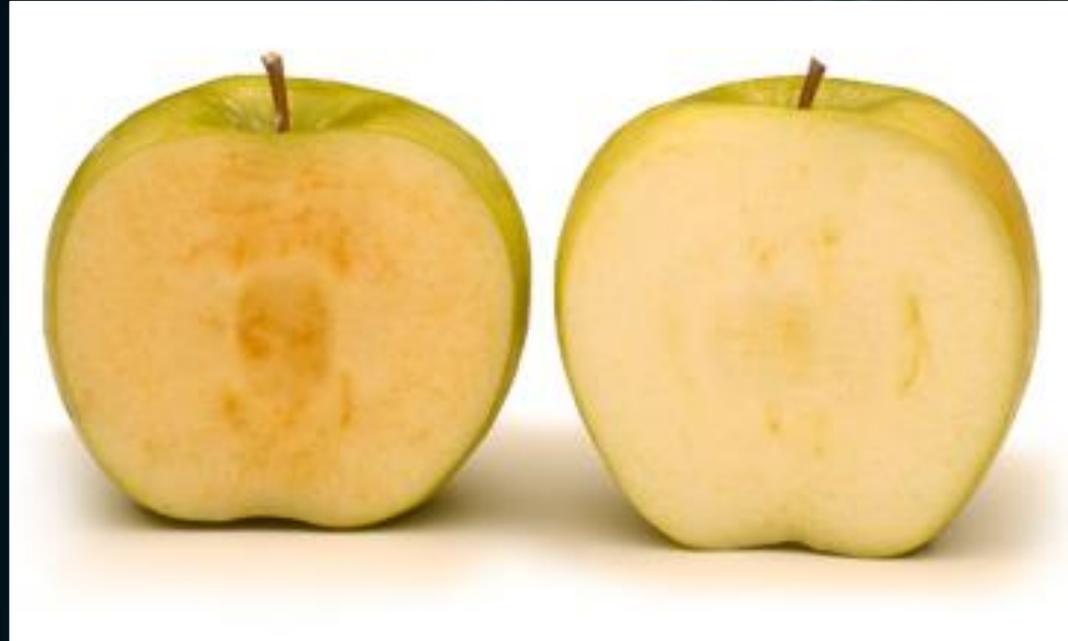
# Agriculture & food

## FRANKENFUNGI UNREGULATED BY USDA

Genetically engineered white button mushroom could be the first of many new CRISPR-edited food products



GMOiNSIDE.org  
Coalition Powered by Green America



BGI announced its plan to sell the micropigs as pets at a summit in Shenzhen, China.

GENE EDITING

## Gene-edited pigs to be sold as pets

SCIENCEINSIDER | EUROPE

## European Parliament votes to ease regulation of gene-edited crops

Move is a major victory for biotechnology, but debate remains over patents and labels

7 FEB 2024 • 6:20 PM ET • BY [ERIK STOKSTAD](#)



# Environment

- ✓ More resilient ecosystems
- ✓ Control invasive species
- ✓ Eradication of disease-carrying pests
- × Ecological (in)balance





# Environment

## Gene Drives

### STANDARD INHERITANCE

Mosquito with modified gene



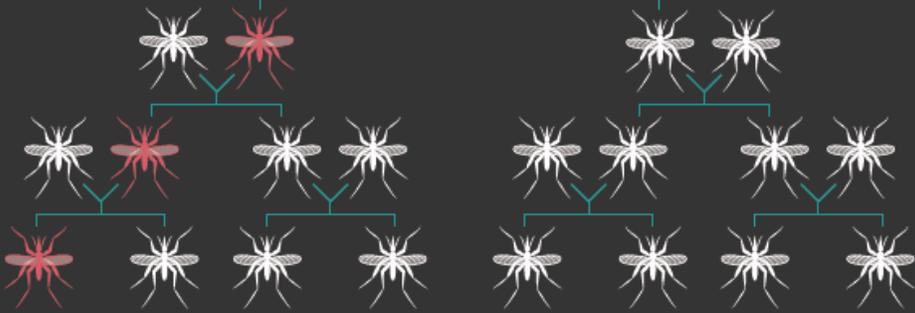
Wild-type mosquito



Each parent passes on one chromosome of a pair to its offspring.



Offspring have a 50% chance of inheriting the modified gene.



Modified gene spreads slowly through population.

### GENE-DRIVE INHERITANCE

The gene-drive system cuts the partner chromosome, then the repair process copies the modification to this chromosome.

Mosquito with modified gene + gene drive.



Wild-type mosquito



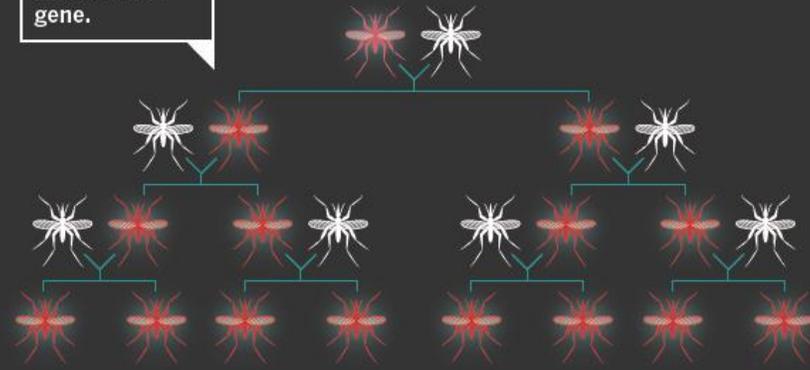
Cut



Repair



Nearly 100% of offspring inherit the modified gene.



Modified gene sweeps rapidly through population.





# Ethics & legislation



*Where do we  
draw the  
line?*



**GENETICS**

## Embryo editing divides scientists

*Researchers disagree over whether making heritable changes to genes crosses an ethical line.*

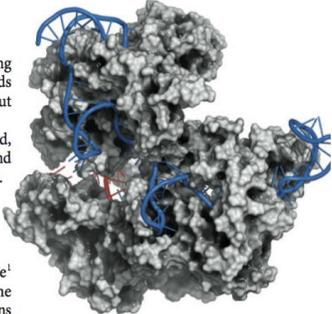
BY DAVID CYRANOSKI

Research that uses powerful gene-editing techniques on human embryos needs to be restricted, scientists agree — but they are split over why.

Some say that if safety fears can be allayed, such applications could have a bright future, and could help to eradicate devastating diseases. Others say that modifying the DNA of embryos, which means that the changes could be passed on to future generations, is an ethical line that should not be crossed.

The concerns are laid out in an article<sup>1</sup> published in *Nature* on 12 March and in one expected to appear in *Science*, amid suspicions that scientists have already edited the genes of human embryos.

CRISPR/Cas9 makes precisely targeted gene edits.



**DESIGNER BABIES**

# Ethics



# Ethics & legislation

# Y'ALL HEARD about

# CRISPR BABIES?



*Where do we  
draw the  
line?*





# Ethics & legislation

Plant breeding

What **IS** a GMO?

Public perception

Accessibility

## Crop Modification Techniques

### Cross Breeding

Combining two sexually compatible species to create a variety with the desired traits of the parents



The Honeycrisp Apple gets its famous texture and flavor by blending the traits of its parents.

### Mutagenesis

Use of mutagens such as radioactivity to induce random mutations, creating the desired trait



Radiation was used to produce a deeper color in the red grapefruit.

### Polyploidy

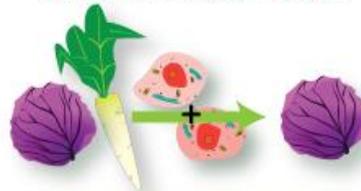
Multiplication of the number of chromosomes in a crop to impact its fertility



Seedless watermelons are created by crossing a plant with 2 sets of chromosomes with another that has 4 sets. The seedless fruit has 3 sets.

### Protoplast Fusion

Fusion of cells or cell components to transfer traits between species



Male sterility is transferred from radishes to red cabbage by fusing their cells. Male sterility helps plant breeders make hybrid crops.

### Transgenesis

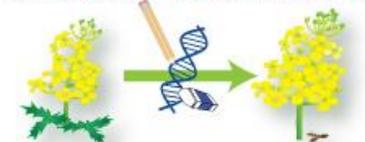
Addition of genes from any species to create a new variety with desired traits



The Rainbow Papaya is modified with a gene that gives it resistance to the Papaya Ringspot Virus.

### Genome Editing

Use of an enzyme system to modify DNA directly within the cell



Genome editing was used to develop herbicide resistant canola to help farmers control weeds.

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By Layla Katiraei (@BiochicaGMO) in collaboration with Karl Haro von Mogel (@kharvml)

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# Take home messages

- CRISPR-Cas is an **adaptive** antiviral immune system in bacteria.
- CRISPR-Cas genome editing is a **disruptive technology** for many different fields
- Many technical, ethical and legislative **hurdles** still left to tackle

Questions?

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# De impact van **CRISPR-Cas** op onze maatschappij

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