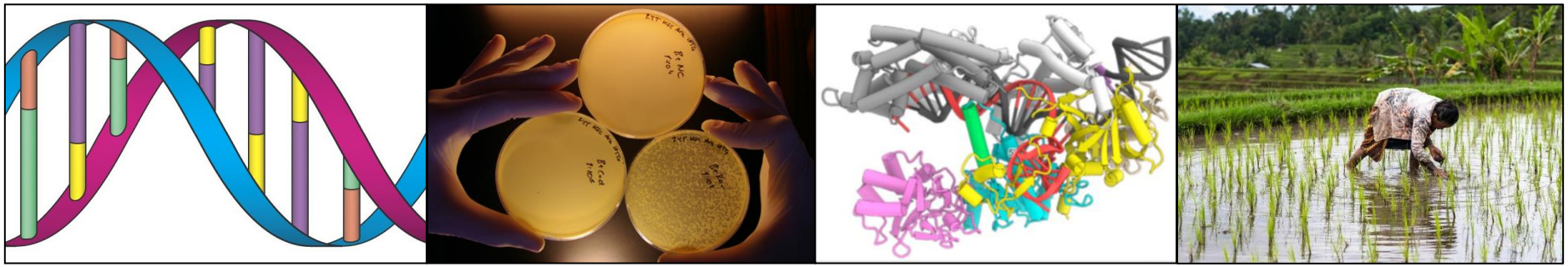
de CRISPR-Cas revolutie

van biologie naar biotechnologie & gen therapie



John van der Oost

Laboratory of Microbiology
Wageningen University

John van der Oost - Disclosure

Employed by Wageningen University & Research

Co-founder & Scientific Advisor of NTrans Technologies (*gene therapy*)

Scientific Advisor of Scope Biosciences (*pathogen diagnostics*)

Consultant of Hudson River Biotechnology (*crop improvement*)

Inventor on several patents and patent applications

Ongoing research projects supported by NWO, ERC & private sponsors

de CRISPR-Cas revolutie

- DNA – wat is het, en waarom is het belangrijk ?
- CRISPR-Cas – van ontdekking tot toepassing
- Recente voorbeelden – van biotechnologie tot gen therapie
- Dilemma – waar trekken we de streep ?
- Surprise act !

de CRISPR-Cas revolutie

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DNA – wat is het ?

- DNA is verantwoordelijk voor de opslag van genetische informatie
- DNA chromosomen komen voor in (bijna) alle organismen
- DNA komt voor in elke levende cel (bacterie, plant, mens)

DNA – wat is het ?

equipment, and to Dr. G. E. R. Deacon and the captain and officers of R.R.S. *Discovery II* for their part in making the observations.

1 Young, F. B., Gerrard, H., and Jevons, W., *Phil. Mag.*, **40**, 149 (1920).

2 Longuet-Higgins, M. S., *Mon. Not. Roy. Astro. Soc., Geophys. Supp.*, **5**, 285 (1949).

3 Von Arx, W. S., Woods Hole Papers in Phys. Oceanog. Meteor., **11** (3) (1950).

4 Ekman, V. W., *Arkiv. Mat. Astron. Fysik. (Stockholm)*, **2** (11) (1905).

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey[1]. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagrams is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Fraser (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

...ure is purely diagrammatic. The two ribbons symbolize the two phosphate–sugar chains, and the horizontal rods the pairs of bases holding the chains together. The vertical line marks the fibre axis

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β-D-deoxyribofuranose residues with 3′,5′ linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Furberg's[2] model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Furberg's 'standard configuration', the sugar being roughly perpendicular to the attached base. There is a residue on each chain every 3·4 A. in the *z*-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 A. The distance of a phosphorus atom from the fibre axis is 10 A. As the phosphates are on the outside, cations have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to tilt so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical *z*-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configurations) it is found that only specific pairs of bases can bond together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on these assumptions the other member must be thymine; similarly for guanine and cytosine. The sequence of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally[3,4] that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data[5,6] on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the results presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

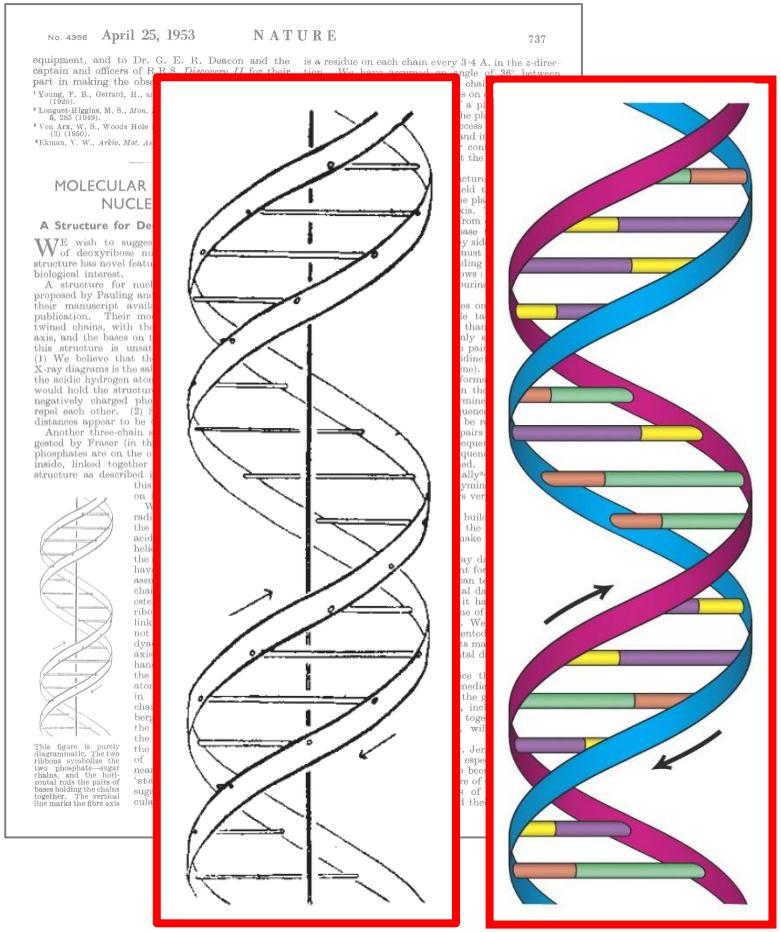
It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Donohue for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at

Watson & Crick 1953

DNA – wat is het ?



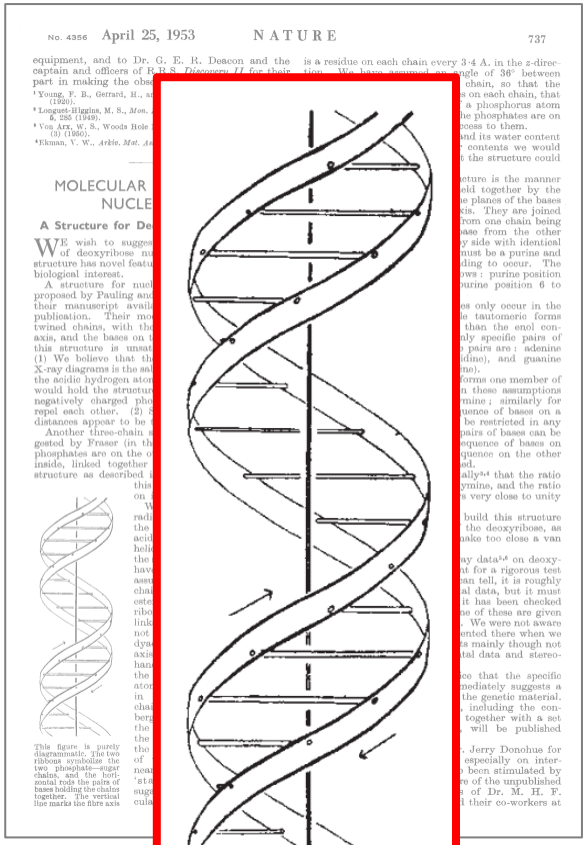
specifieke
base paring
G-C en A-T

“ This structure has novel features which are of considerable biological interest.

*It has not escaped our notice that the specific **pairing** we have postulated, suggests a possible copying mechanism for the genetic material. “*

Watson & Crick 1953

DNA – wat is het ?



No. 4356 April 25, 1953 NATURE 737

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MOLECULAR ... NUCLE...

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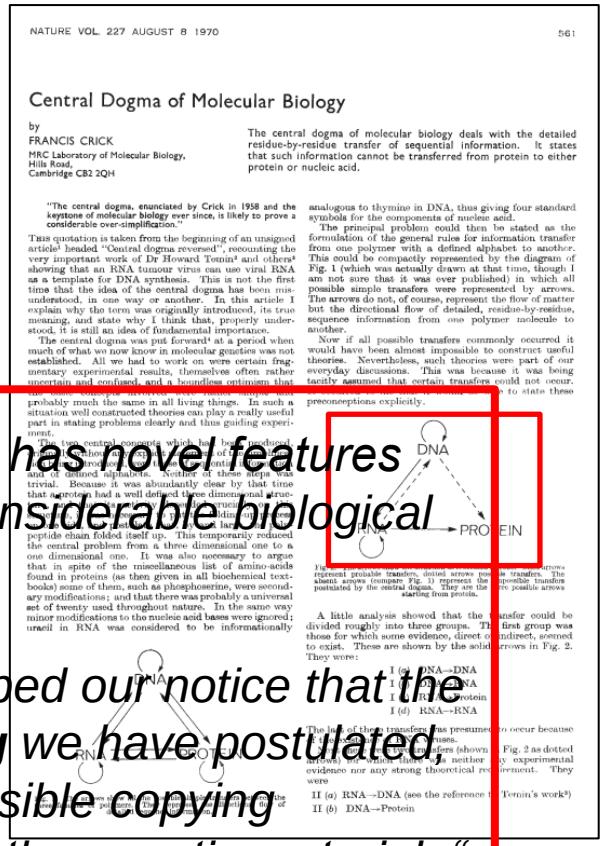


NATURE VOL. 227 AUGUST 8 1970 561

Central Dogma of Molecular Biology

by

FRANCIS CRICK

MRC Laboratory of Molecular Biology, Hills Road, Cambridge CB2 2QH

The central dogma of molecular biology deals with the detailed residue-by-residue transfer of sequential information. It states that such information cannot be transferred from protein to either protein or nucleic acid.

"The central dogma, enunciated by Crick in 1958 and the keystone of molecular biology ever since, is likely to prove a considerable over-simplification."

This quotation is taken from the beginning of an unsigned article[1] headed "Central dogma reversed", recounting the very important work of Dr Howard Temin[2] and others[3] showing that an RNA tumour virus can use viral RNA as a template for DNA synthesis. This is not the first time that the idea of the central dogma has been misunderstood, in one way or another. In this article I explain why the term was originally introduced, its true meaning, and state why I think that, properly understood, it is still an idea of fundamental importance.

The central dogma was put forward[4] at a period when much of what we now know in molecular genetics was not established. All we had to work on were certain fragmentary experimental results, themselves often rather uncertain and confused, and a boundless optimism that probably much the same in all living things. In such a situation well constructed theories can play a really useful part in stating problems clearly and thus guiding experiment.

The two central concepts which had been produced ... and of defined alphabets. Neither of these steps was trivial. Because it was abundantly clear by that time that a protein had a well defined three dimensional structure ... peptide chain folded itself up. This temporarily reduced the central problem from a three dimensional one to a one dimensional one. It was also necessary to argue that in spite of the miscellaneous list of amino-acids found in proteins (as then given in all biochemical textbooks) some of them, such as phosphoserine, were secondary modifications; and that there was probably a universal set of twenty used throughout nature. In the same way minor modifications to the nucleic acid bases were ignored; uracil in RNA was considered to be informationally analogous to thymine in DNA, thus giving four standard symbols for the components of nucleic acid.

The principal problem could then be stated as the formulation of the general rules for information transfer from one polymer with a defined alphabet to another. This could be compactly represented by the diagram of Fig. 1 (which was actually drawn at that time, though I am not sure that it was ever published) in which all possible simple transfers were represented by arrows. The arrows do not, of course, represent the flow of matter but the directional flow of detailed, residue-by-residue, sequence information from one polymer molecule to another.

Now if all possible transfers commonly occurred it would have been almost impossible to construct useful theories. Nevertheless, such theories were part of our everyday discussions. This was because it was being tacitly assumed that certain transfers could not occur. ... to state these preconceptions explicitly.

... represent probable transfers, dotted arrows possible transfers. The absent arrows (compare Fig. 1) represent the impossible transfers postulated by the central dogma. They are the ... possible arrows starting from protein.

A little analysis showed that the ... transfer could be divided roughly into three groups. The first group was those for which some evidence, direct or indirect, seemed to exist. These are shown by the solid arrows in Fig. 2. They were:

I (*a*) DNA→DNA
I (*b*) RNA→RNA
I (*c*) RNA→Protein
I (*d*) RNA→RNA

The ... of these transfers was presumed to occur because ... uses. ... Fig. 2 as dotted ... arrows. There are neither any experimental evidence nor any strong theoretical reasons for them. They were

II (*a*) RNA→DNA (see the reference to Temin's work[3])
II (*b*) DNA→Protein

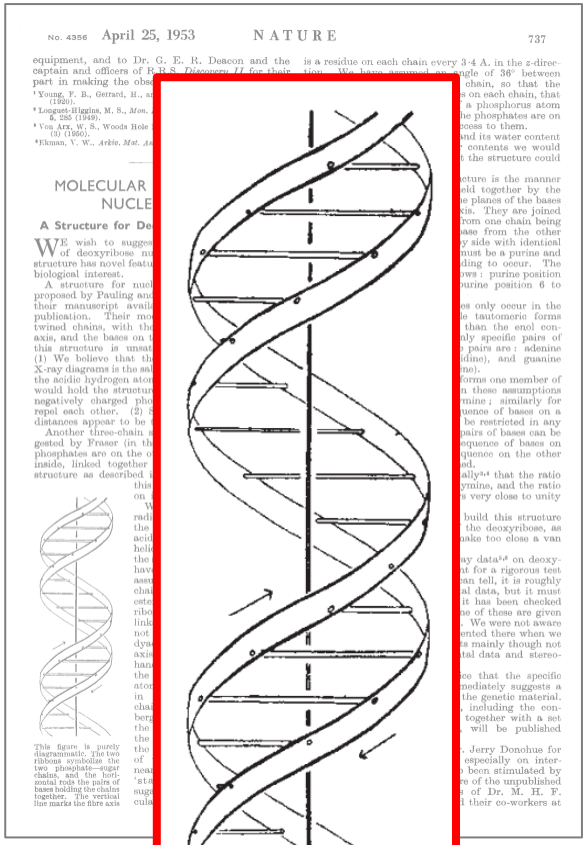
" This structure has novel features which are of considerable biological interest.

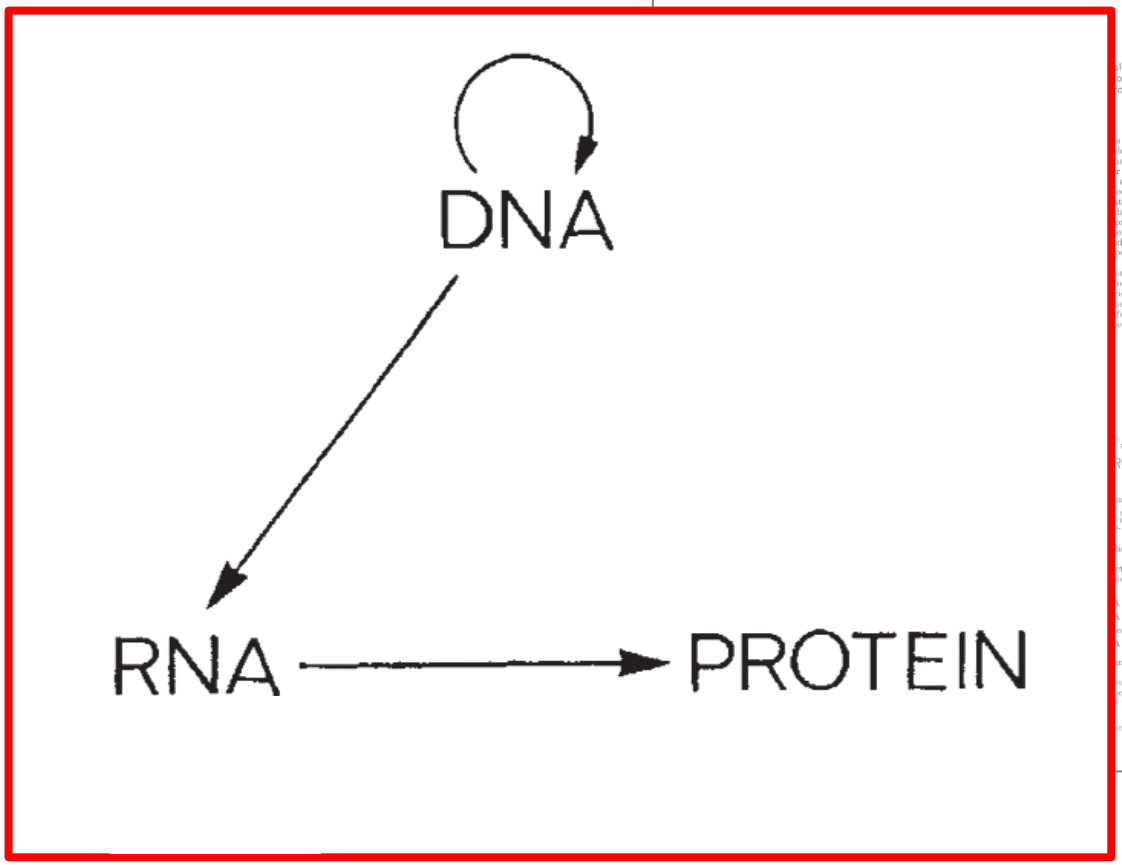
*It has not escaped our notice that the specific **pairing** we have postulated, suggests a possible copying mechanism for the genetic material. "*

Watson & Crick 1953

Crick 1958, 1970

DNA – wat is het ?





*the **Central Dogma of Molecular Biology** is defined as the directional flow of detailed, residue-by-residue, sequence information from one polymer molecule to another:* **DNA < DNA > RNA > PROTEIN**

Watson & Crick 1953

Crick 1958, 1970

DNA – waarom is het belangrijk ?

- DNA is verantwoordelijk voor de opslag van genetische informatie
- DNA chromosomen komen voor in (bijna) alle organismen
- DNA komt voor in elke levende cel (bacterie, plant, mens)
- DNA wordt verdubbeld voor celdeling (als organisme groeit)
- DNA kopieer-fouten komen voor (soms in mensen, vaak in virussen)
- DNA veranderingen kunnen nadelig zijn (genetische ziekte)
- DNA veranderingen kunnen ook voordelig zijn (evolutie)

de CRISPR-Cas revolutie

- DNA – wat is het, en waarom is het belangrijk ?
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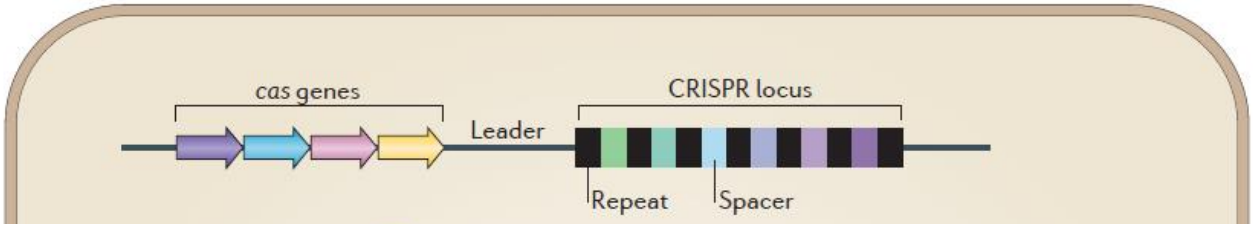
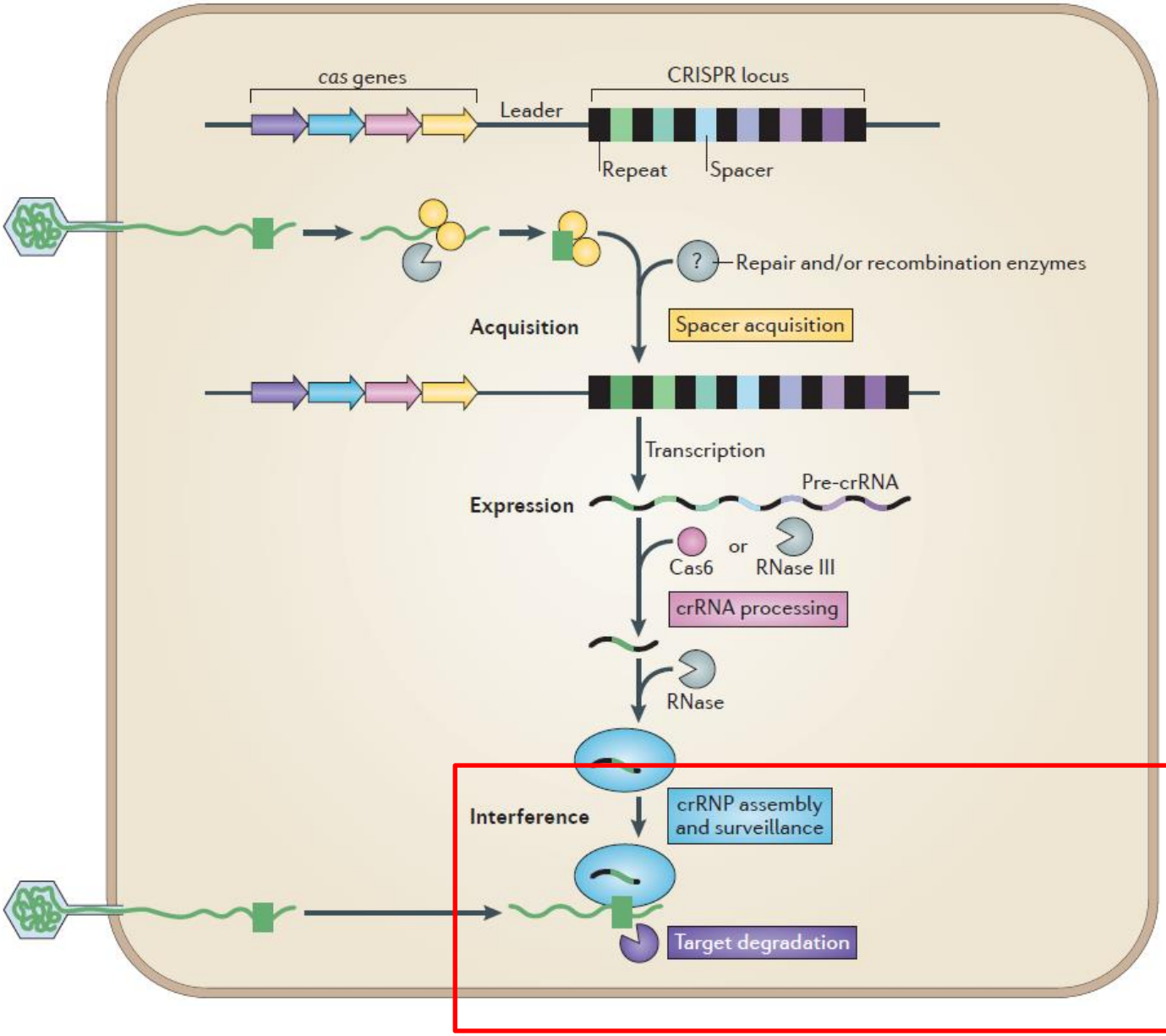
CRISPR-Cas mechanisme



CRISPR = clustered regularly interspaced short palindromic repeats

Cas = CRISPR-associated proteins

CRISPR-Cas mechanisme

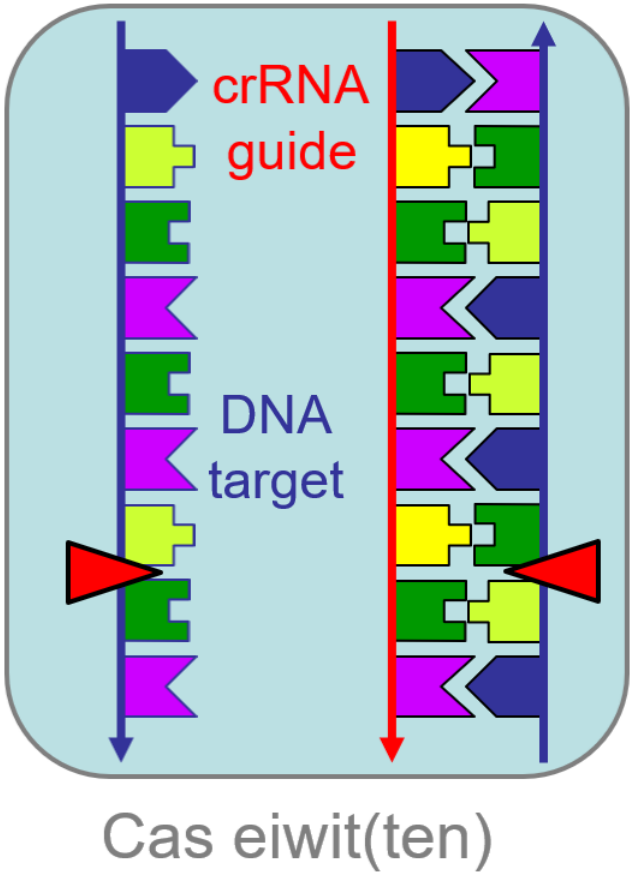


1. Spacer inbouw

2. Guide expressie

3. Target aanval

crRNA guides Cas nuclease to DNA target



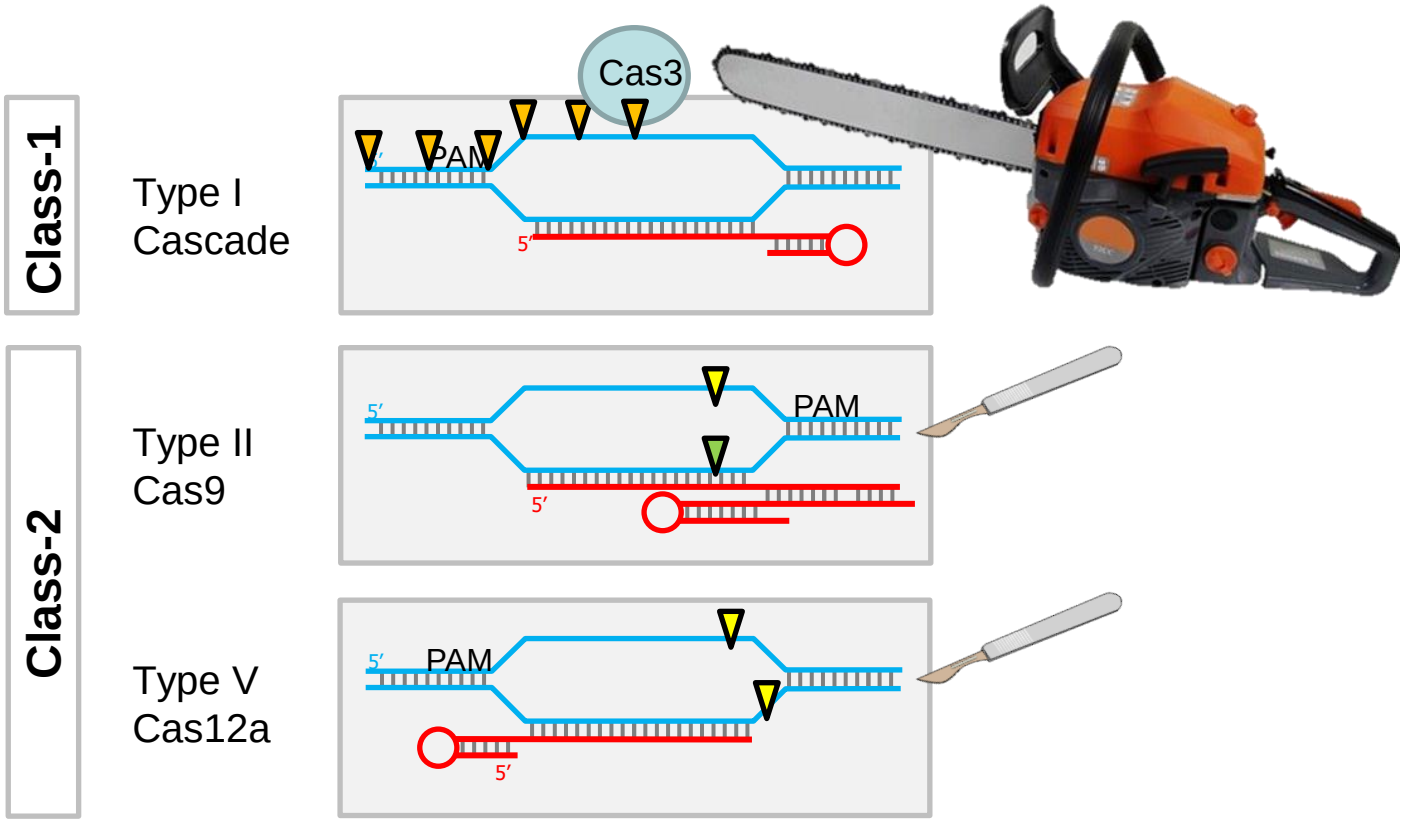
in dit voorbeeld is
een crRNA guide gebruikt
van 9 letters
(GATCTCATC),
dit “woord” komt 10.000x
voor in het humane genome ...

in een echt CRISPR systeem,
zijn guides vaak 20 letters
(GATCTCATCATGATCTCATC),
dit “woord” komt slechts 1x
voor in het humane genome ...

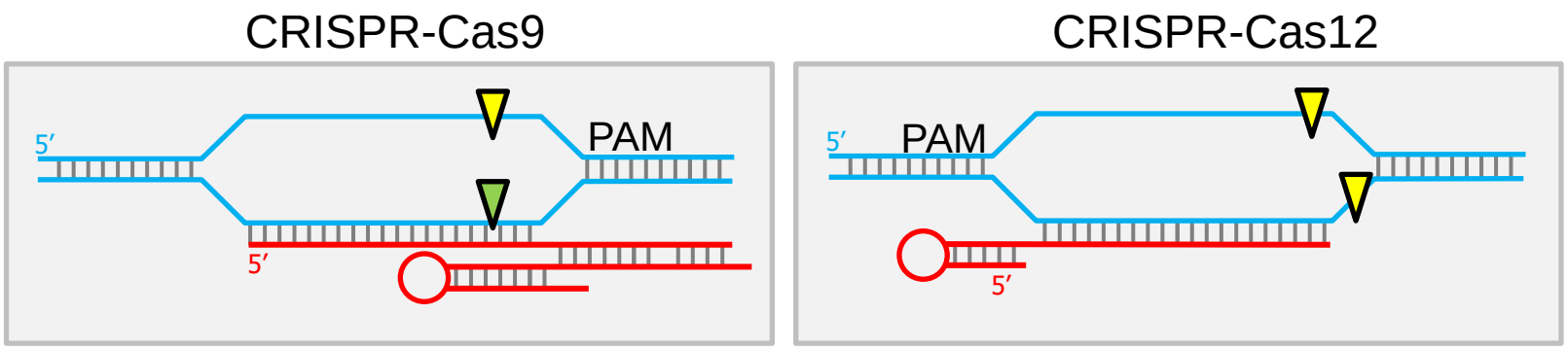
dus, we kunnen een guide
ontwerpen die heel specifiek
één enkele plek
kan vinden en knippen
op het humane DNA
(net als Ctrl-F / Ctrl-X)

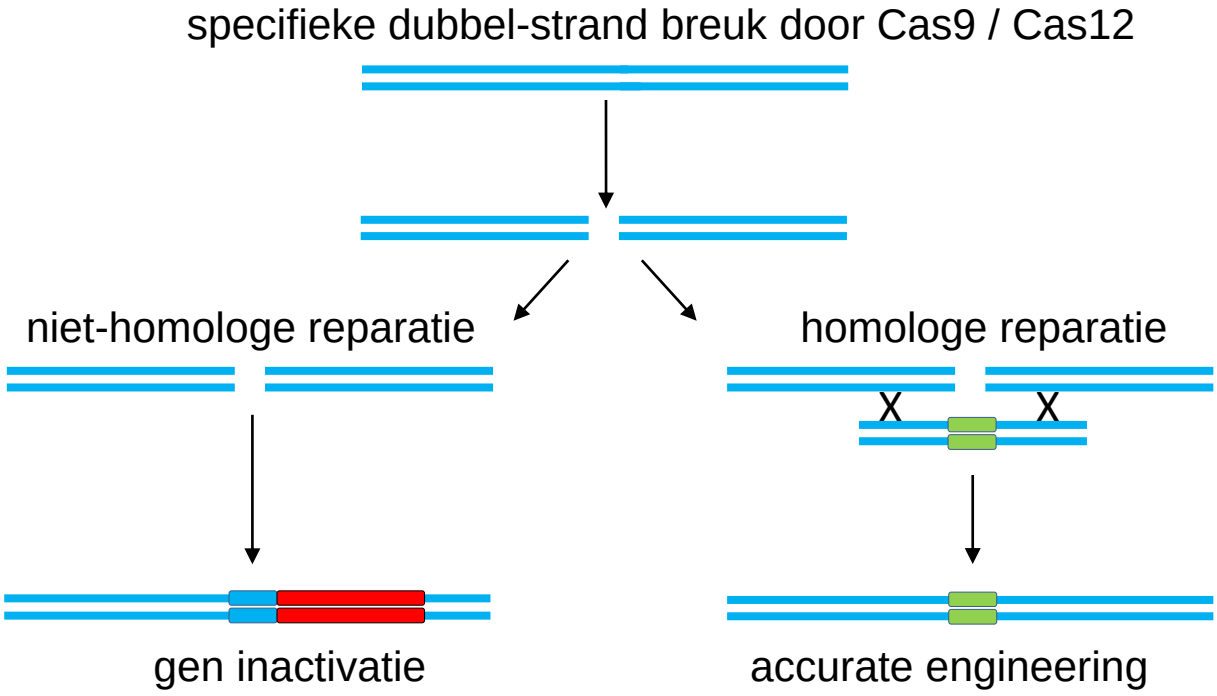
dit maakt specifieke
genome editing mogelijk

CRISPR-Cas – DNA editing

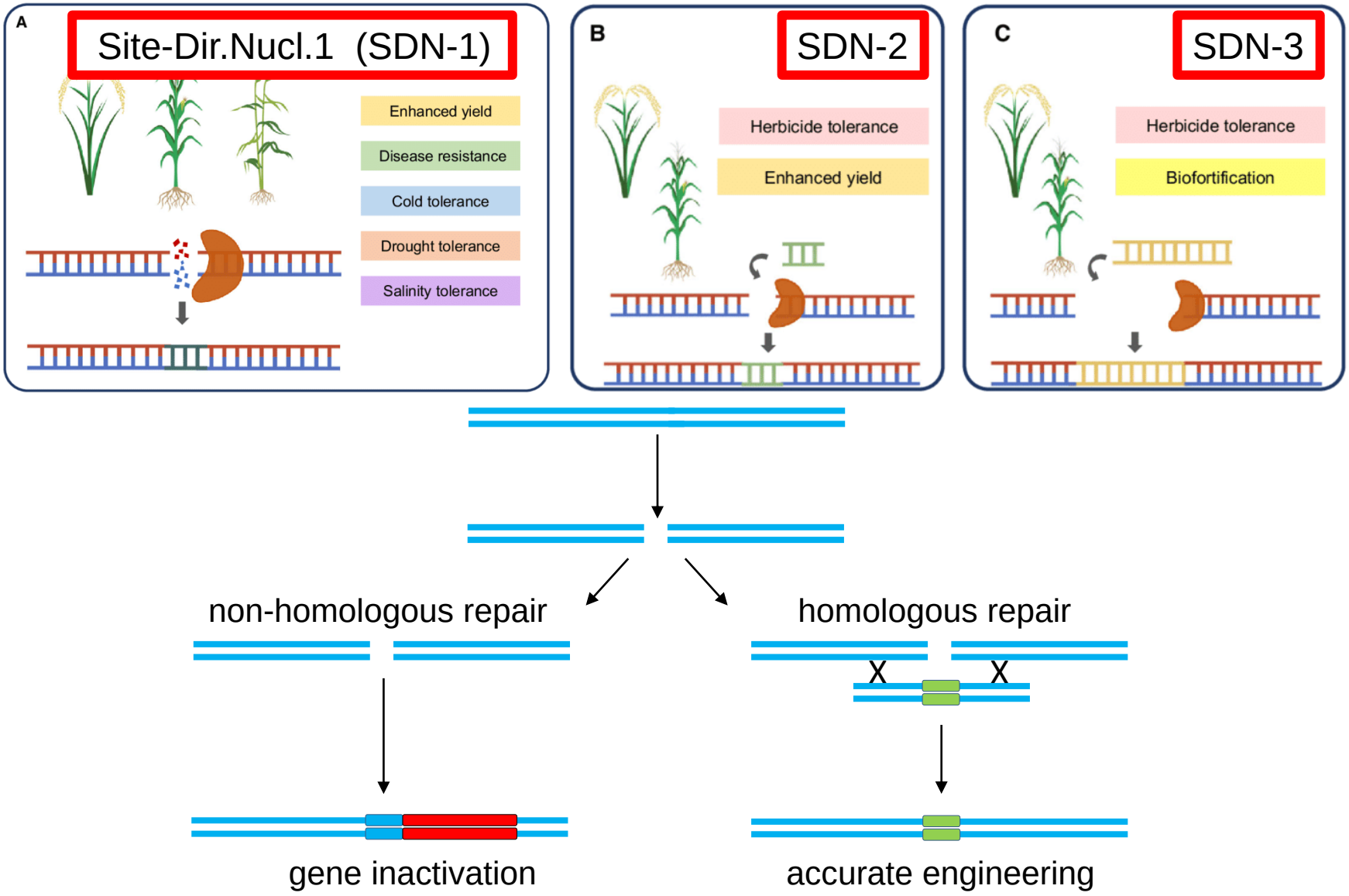


CRISPR-Cas – DNA editing





CRISPR-Cas – DNA editing



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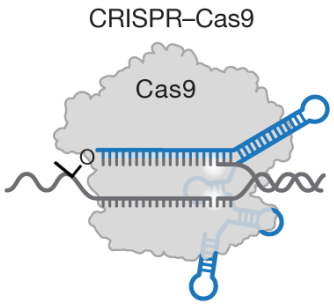
Cas9 & Cas12 – humane genome editing

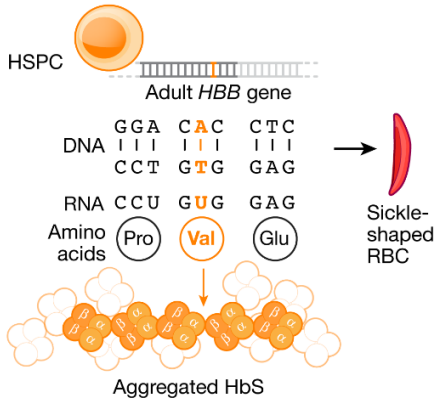
Genome editing

- Insertion of gene(s), deletion of gene(s), replacement of gene(s) by DSB
- 1–1,000s of nucleotides
- Permanent
- Other tools: meganucleases, TALENS, ZFNs, other CRISPR nucleases

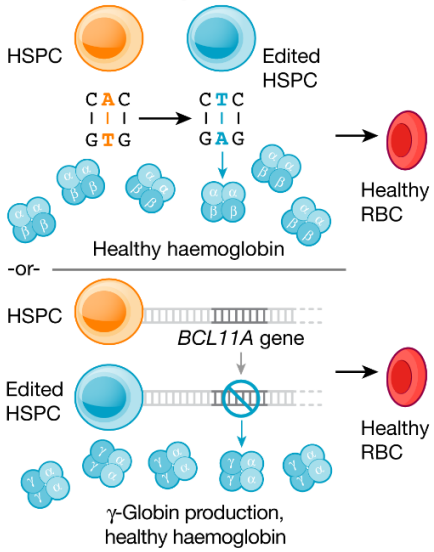


ex vivo

Sickle cell disease

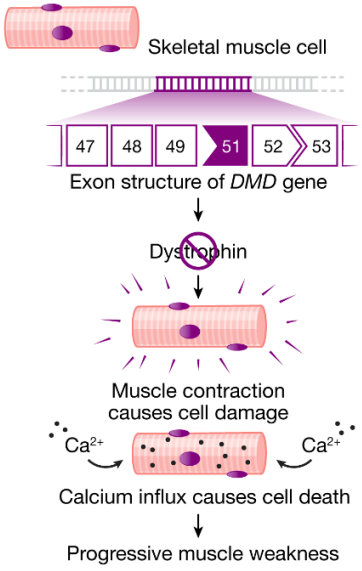


Blood cell editing

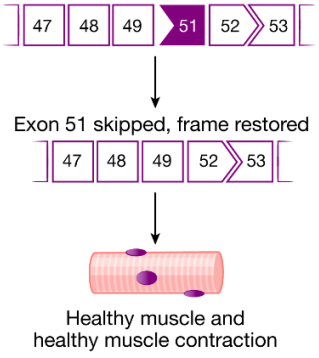


in vivo

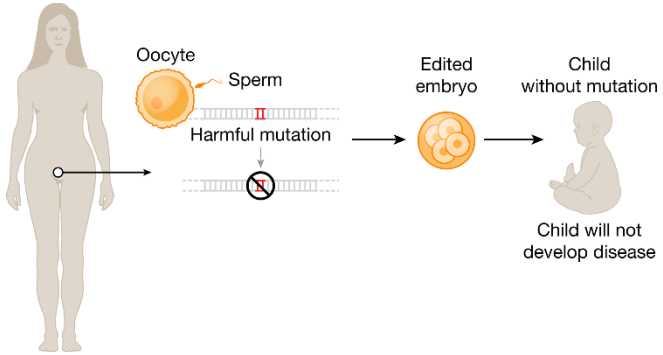
Duchenne muscular dystrophy



Muscle-cell editing



"in ovo"



reviewed by Doudna (2019) Nature

Mei 2022 – CRISPR therapy in Nederland

"hereditair angio-oedeem" is een zeldzame erfelijke aandoening, veroorzaakt door een tekort aan het eiwit *C1-esteraseremmer*. Als deze remmer ontbreekt, krijgt het zogeheten boodschapper-eiwit *kallikreine* vrij spel. En daardoor kunnen op allerlei plekken in het lichaam plotselinge zwellingen ontstaan.
CRISPR-Cas9 onderdrukt de aanmaak van een belangrijk boodschapper-eiwit (prekallikreïne), zodat het signaal dat leidt tot zwellingen niet meer kan worden doorgegeven."

Juli 2022 – CRISPR therapie voor SCD

editas MEDICINE

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Research and Pipeline | CRISPR Gene Editing | For Patients | Who We Are | Join Our Team | Investors

Overview
Press Releases
Events & Presentations

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Documents & Charters
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Board of Directors
Committee Composition
Annual Meeting Materials

Financials & Filings
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Annual Reports

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PRESS RELEASE

Editas Medicine Announces Clinical Achievements In The Development Of EDIT-301 For Sickle Cell Disease

July 27, 2022 at 6:30 AM EDT

Download PDF

Successful engraftment of first patient dosed with EDIT-301 for sickle cell disease

FDA removed partial clinical hold for the RUBY trial in EDIT-301

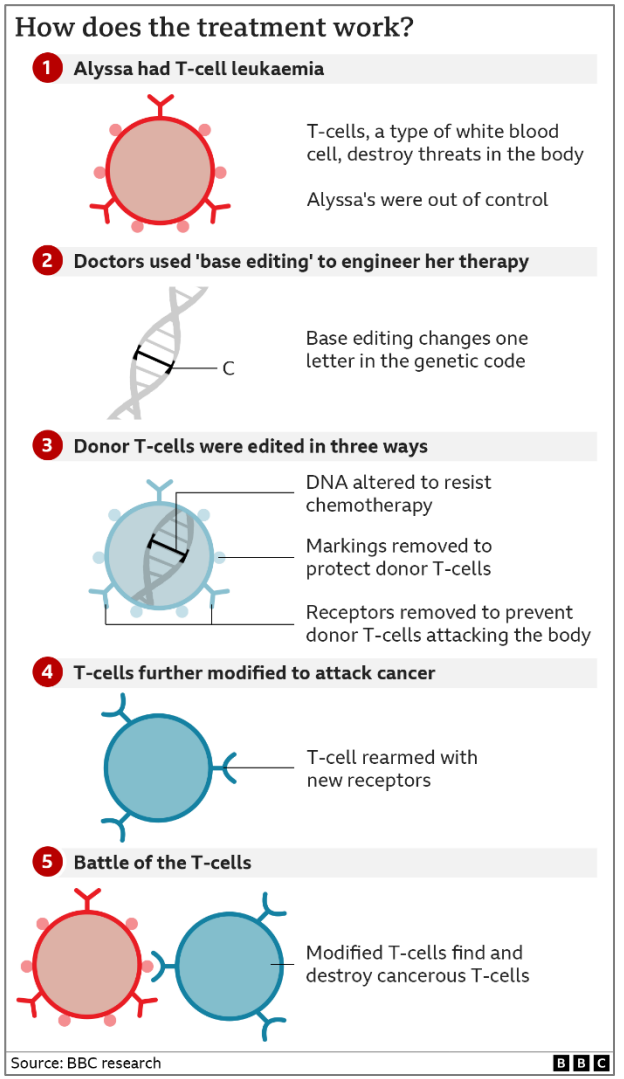
First clinical use of Editas-engineered AsCas12a enzyme

Initial clinical data from the RUBY trial expected by year-end

Dec 2022 – CRISPR therapie voor leukemie

Base editing: Revolutionary therapy clears girl's incurable cancer

11 December 2022



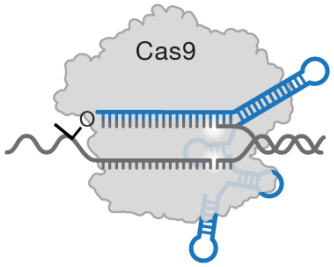
https://www.bbc.com/news/health-63859184

Sept 2022 – plant genome editing

Genome editing

- Insertion of gene(s), deletion of gene(s), replacement of gene(s) by DSB
- 1–1,000s of nucleotides
- Permanent
- Other tools: meganucleases, TALENS, ZFNs, other CRISPR nucleases

CRISPR–Cas9



CRISPR-Cas is gebruikt om de voedingswaarde te verbeteren van tomaat.

Deze tomaat is onlangs geintroduceerd op de Japanse markt.

Door inactivatie van een natief gen, is de concentratie verhoogd van een stofje met de naam gamma-aminobutyric acid (GABA), wat kan leiden tot bloeddruk-verlaging van de consument

https://www.isaaa.org/kc/cropbiotechupdate/article/default.asp?ID=18668

de CRISPR-Cas revolutie

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Dilemma – humane genome editing

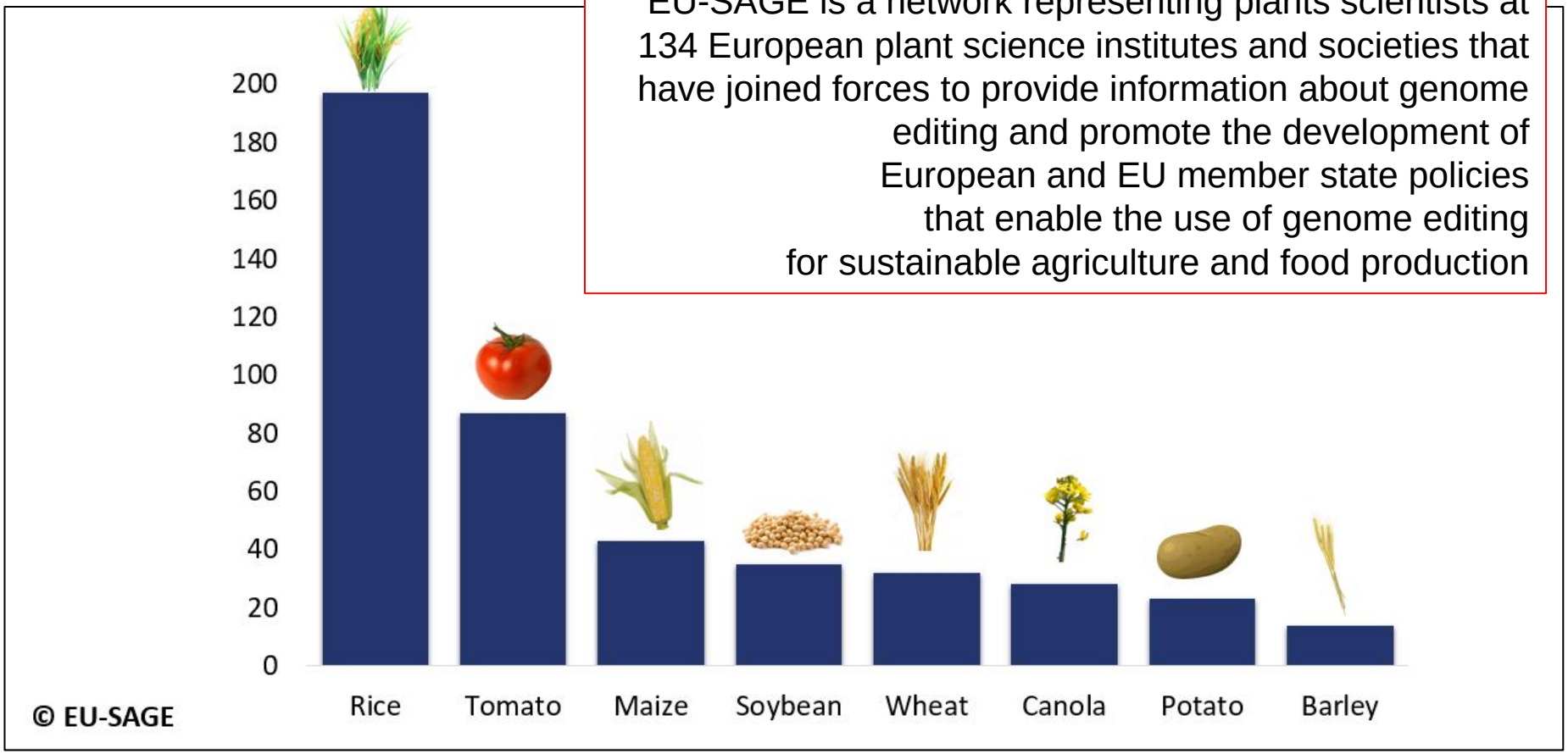
Humane genome editing

- gene therapie – buiten lichaam, in lichaam, in embryo
- designer baby's – van uiterlijk tot talent tot meer ...
- gen doping - ter compensatie voor minder talent talent ...

Dilemma – plant genome editing

genome editing gebruikt voor steeds meer voedingsgewassen

EU-SAGE is a network representing plants scientists at 134 European plant science institutes and societies that have joined forces to provide information about genome editing and promote the development of European and EU member state policies that enable the use of genome editing for sustainable agriculture and food production



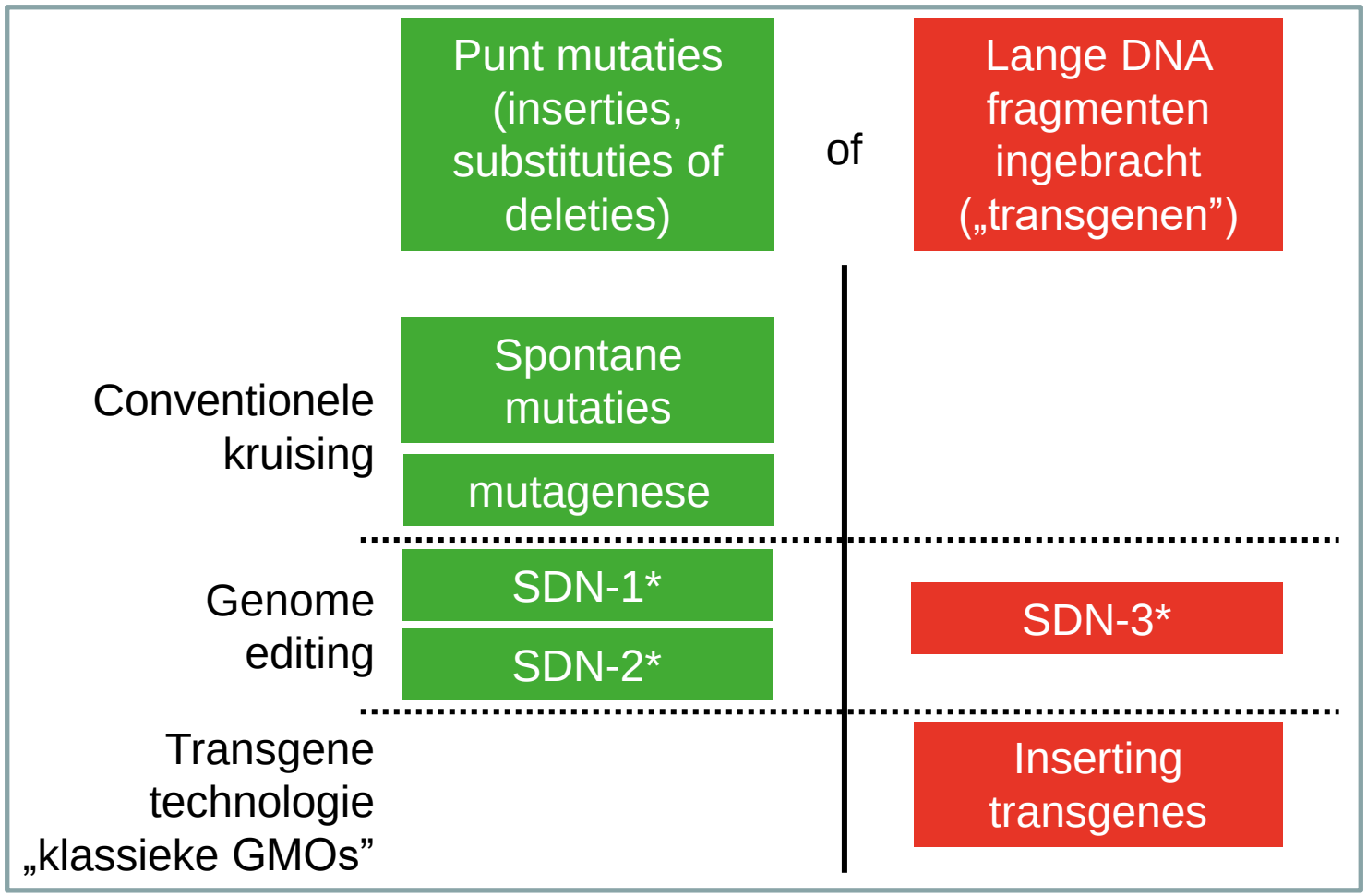
Dilemma – plant genome editing

voordelen voor producenten en/of consumenten

Trait category	%	Trait category explanation
Improved food/feed quality	23	improve nutritional value.
Plant yield and growth	23	increased yield related to fruit size or weight or to increased number of flowers, seeds and fruits.
Biotic stress tolerance	18	resistance to plant diseases caused by bacteria, viruses, fungi or nematodes
Industrial utilisation	15	bio-fuel production
Herbicide tolerance	8	tolerance of plants to various types of herbicides
Abiotic stress tolerance	7	resistance to abiotic stress factors such as: drought, heat, salt and UV radiation
Product flavour/colour	6	modified flavour or colour
Storage performance	2	increased shelf-life, non-browning properties

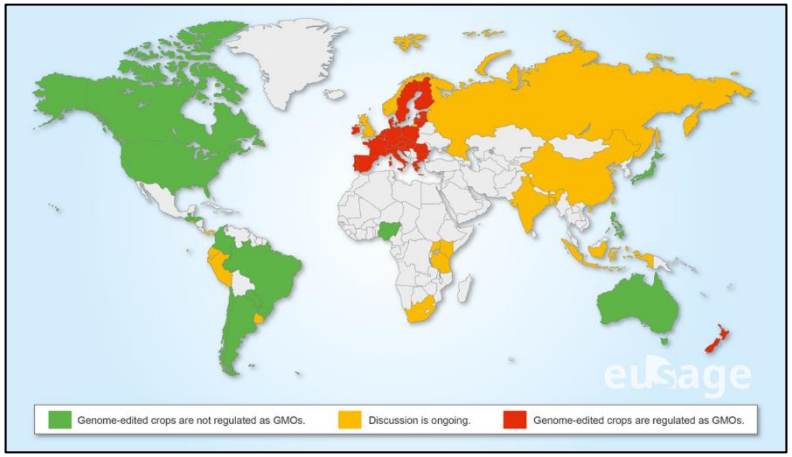
Dilemma – plant genome editing

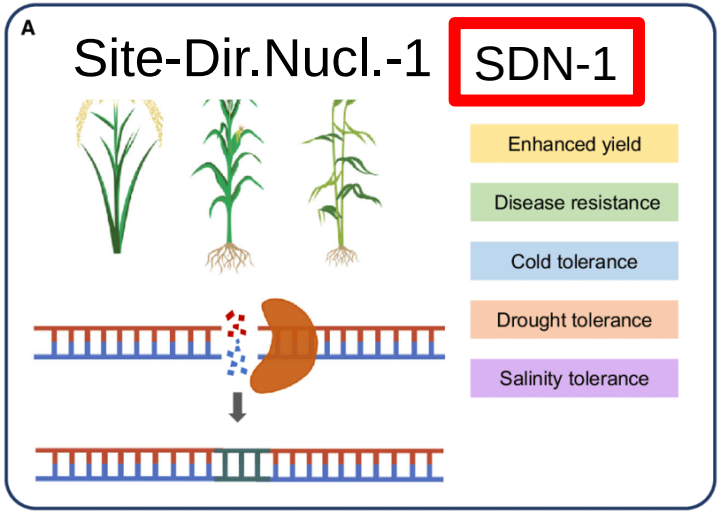
verschillende categoriën van genetische aanpassing

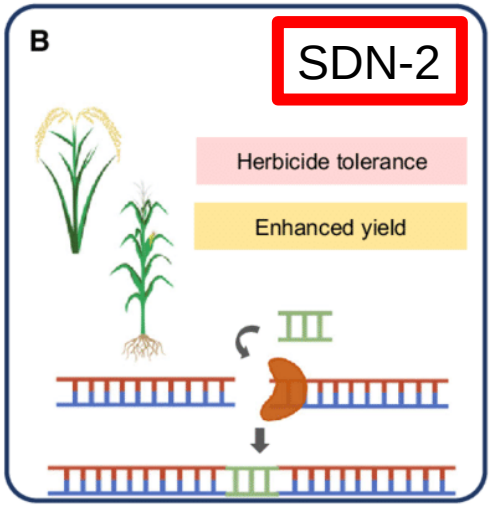


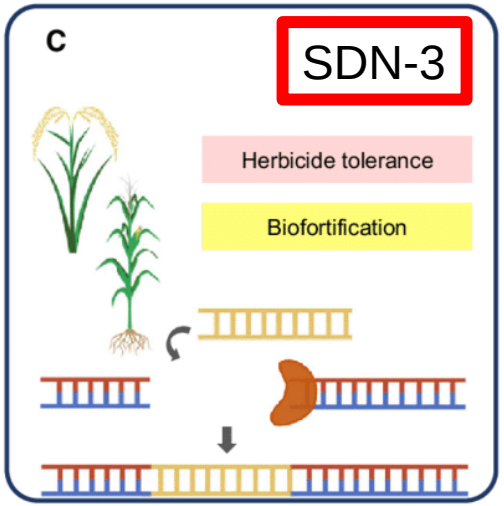
Dilemma – plant genome editing

in **EU**: “alle genome editing planten zijn GMO (SDN-3)”



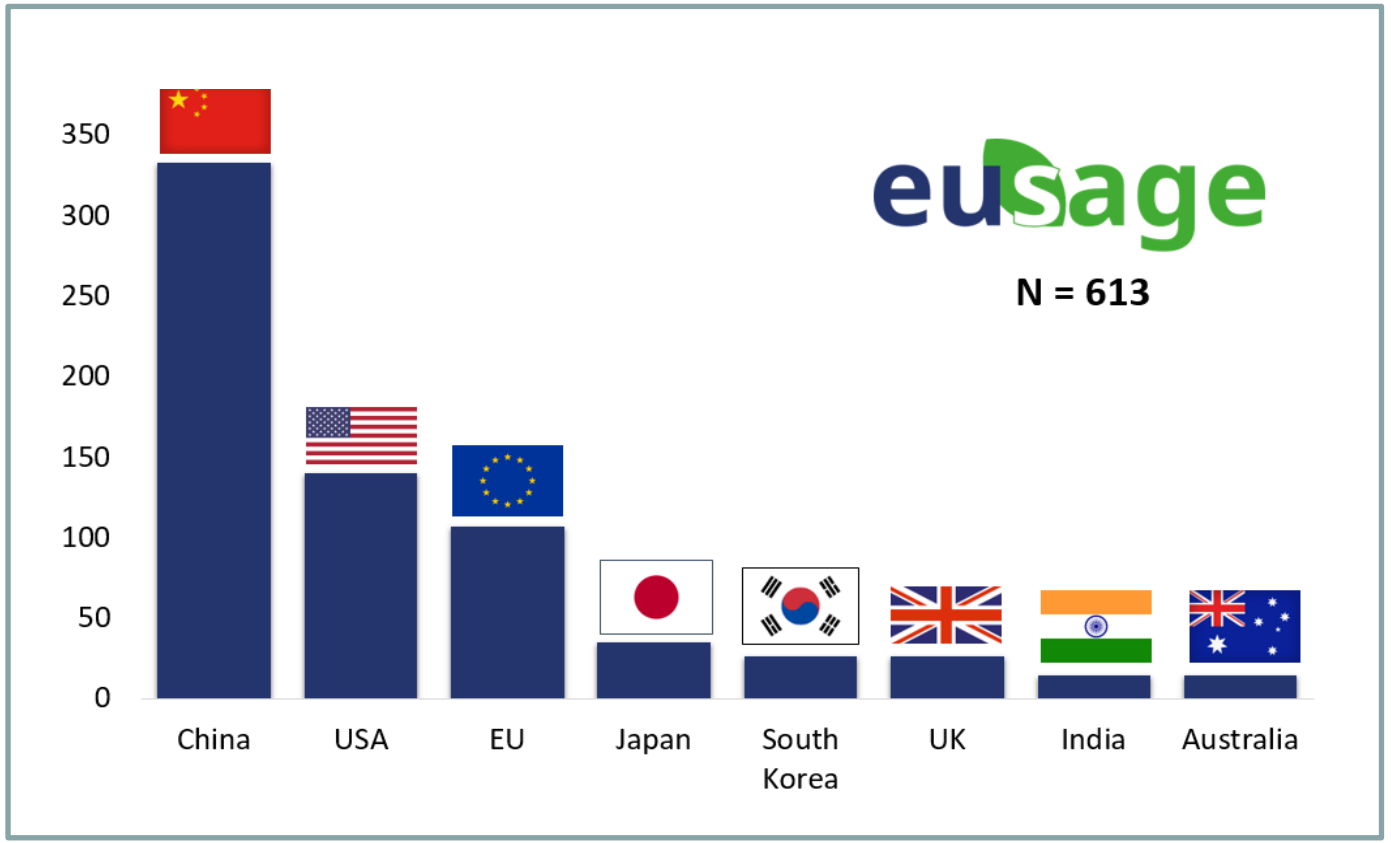






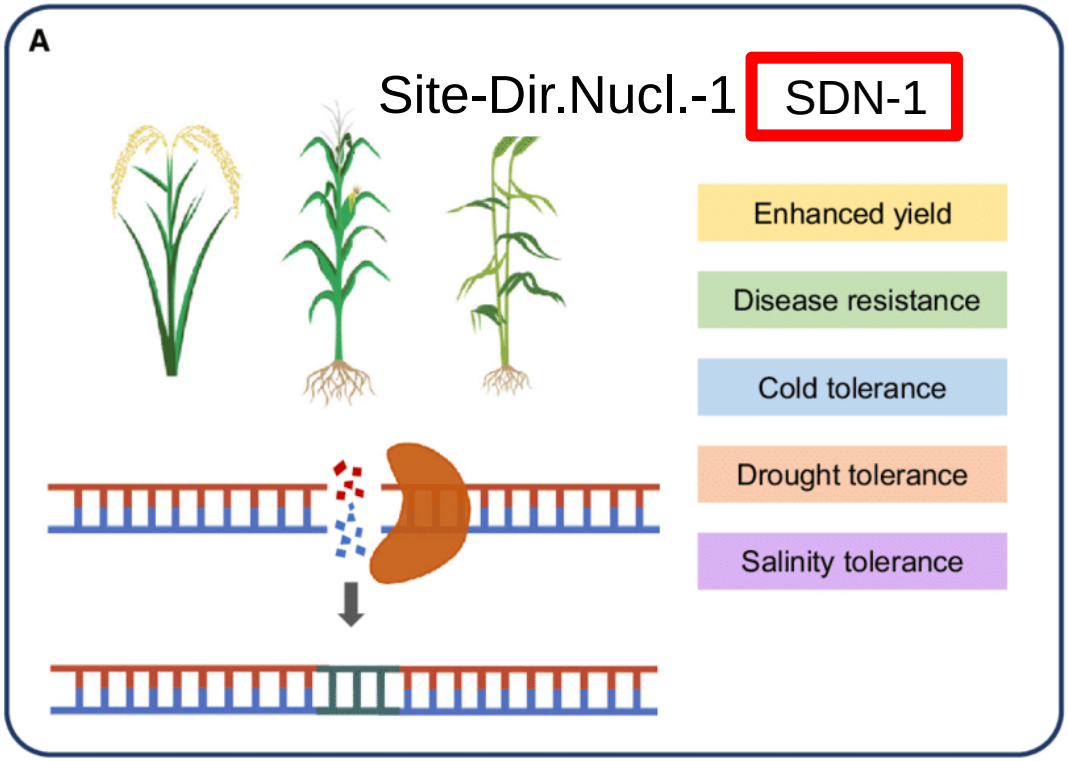
Dilemma – plant genome editing

The EU is lagging behind in the development of GE-crops



plant genome editing – (mijn) conclusies

- edits should benefits society: consumers & planet (“the Norway model”)
- small edits that do not introduce foreign DNA (SDN-1, SDN-2) = non-GMO
- bigger edits by introduction foreign DNA (SDN-3) = GMO



de CRISPR-Cas revolutie

- DNA – wat is het, en waarom is het belangrijk ?
- CRISPR-Cas – van ontdekking tot toepassing
- Recente voorbeelden – van biotechnologie tot gen therapie
- Dilemma – waar trekken we de streep ?

Surprise act !

CRISPR patenten & licenties

- duizenden CRISPR-Cas patenten (MIT-BROAD, UC-Berkeley, ...)
- ook WUR heeft een paar CRISPR-Cas patenten

Toepassingen

- Biotechnologie – microorganismen & planten
- Diagnostiek van ziekteverwekkers - virussen & bacteriën
- Gen therapie – buiten lichaam (ex vivo) & in lichaam (in vivo)

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CRISPR patenten & licenties

Waive CRISPR patents to meet food needs in low-income countries

Wageningen University & Research announced this week that it will provide non-profit organizations with free licences to use its CRISPR–Cas gene-editing technology for non-commercial applications. CRISPR tools can then be used, for instance, to help make food production sustainable, nutritious and safe. The university hopes that the move will inspire a worldwide change in CRISPR–Cas intellectual-property policy.

Van der Oost & Fresco (2021) Nature 597, 178

SurpRICE project

zout - & droogte-tolerante RICE (steun via WUF)

- optimalisatie Thermo-Cas9 – Microbiologie (WUR)
- analyse verbeterde ThermoCas9 in Rijst – Planten Physiologie (WUR)

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- daarna: zout - & droogte-tolerante Rijst – IRRI (Philippines), ...

DEPARTMENT OF AGRICULTURE 1898

CGIAR

IRRI

SurpRICE 2.0

zout - & droogte-tolerante RICE (steun via WUF)

we hopen dat dit initiatief een stimulatie zal zijn voor genome editing van belangrijke voedingsgewassen, en misschien ook andere patent-eigenaren zal overtuigen om ook vrije licenties te verlenen voor gebruik van de CRISPR technologie door non-profit instituten in ‘arme landen’, met uiteindelijk als doel om honger de wereld uit te krijgen !

wat is jullie conclusie ...?

EU besluit dat “CRISPR = GMO“

een evaluatie op basis van solide argumenten

European Commission

Statement by the Group of Chief Scientific Advisors

A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive

On 25 July 2018, the Court of Justice of the European Union ('the Court') decided that organisms obtained by the new techniques of directed mutagenesis are genetically modified organisms (GMOs), within the meaning of the Directive 2001/18/EC on the release of genetically modified organisms into the environment ('GMO Directive')[1,2], and that they are subject to the obligations laid down by the GMO Directive.

New techniques of directed mutagenesis include gene editing such as CRISPR/Cas9 methodologies. The legal status of the products of such techniques was uncertain, because it was unclear whether they fell within the scope of the GMO Directive.

These techniques enable the development of a wide range of agricultural applications and the ethical, legal, social and economic issues of their use are discussed intensively. The European Commission's Group of Chief Scientific Advisors (the 'Chief Scientific Advisors')[3] recognises the complex nature

Biotechnology' (SAM, 2017a), we have examined the GMO Directive taking into account current knowledge and scientific evidence.

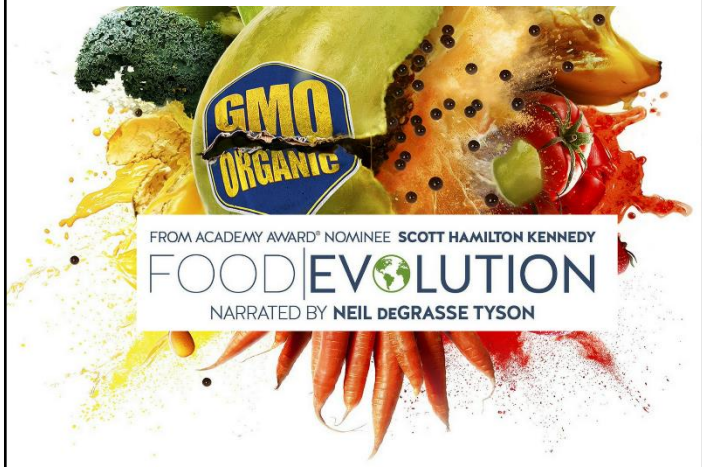
1. The Ruling of the Court of Justice

On request by the French *Conseil d'État*, the Court was asked to determine whether organisms obtained by mutagenesis[4] should be considered GMOs and which of those organisms are exempt according to the provisions of the GMO Directive. In particular, the Court was asked to determine whether organisms obtained by new directed mutagenesis techniques are exempt from the obligations imposed by the GMO Directive, as are those obtained by conventional, random mutagenesis techniques that existed before the adoption of the Directive, or are regulated like those obtained by established techniques of genetic modification (ETGM).

The Court declared that organisms produced by

https://ec.europa.eu/info/sites/info/files/2018_11_gcsa_statement_gene_editing_1.pdf

documentaire over organisch & GE voedsel



https://www.youtube.com/watch?v=t654yDVlDpo

(mijn) conclusies

Editing van mensen alleen voor genezen van genetische ziektengenetic diseases

GMO classificatie van planten niet nodig in geval van kleine aanpassingen

Editing van voedselgewassen: “Noorwegen model” ipv “Monsanto model”

Streven naar een compromise tussen voor- & tegen-standers genome editing

vaak zijn hun doelen hetzelfde:

- MINDER – water, kunstmest, betrijdingsmiddelen & energie
- MEER – duurzame productie van veilig, gezond, & lekker eten

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