6th Seed Congress of the Americas

Promoting Seed Business in the Americas | September 5-7 2017 - Colombia Cartagena de Indias

PLAN BREEDING INNOVATION

Técnica / Conocimiento, Acceso y Ambiente Regulatorio

Dr. Miguel Rapela

Cartagena, 6 de septiembre 2017

ARTICLE

Correction of a pathogenic gene mutation in human embryos

Hong Ma[1]*, Nuria Marti-Gutierrez[1]*, Sang-Wook Park[2]*, Jun Wu[3]*, Yeonmi Lee[1], Keiichiro Suzuki[3], Amy Tomonari Hayama[1], Riffat Ahmed[1], Hayley Darby[1], Crystal Van Dyken[1], Ying Li[1], Eunju Kang[1], A.-Reum P Sang-Tae Kim[2], Jianhui Gong[5,6,7,8], Ying Gu[5,6,7], Xun Xu[5,6,7], David Battaglia[1,9], Sacha A. Krieg[9], David M. Don P. Wolf[1], Stephen B. Heitner[10], Juan Carlos Izpisua Belmonte[3]§, Paula Amato[1,9]§, Jin-Soo Kim[2,4]§, San Shoukhrat Mitalipov[1,10]§

Genome editing has potential for the targeted correction of germline mutations. Here we descri the heterozygous *MYBPC3* mutation in human preimplantation embryos with precise CRISPR-C accuracy and high homology-directed repair efficiency by activating an endogenous, germline- response. Induced double-strand breaks (DSBs) at the mutant paternal allele were predominantl homologous wild-type maternal gene instead of a synthetic DNA template. By modulating the cell the DSB was induced, we were able to avoid mosaicism in cleaving embryos and achieve a high y embryos carrying the wild-type *MYBPC3* gene without evidence of off-target mutations. The effic safety of the approach presented suggest that it has potential to be used for the correction of heritable embryos by complementing preimplantation genetic diagnosis. However, much remains to be consi applications, including the reproducibility of the technique with other heterozygous mutations.

More than 10,000 monogenic inherited disorders have been identified, affecting millions of people worldwide. Among these are autosomal dominant mutations, where inheritance of a single copy of a defective gene can result in clinical symptoms. Genes in which dominant mutations manifest as late-onset adult disorders include *BRCA1* and *BRCA2*, which are associated with a high risk of breast and ovarian cancers[1], and *MYBPC3*, mutation of which causes hypertrophic cardiomyopathy (HCM)[2]. Because of their delayed manifestation, these mutations escape natural selection and are often transmitted to the next generation. Consequently, the frequency of some of these founder mutations in particular human populations is very high. For example, the *MYBPC3* mutation is found at frequencies ranging from 2% to 8%[3] in major Indian populations, and the estimated frequency of both *BRCA1* and *BRCA2* mutations among Ashkenazi Jews exceeds 2%[4].

HCM is a myocardial disease characterized by left ventricular hypertrophy, myofibrillar disarray and myocardial stiffness; it has an estimated prevalence of 1:500 in adults[5] and manifests clinically with heart failure. HCM is the commonest cause of sudden death in otherwise healthy young athletes. HCM, while not a uniformly fatal condition, has a tremendous impact on the lives of individuals, including physiological (heart failure and arrhythmias), psychological (limited activity and fear of sudden death), and genealogical concerns. *MYBPC3* mutations account for approximately 40% of all genetic defects causing HCM and are also responsible for a large fraction of other inherited cardiomyopathies, including dilated cardiomyopathy and left ventricular non-compaction[6]. *MYBPC3* encodes the thick filament-associated cardiac myosin-binding protein C (cMyBP-C), a signalling node in cardiac myocytes that contributes to the maintenan and regulation of both contraction and rela

Current treatment options for HCM pro relief without addressing the genetic cause development of novel strategies to prever of founder mutations is desirable. One second-generation transmission is preimpl (PGD) followed by selection of non-mutant context of an *in vitro* fertilization (IVF) cyc carries a heterozygous mutation, 50% of the en free and available for transfer, while the rem discarded. Gene correction would rescue the number of embryos available for transf pregnancy rates.

Recent developments in precise genome-e successful applications in animal models ha correcting human germline mutations. In pa versatile tool for recognizing specific genom DSBs[7–10]. DSBs are then resolved by endog anisms, preferentially using a non-homolo pathway. Obviously, NHEJ is inappropriate cations because it introduces additional mut tions or deletions at the DSB site, commonly referred to as indels. In some cases, however, targeted cells activate an alternative DNA repair pathway called homology-directed repair (HDR) that rebuilds the DSB site using the non-mutant homologous chromosome or a supplied exogenous DNA molecule as a template, leading to correction of the

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El salto del laboratorio a los medios

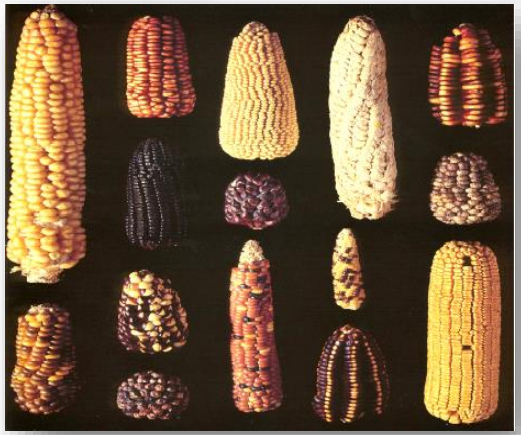
PBI: factores claves en el mejoraniento vegetal

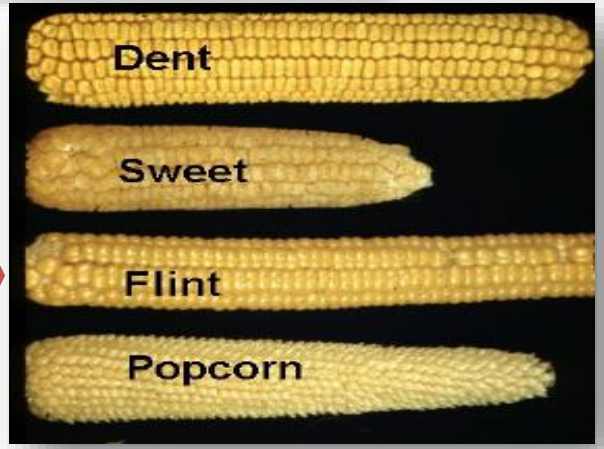
1. Técnica / Conocimiento
2. Acceso
3. Ambiente Regulatorio

PBI: factores claves en el mejoraniento vegetal

1. **Técnica / Conocimiento**
2. Acceso
3. Ambiente Regulatorio

El contexto del mejoramiento vegetal





El contexto del mejoramiento vegetal

Brassica oleraceae

Brassica oleracea

http://lsvl.la.asu.edu/plb598/kpigg/Brassica.htm
http://www.fishing-in-wales.com/_pics/plantpic/seaspics/wildcabb.jpg

selección artificial

Brócoli

Repollo

Coliflor

Repollito de Bruselas

Col Berza

Collard Greens

Colirrábano

El contexto del mejoramiento vegetal

Mejoramiento por mutagénesis inducida (al azar)

Crisantemo:
rayos gamma

Pomelo Rosado: *neutrones*

Lino: *etilmetanosulfonato (EMS)*

Incorporación de tecnologías al mejoramiento vegetal

¿Proceso continuo y aditivo?

- Domesticación
- Selección de los mejores ejemplares
- Cruza entre individuos
- Introgresión de genes de otras especies
- Mejoramiento de líneas
- Híbridos
- Mutagénesis inducida (al azar)
- Marcadores moleculares
- Transgénesis
- Silenciamiento de genes (RNAi)
- “Ómicas”
- Técnicas de edición génica/genómica
- Biología sintética
- ¿?

Incorporación de tecnologías al mejoramiento vegetal

- Domesticación
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¿Proceso disruptivo?

- Transgénesis
- Silenciamiento de genes (RNAi)
- “Ómicas”

- Técnicas de edición génica/genómica
- Biología sintética
- ¿?

¿Qué son las New Breeding Techniques (NBT)?

2007 - Creación del Grupo de Trabajo sobre NBTs de la CE
2011 – informe del Joint Research Center + Reunión en Sevilla

- Zinc finger nuclease technology (ZFN-1, 2, 3)
- Oligonucleotide directed mutagenesis (ODM)
- Cisgenesis and intragenesis
- RNA-dependent DNA methylation (RdDM)
- Grafting (on GM rootstock)
- Reverse breeding
- Agro-infiltration, agro-inoculation, floral dip
- Synthetic genomics/biology

Agrupación “forzada” de las técnicas
Algunas técnicas no son nuevas
Algunas técnicas con definición incierta
Algunas técnicas de dudosa aplicación

Plant Breeding Innovation

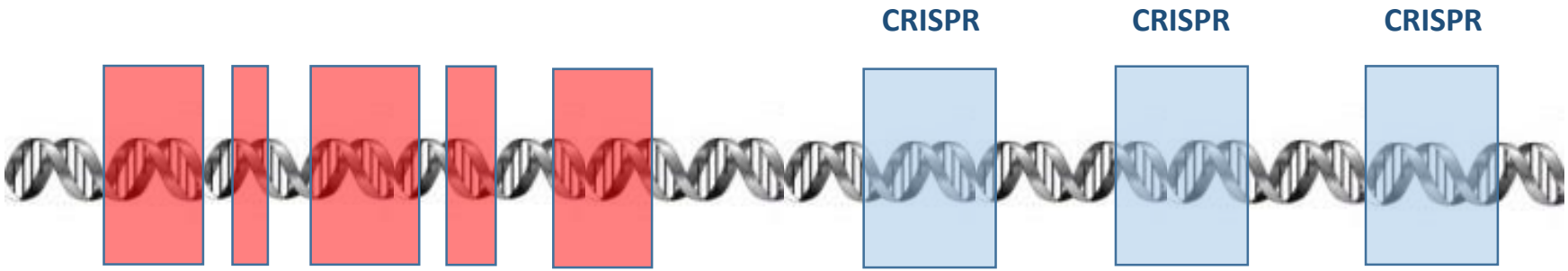
- **EDICIÓN GÉNICA**
  - **CRISPR-Cas**

EL DESCUBRIMIENTO

El descubrimiento

Dr. Francisco MOJICA

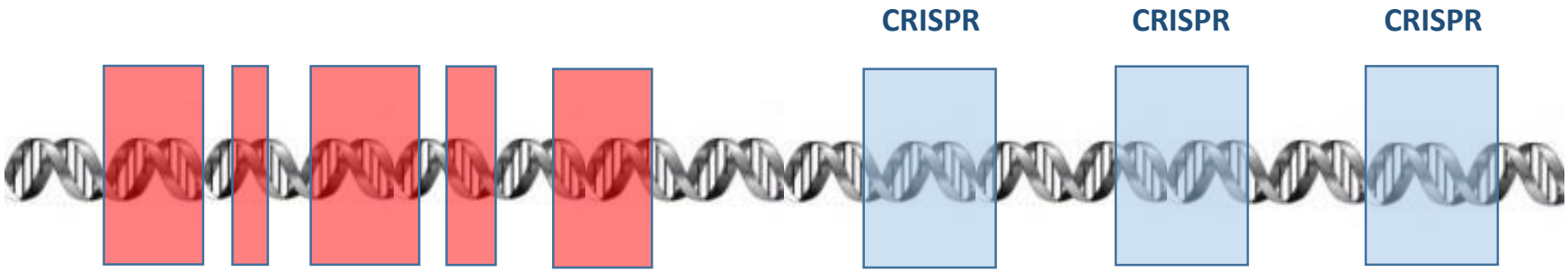
El descubrimiento



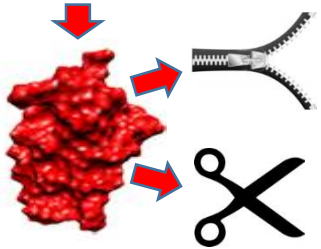
Dr. Francisco MOJICA

C (Clustered / Agrupadas)
R (Regularly / Regularmente)
I (Interspaced / Interespaciadas)
S (Short / Cortas)
P (Palindromic / Palindrómicas)
R (Repeats / Repeticiones)

El descubrimiento

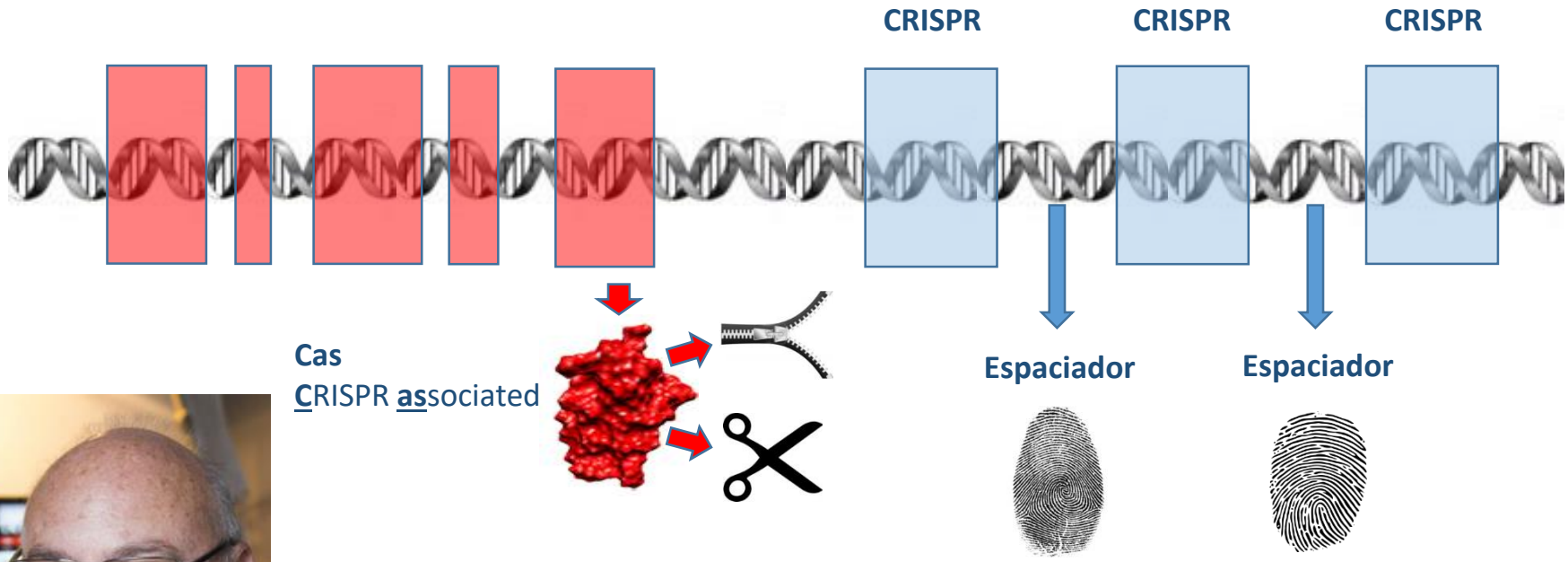


Cas
CRISPR **as**sociated



Dr. Francisco MOJICA

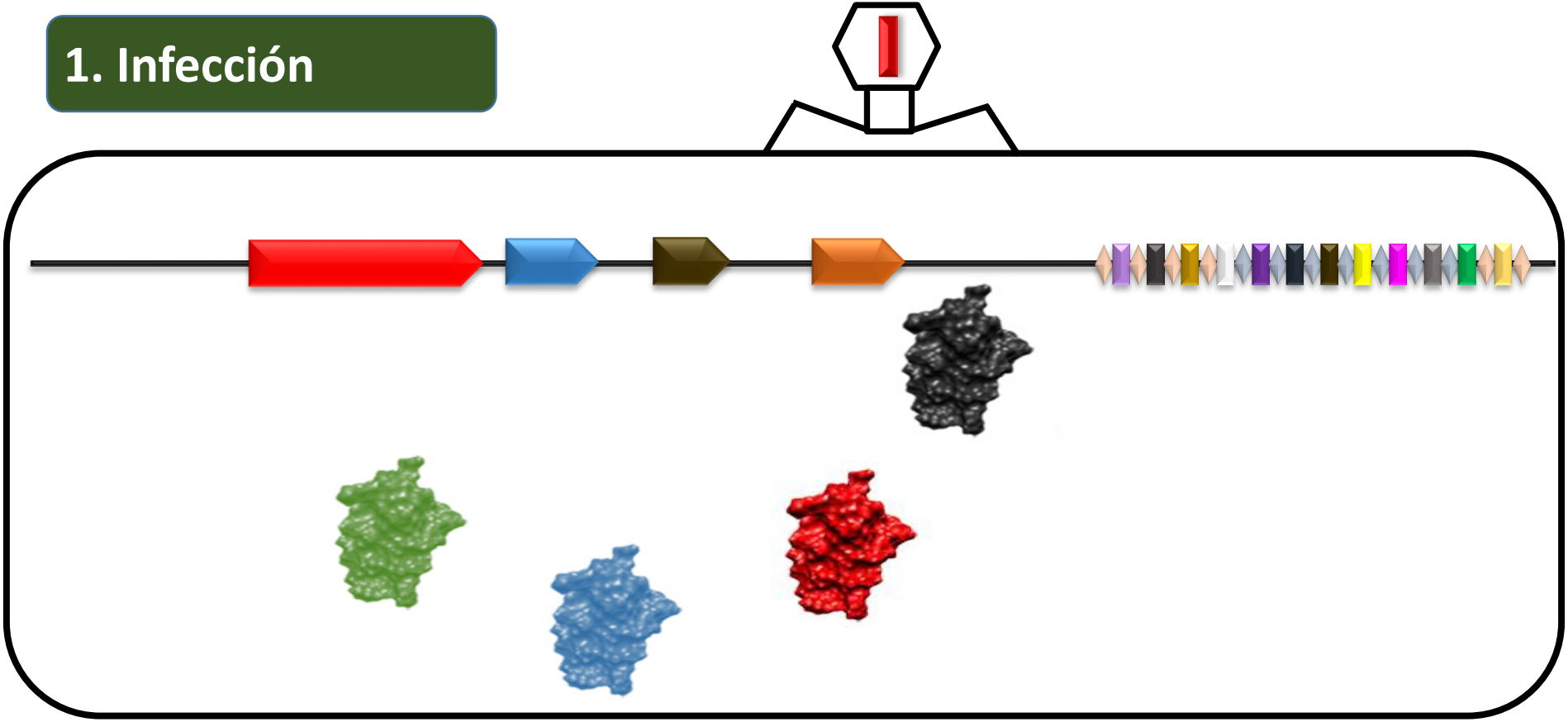
El descubrimiento



Dr. Francisco MOJICA

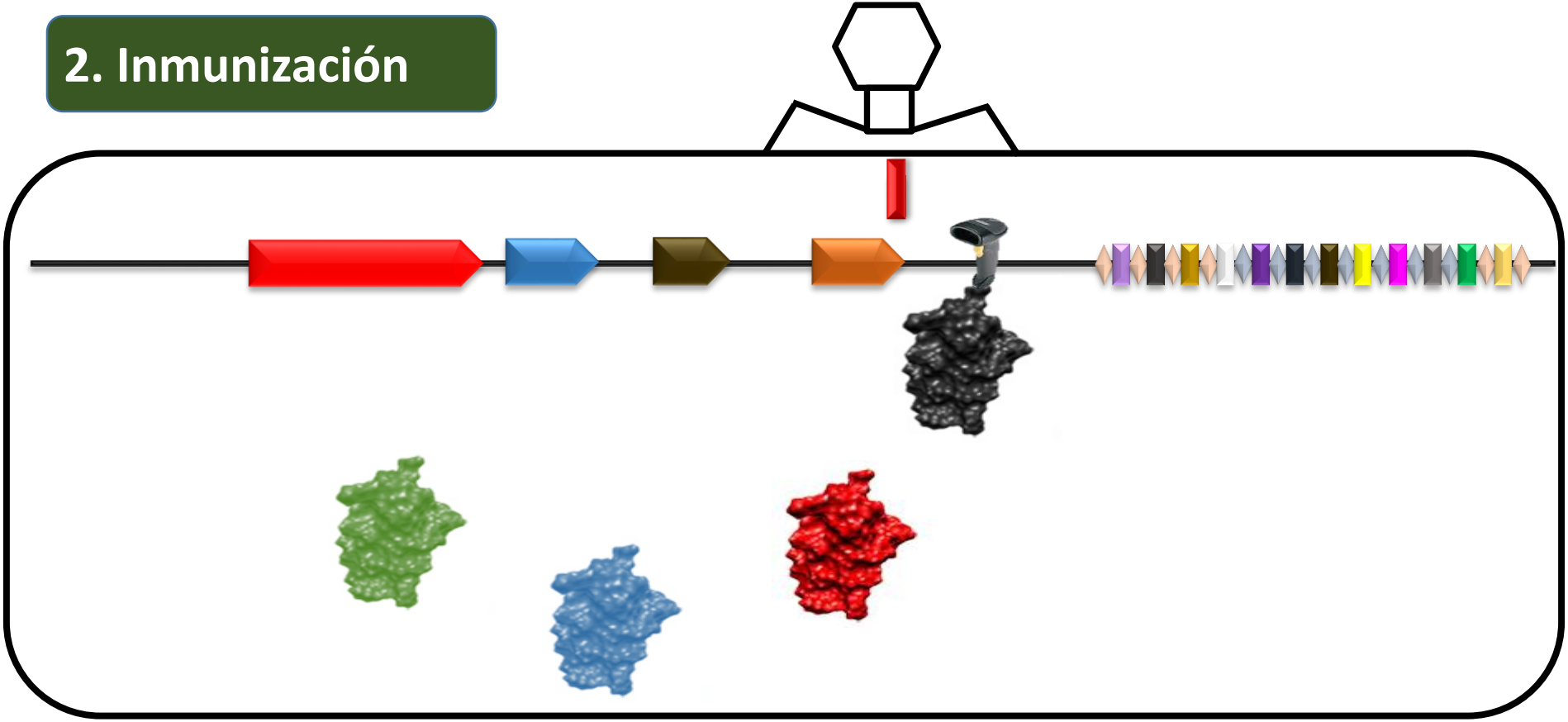
BACTERIAS + ARQUEAS
Sistema Inmuno-adaptativo defensivo

1. Infección



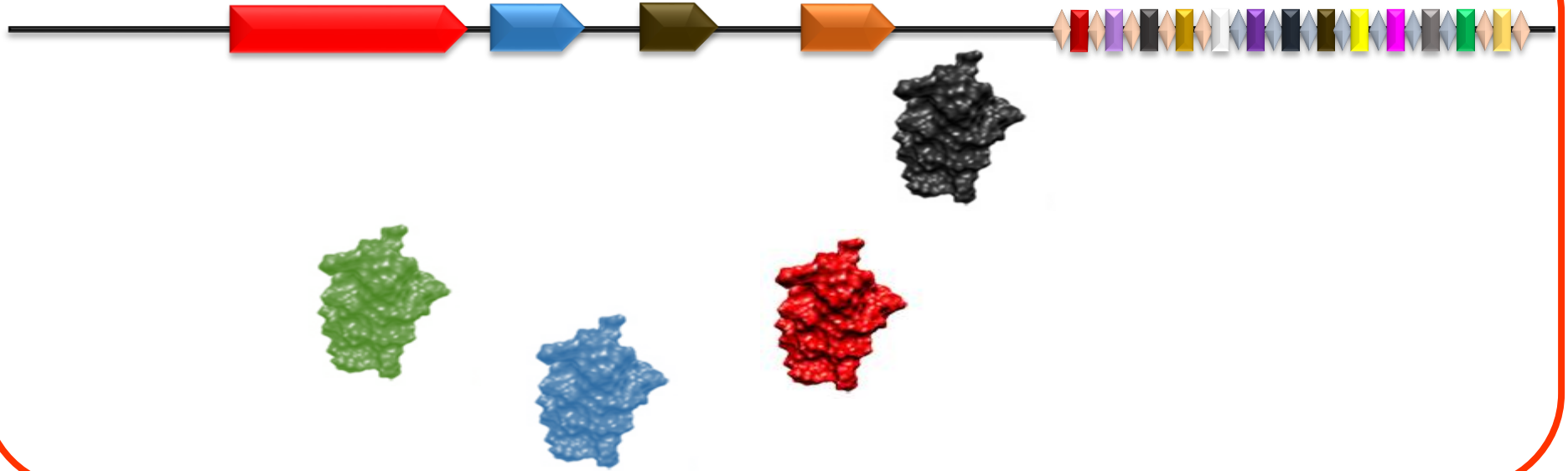
Animación: F. Mojica, con autorización

2. Inmunización



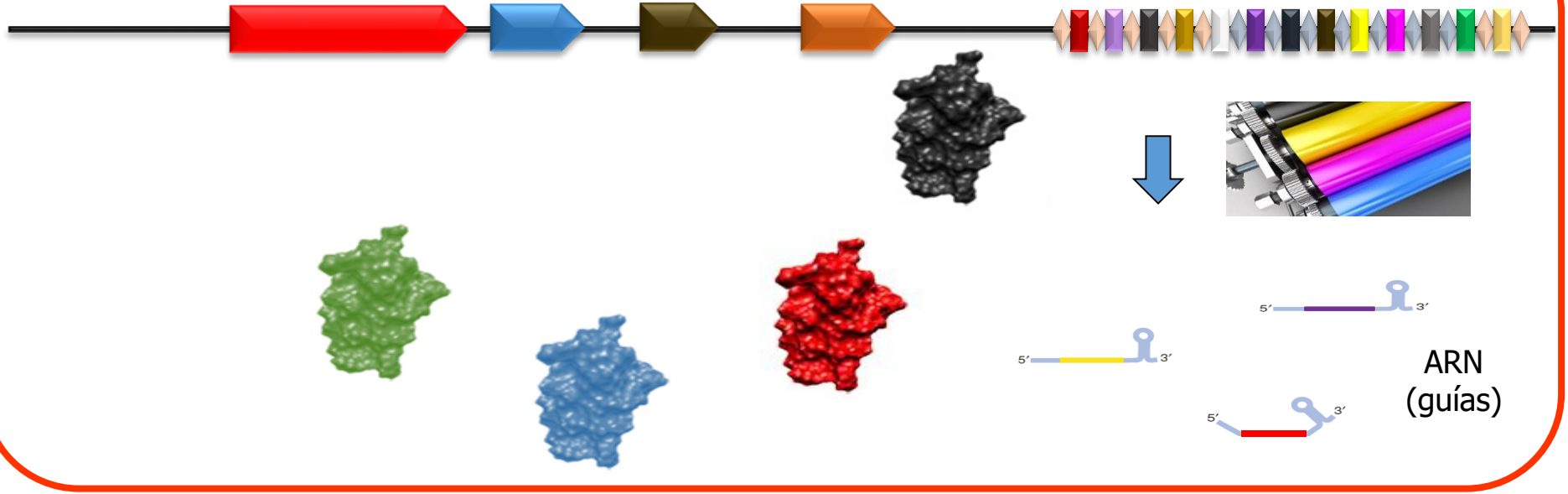
Animación: F. Mojica, con autorización

3. Bacteria inmunizada



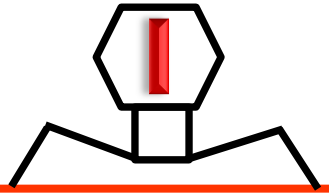
Animación: F. Mojica, con autorización

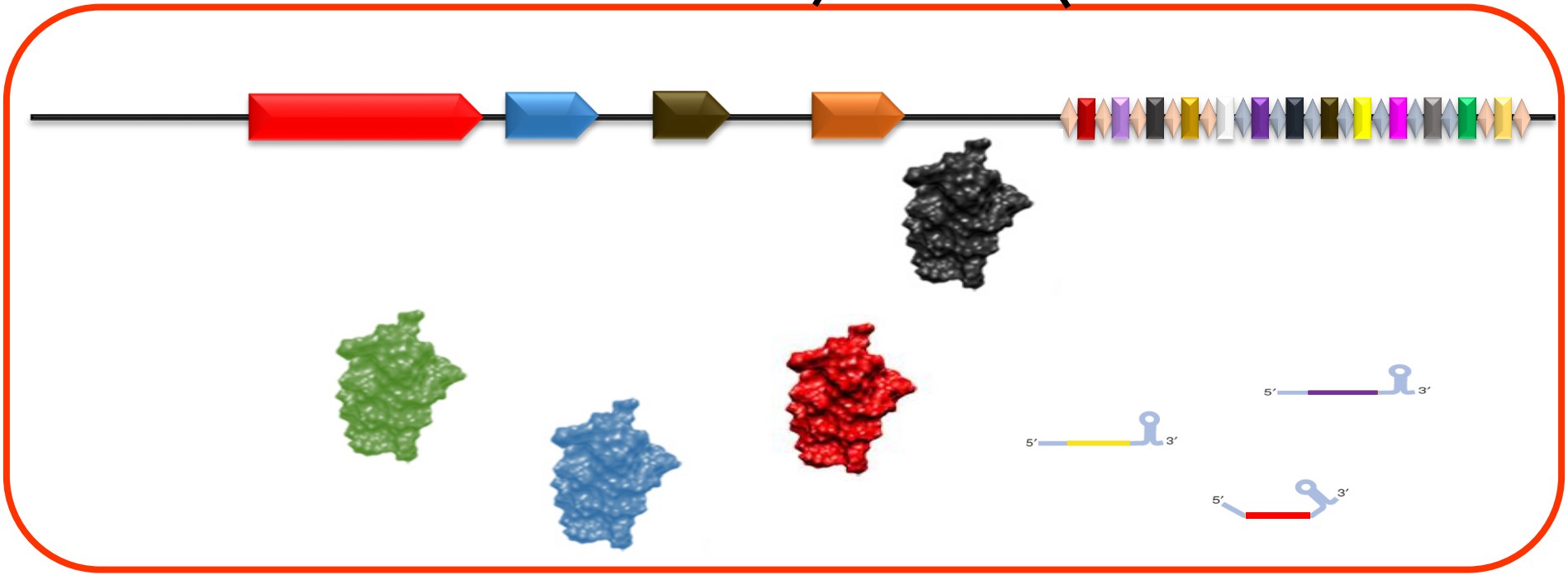
4. Producción de defensas



Animación: F. Mojica, con autorización

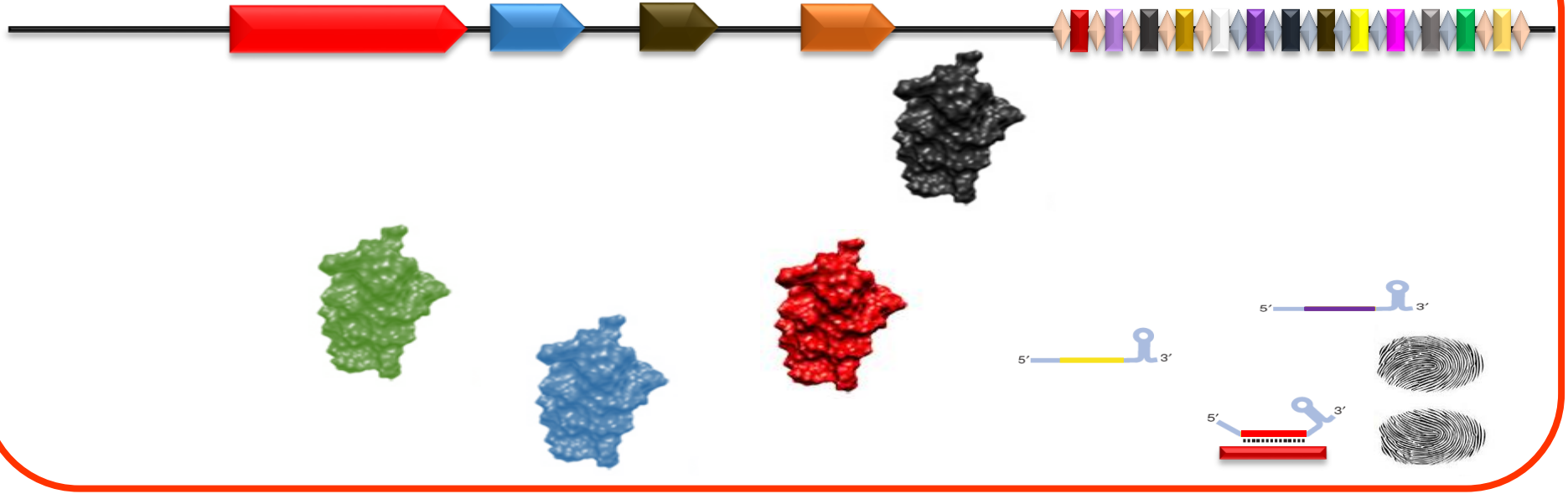
5. Reinfección





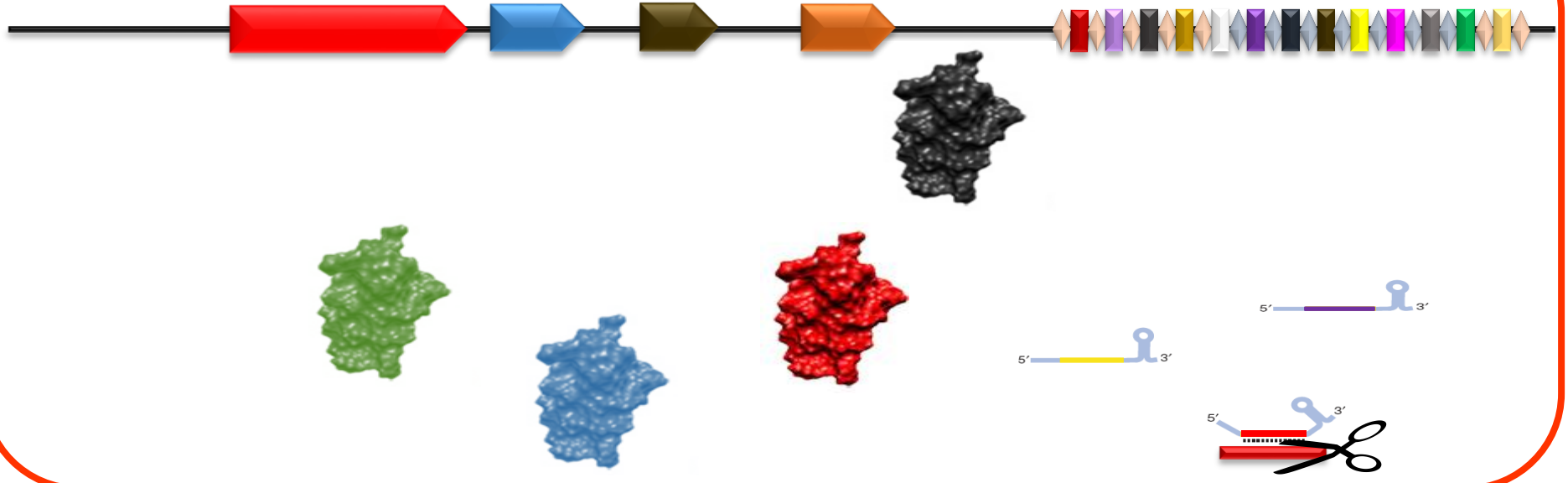
Animación: F. Mojica, con autorización

6. Reconocimiento



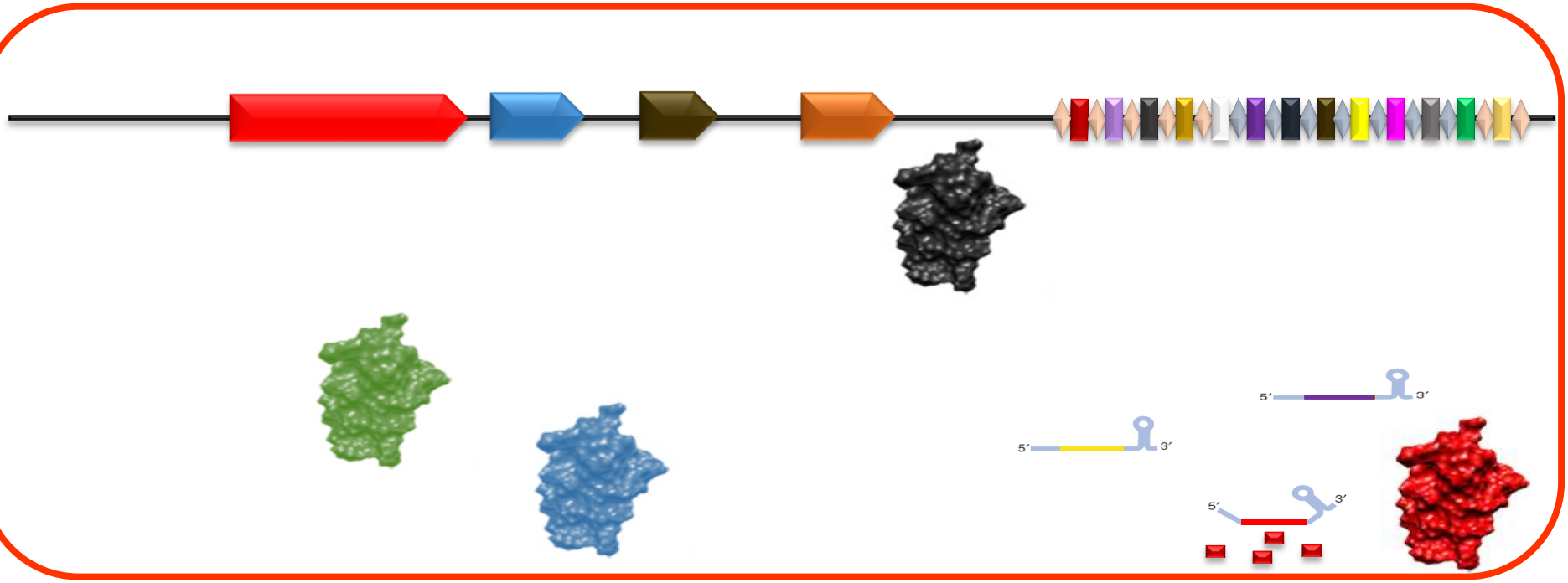
Animación: F. Mojica, con autorización

7. Destrucción



Animación: F. Mojica, con autorización

8. Sistema de Inmunidad Adquirida



Animación: F. Mojica, con autorización

La demostración experimental

Philippe Horvath

CRISPR Provides Acquired Resistance Against Viruses in Prokaryotes

SCIENCE VOL 315 23 MARCH 2007

Rodolphe Barrangou,[1] Christophe Fremaux,[2] Hélène Deveau,[3] Melissa Richards,[1] Patrick Boyaval,[2] Sylvain Moineau,[3] Dennis A. Romero,[1] Philippe Horvath[2]*

LA INVENCIÓN

De los procariotas a los eucariotas

Science
AAAS

Luciano Marraffini Erik Sontheimer

CRISPR Interference Limits Horizontal Gene Transfer in Staphylococci by Targeting DNA

Luciano A. Marraffini and Erik J. Sontheimer*

Horizontal gene transfer (HGT) in bacteria and archaea occurs through phage transduction, transformation, or conjugation, and the latter is particularly important for the spread of antibiotic resistance. Clustered, regularly interspaced, short palindromic repeat (CRISPR) loci confer sequence-directed immunity against phages. A clinical isolate of *Staphylococcus epidermidis* harbors a CRISPR spacer that matches the *nickase* gene present in nearly all staphylococcal conjugative plasmids. Here we show that CRISPR interference prevents conjugation and plasmid transformation in *S. epidermidis*. Insertion of a self-splicing intron into *nickase* blocks interference despite the reconstitution of the target sequence in the spliced mRNA, which indicates that the interference machinery targets DNA directly. We conclude that CRISPR loci counteract multiple routes of HGT and can limit the spread of antibiotic resistance in pathogenic bacteria.

SCIENCE VOL 322 19 DECEMBER 2008

De los procariotas a los eucariotas

Science
AAAS

Jennifer Doudna

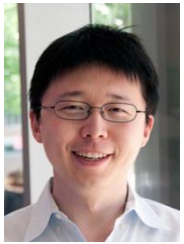
Emmanuelle Charpentier

A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity

Martin Jinek,[1,2]* Krzysztof Chylinski,[3,4]* Ines Fonfara,[4] Michael Hauer,[2]†
Jennifer A. Doudna,[1,2,5,6]‡ Emmanuelle Charpentier[4]‡

17 AUGUST 2012 VOL 337 SCIENCE

De los procariotas a los eucariotas



Feng Zhang

Science. 2013 February 15; 339(6121): 819–823. doi:10.1126/science.1231143.

Multiplex Genome Engineering Using CRISPR/Cas Systems

Le Cong[1,2,*], **F. Ann Ran**[1,4,*], **David Cox**[1,3], **Shuailiang Lin**[1,5], **Robert Barretto**[6], **Naomi Habib**[1], **Patrick D. Hsu**[1,4], **Xuebing Wu**[7], **Wenyan Jiang**[8], **Luciano A. Marraffini**[8], and **Feng Zhang**[1,†]

Luciano Marraffini

Nature Biotechnology (2013) 31: 233–239 (2013)

RNA-guided editing of bacterial genomes using CRISPR-Cas systems

Wenyan Jiang, David Bikard, David Cox, Feng Zhang and Luciano Marraffini

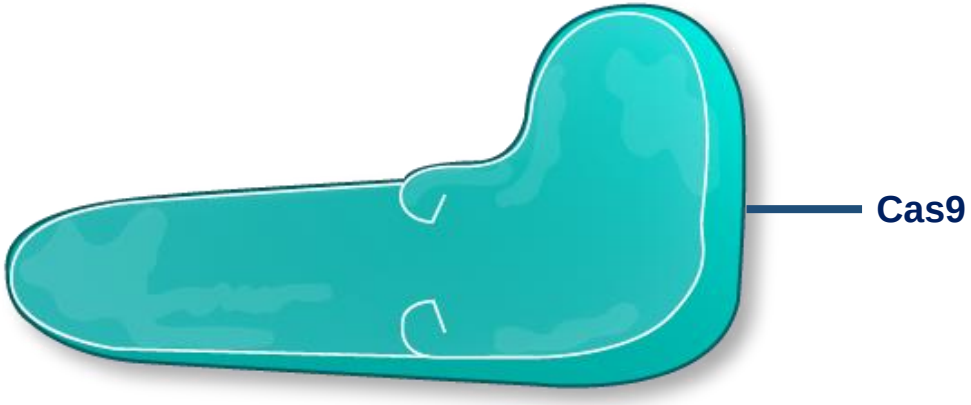
George Church

Science. 2013 February 15; 339(6121): 823–826. doi:10.1126/science.1232033.

RNA-Guided Human Genome Engineering via Cas9

Prashant Mali[1,5], **Luhan Yang**[1,3,5], **Kevin M. Esvelt**[2], **John Aach**[1], **Marc Guell**[1], **James E. DiCarlo**[4], **Julie E. Norville**[1], and **George M. Church**[1,2,*]

De los procariotas a los eucariotas



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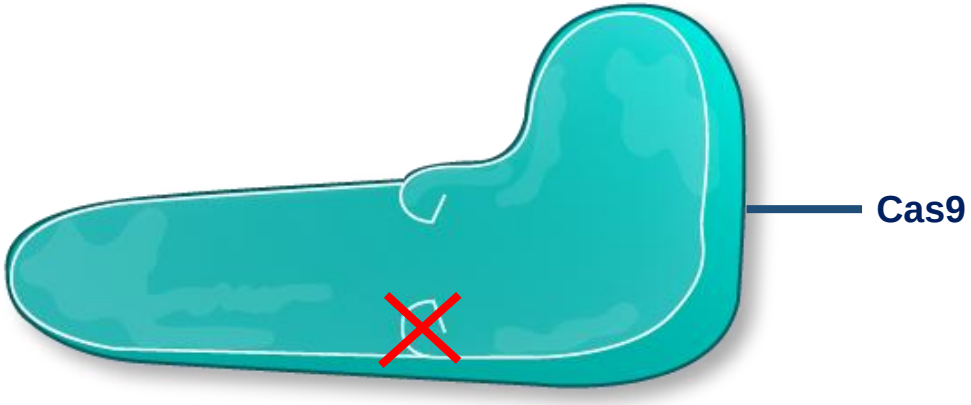

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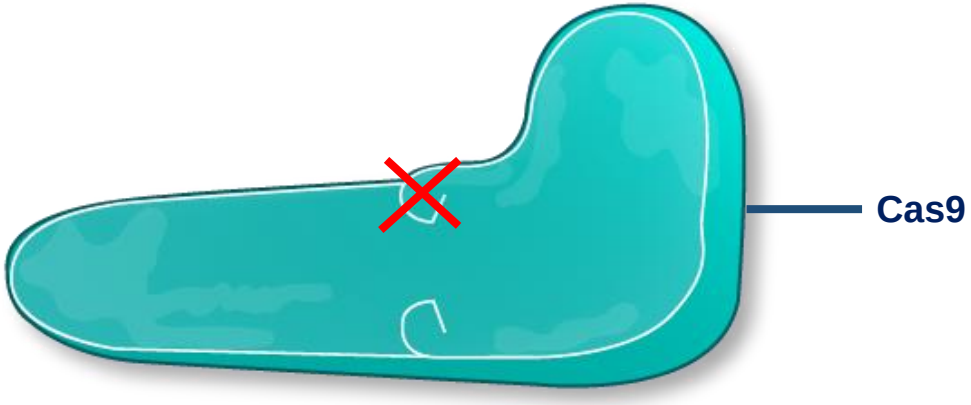

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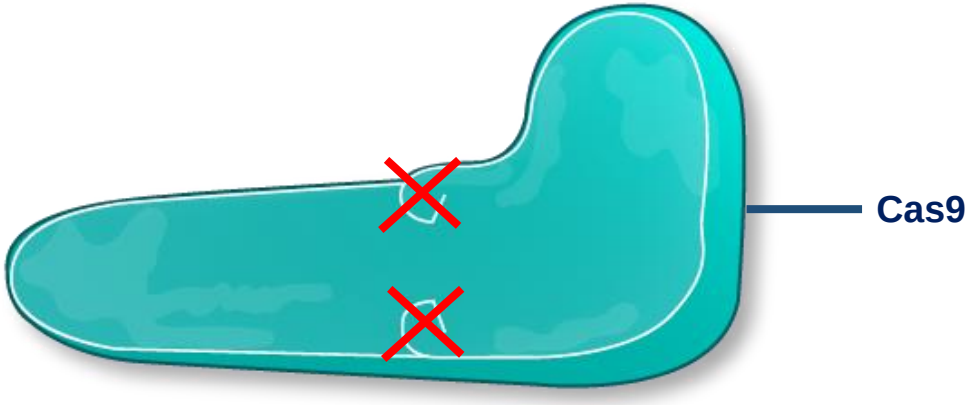

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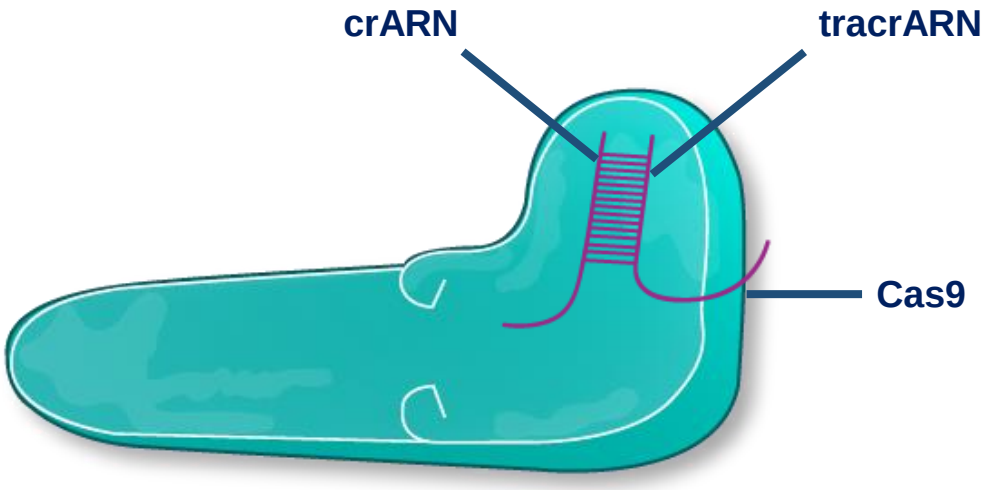

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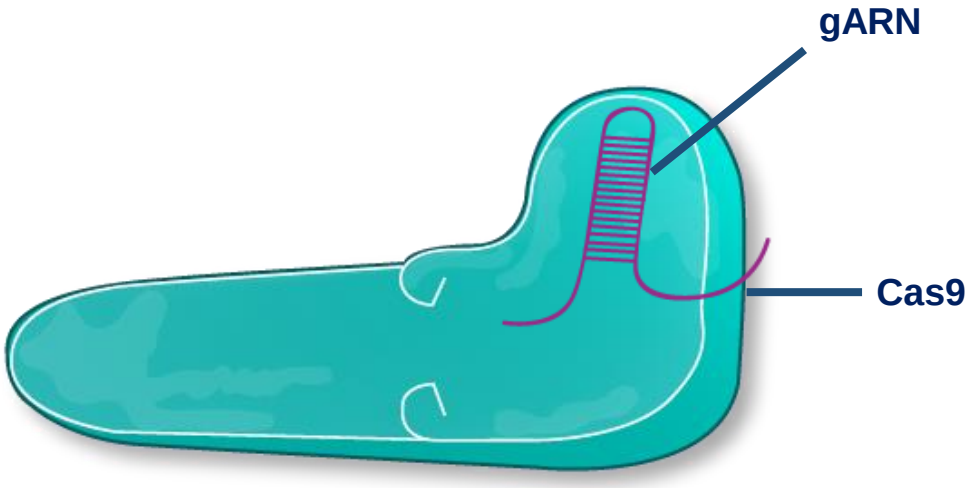

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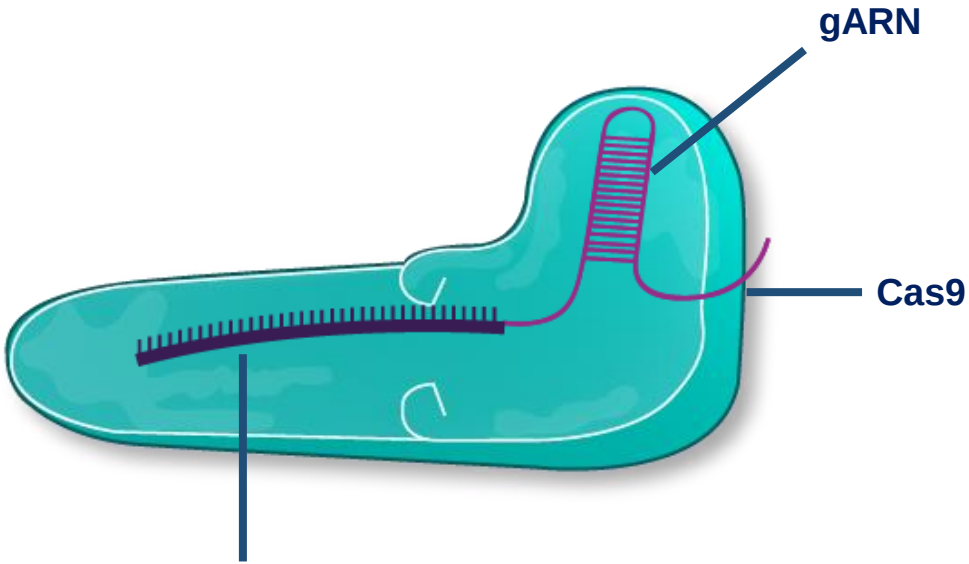

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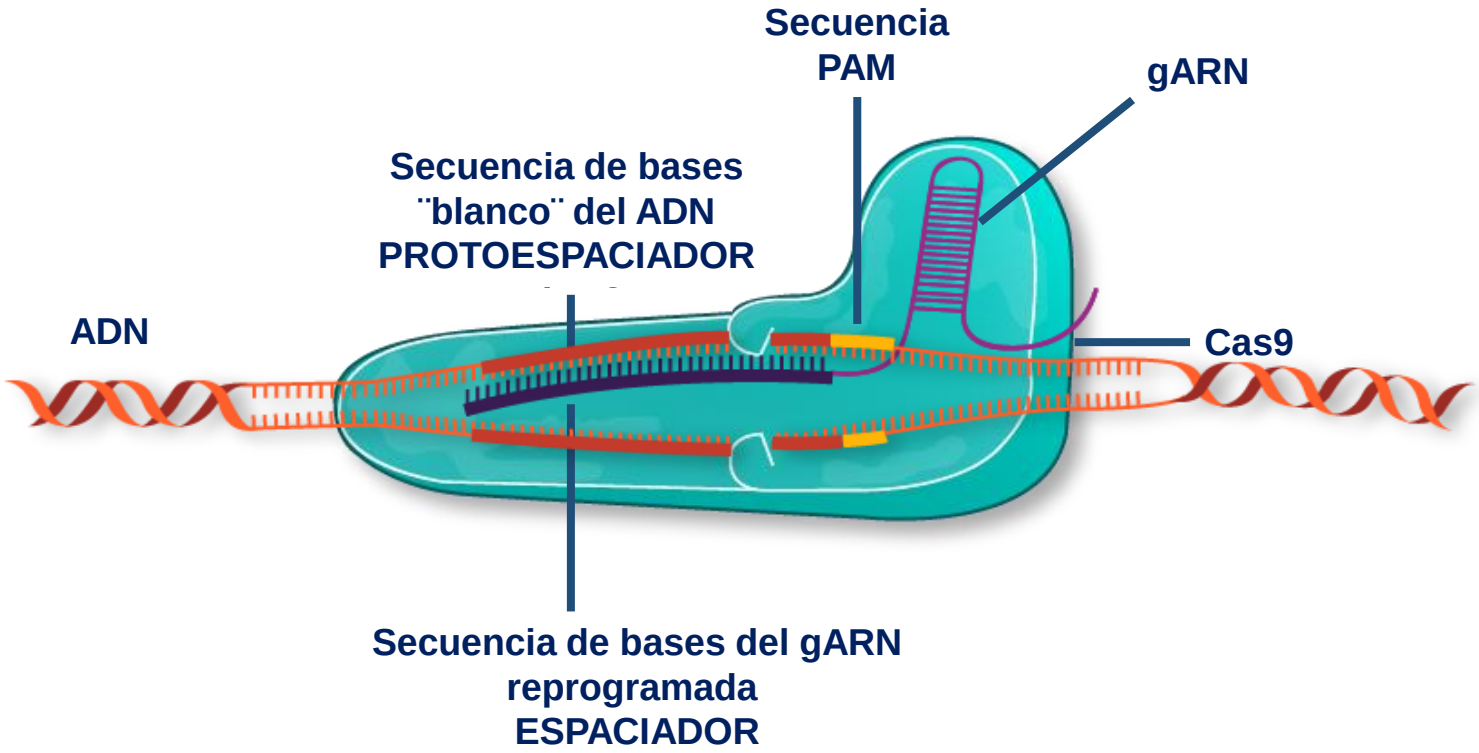
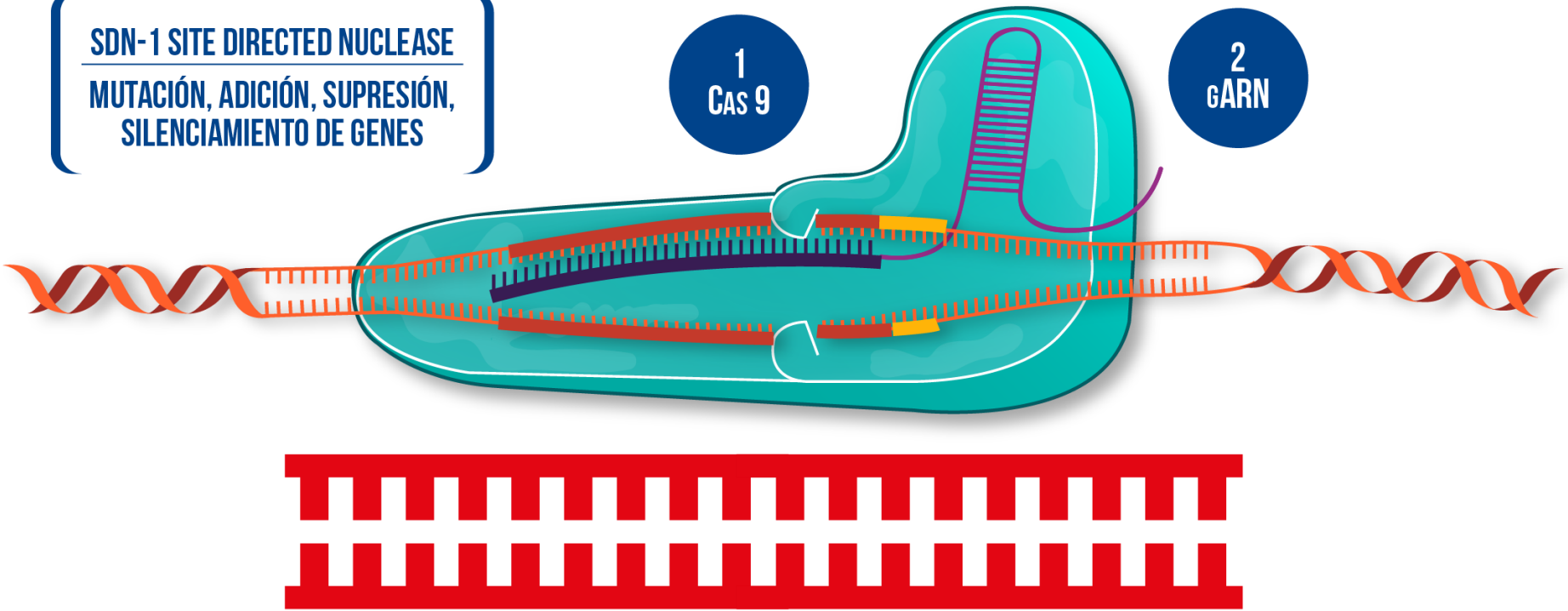


Edición de Genomas mediante CRISPR-Cas9

SDN-1 SITE DIRECTED NUCLEASE

MUTACIÓN, ADICIÓN, SUPRESIÓN, SILENCIAMIENTO DE GENES



Edición de Genomas mediante CRISPR-Cas9

SDN-1 SITE DIRECTED NUCLEASE

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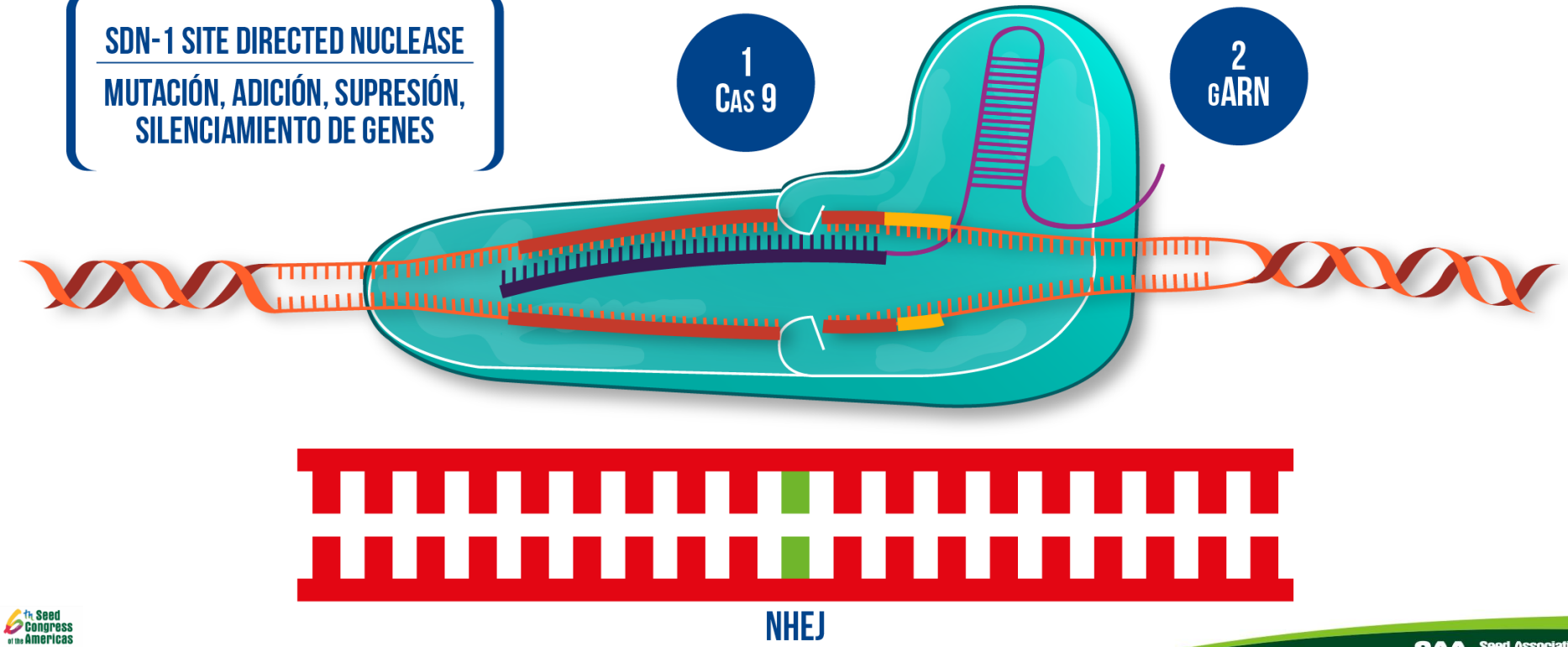
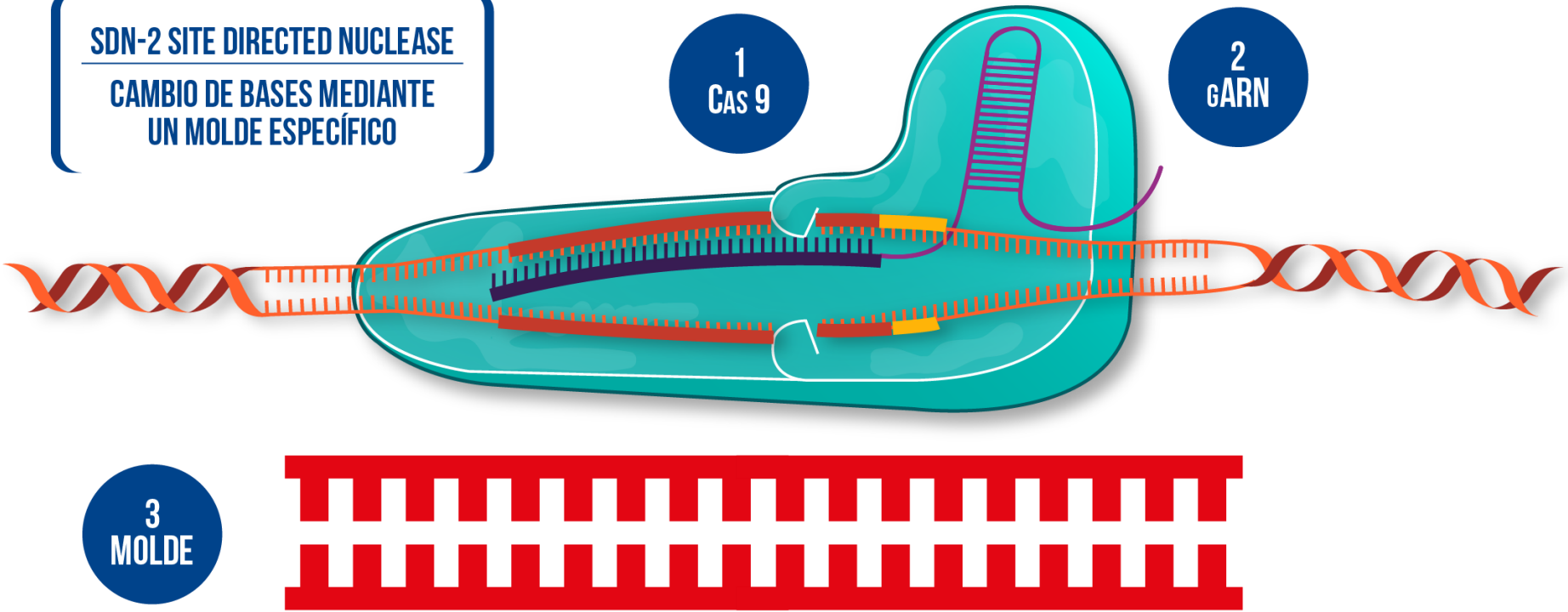


Edición de Genomas mediante CRISPR-Cas9

SDN-2 SITE DIRECTED NUCLEASE

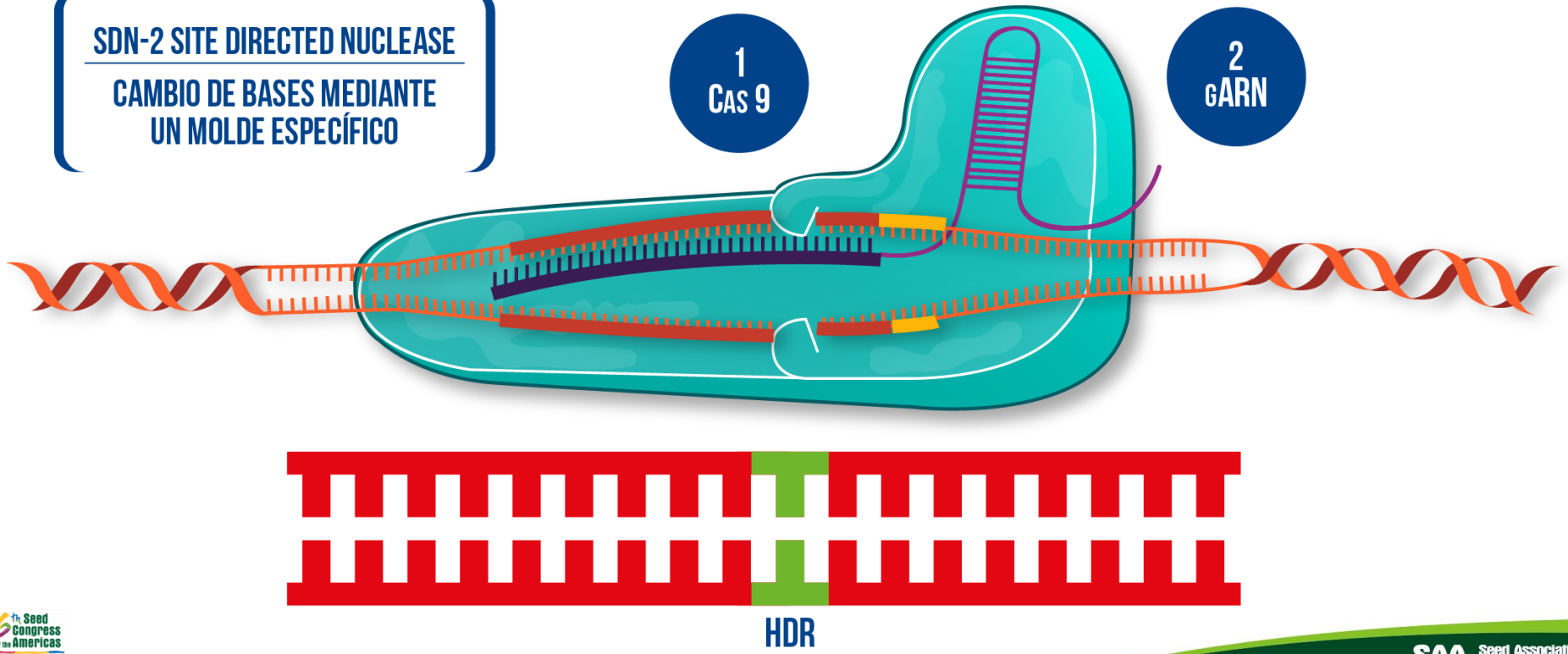
CAMBIO DE BASES MEDIANTE UN MOLDE ESPECÍFICO



Edición de Genomas mediante CRISPR-Cas9

SDN-2 SITE DIRECTED NUCLEASE

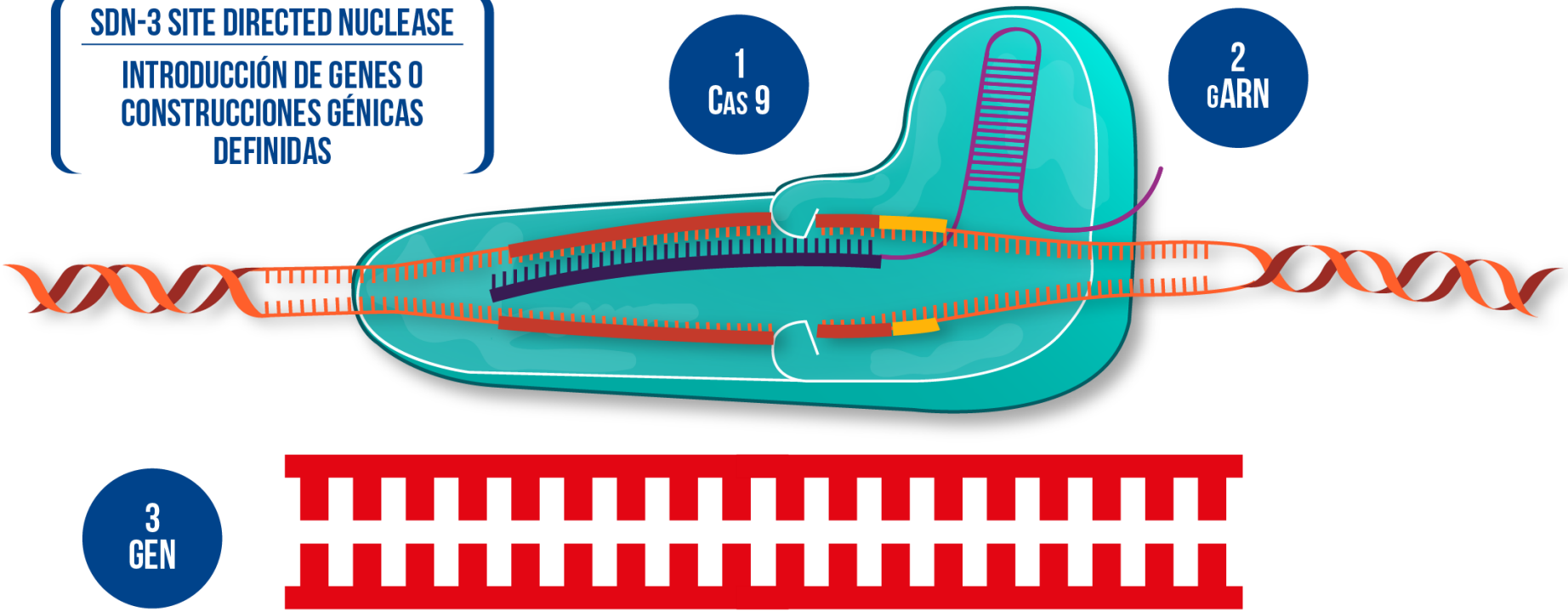
CAMBIO DE BASES MEDIANTE UN MOLDE ESPECÍFICO



Edición de Genomas mediante CRISPR-Cas9

SDN-3 SITE DIRECTED NUCLEASE

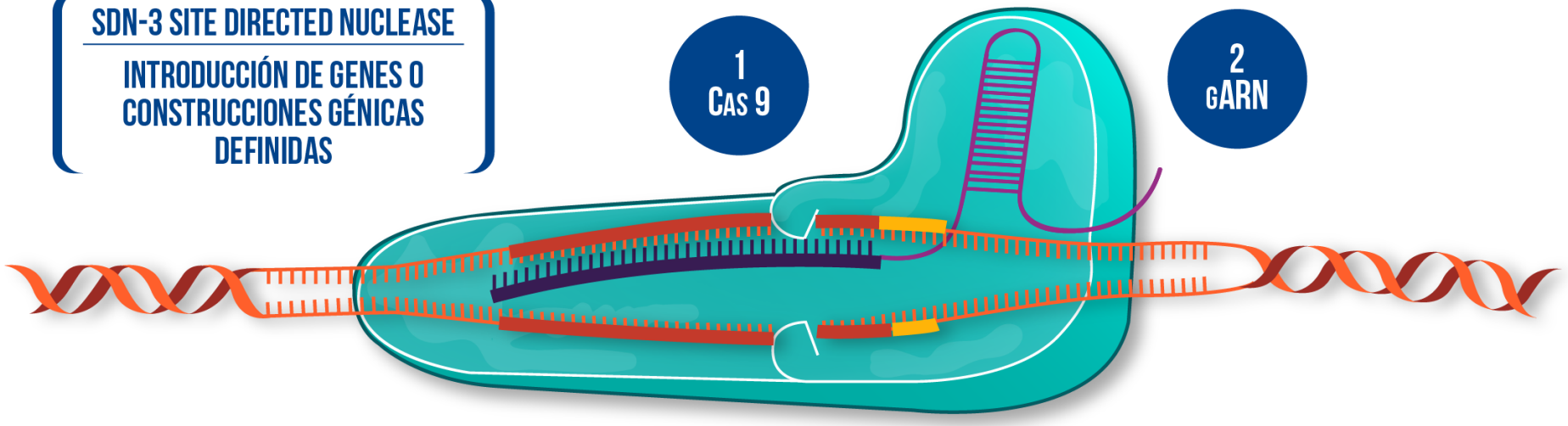
INTRODUCCIÓN DE GENES O CONSTRUCCIONES GÉNICAS DEFINIDAS



Edición de Genomas mediante CRISPR-Cas9

SDN-3 SITE DIRECTED NUCLEASE

INTRODUCCIÓN DE GENES O CONSTRUCCIONES GÉNICAS DEFINIDAS



- REEMPLAZO ALÉLICO
- CISGÉNESIS
- INTRAGÉNESIS
- TRANSGÉNESIS

HDR

Aplicaciones CRISPR-Cas9

- Levaduras
- Protozoos: leishmaniasis, toxoplasmosis, malaria…
- Plantas: arroz, naranjo, trigo, soja, maíz, melón, patata, tomate, tabaco…
- Insectos
- Moluscos
- Reptiles
- Anfibios
- Peces
- Aves
- Mamíferos: ratón, conejo, cabra, rata, cerdo, perro, primates, humanos…

Edición de Genomas con Nucleasas Sintéticas

Ventajas del sistema CRISPR sobre todas las anteriores técnicas de edición génica

- **Versátil;**
- **Sencillo;**
- **Económico;**
- **Preciso;**
- **Rápido;**
- **Eficiente**
- **Predecible**

PBI: factores claves en el mejoraniento vegetal

1. Técnica / Conocimiento
2. **Acceso**
3. Ambiente Regulatorio

Conflicto por Patentes

CRISPR-Cas9 no puede patentarse.

Las unidades CRISPR con sus secuencias repetidas y los espaciadores no repetidos, junto con los genes que codifican para las proteínas Cas están presentes en la naturaleza y son parte del sistema inmunológico de las bacterias.

Sí se pueden patentar:

- **gARN diseñados para el sistema CRISPR-Cas9**
- **Modificaciones del sistema llevadas a cabo para editar el genoma de las células de mamífero u otros organismos, en los que normalmente no se encuentran los componentes del sistema.**

¿De quién es CRISPR?

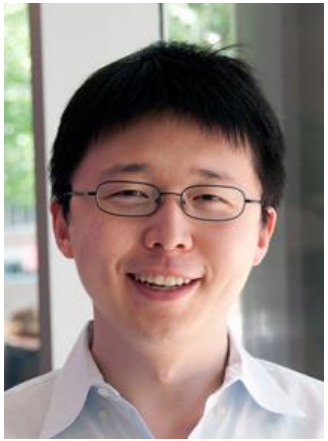
The Scientist » News & Opinion » News Analysis

Who Owns CRISPR?

With one US patent awarded and many other applications under consideration for the popular genome-editing technology, companies are adopting multiple strategies to navigate the complex intellectual property landscape.

Jennifer Doudna

Emmanuelle Charpentier

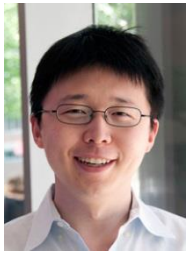


Feng Zhang

Francisco Mojica

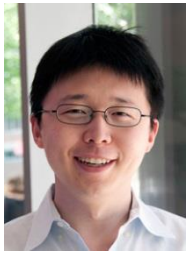
Luciano Marrafini

Acceso



editas MEDICINE

Acceso



addgene
The nonprofit plasmid repository

BROAD INSTITUTE

editas MEDICINE

Intellia THERAPEUTICS

CARIBOU BIOSCIENCES

CRISPR THERAPEUTICS

ers GENOMICS

MONSANTO

04-01-17
Worldwide, non-exclusive rights to agricultural applications of the CRISPR/Cpf1 system.
BROAD INSTITUTE

NOVARTIS

DOW

DUPONT

BAYER

DUPONT PIONEER

27-06-17
Exclusive rights to the **ERS** patent portfolio covering CRISPR-Cas genome editing technology for all agricultural uses and applications in plants.

Acceso

February 17, 2017

The CRISPR patent battle spans two continents

Isobel Finnie and Catherine Williamson, GEN Exclusives, 6 February 2017, http://www.genengnews.com/gen-exclusives/crispr-patent-wars/77900842

The CRISPR/Cas9 patent battle has been closely watched in the United States with a decision expected in the next few months. Less attention has been paid to the ongoing European patent battle. Like in the US, both UC-Berkeley and The Broad Institute have submitted competing patent applications. Currently the Broad Institute has received all granted patents over UC-Berkeley, however the Broad is facing challenges to these decisions.

Acceso

February 24, 2017

Broad Institute prevails over UC-Berkeley in patent battle

Heidi Ledford, Nature News, 15 February 2017 http://www.nature.com/news/broad-institute-wins-bitter-battle-over-crispr-patents-1.21502

The US patent office judges have ruled that the Broad Institutes and UC-Berkeley's patents do not interfere, providing a win for the Broad. This effectively allows both UC-Berkeley and the Broad to have patents covering portions of the CRISPR intellectual property landscape, possibly requiring companies to license patents from both institutions. This decision may be appealed to the circuit courts by UC-Berkeley.

Acceso

April 21, 2017

University of California Appeals CRISPR Patent Decision

Sharon Begley, 13 April 2017, STAT News, https://www.statnews.com/2017/04/13/crispr-patent-uc-appeal/
UC-Berkeley has filed an appeal with the federal Court of Appeals. UC-Berkeley was joined in its appeal by the University of Vienna and Emmanuelle Charpentier. Previously, the US Patent office had ruled that UC-Berkeley's and the Broad Institute's patents did not interfere, leaving them both able to pursue unique patents. In this appeal, UC-Berkeley hopes to establish that the teams led by Doudna and Charpentier were the first to engineer CRISPR/Cas9 in all cell types.

Acceso

April 13, 2017

UC-Berkeley Awarded CRISPR Patents in Europe

Jef Akst, The Scientist, 24 March 2017, http://www.the-scientist.com/?articles.view/articleNo/48987/title/UC-Berkeley-Receives-CRISPR-Patent-in-Europe/

The European patent office has announced its intention to award broad CRISPR patents to the University of California-Berkeley and the University of Vienna. The awarded patents will cover the use of the CRISPR technology in both prokaryotic and eukaryotic cells/organisms, contrasting with the US patent office which denied UC-Berkeley the rights to eukaryotic cells.

Acceso

July 16, 2017

Intellia Therapeutics Wins China CRISPR Patent

GEN News Highlights, 19 June 2017, http://www.genengnews.com/gen-news-highlights/intellia-holder-of-rights-to-ucs-crispr-technology-to-win-china-patent/81254529

Intellia Therapeutics, founded by Jennifer Doudna, has been awarded a broad patent for the CRISPR/Cas9 single guide gene editing system. Intellia has licensed the CRISPR technology developed by Jennifer Doudna at the University of California-Berkeley. This latest announcement comes on the tails of the European Patent Office's announcement favoring UC-Berkeley as well.

Acceso

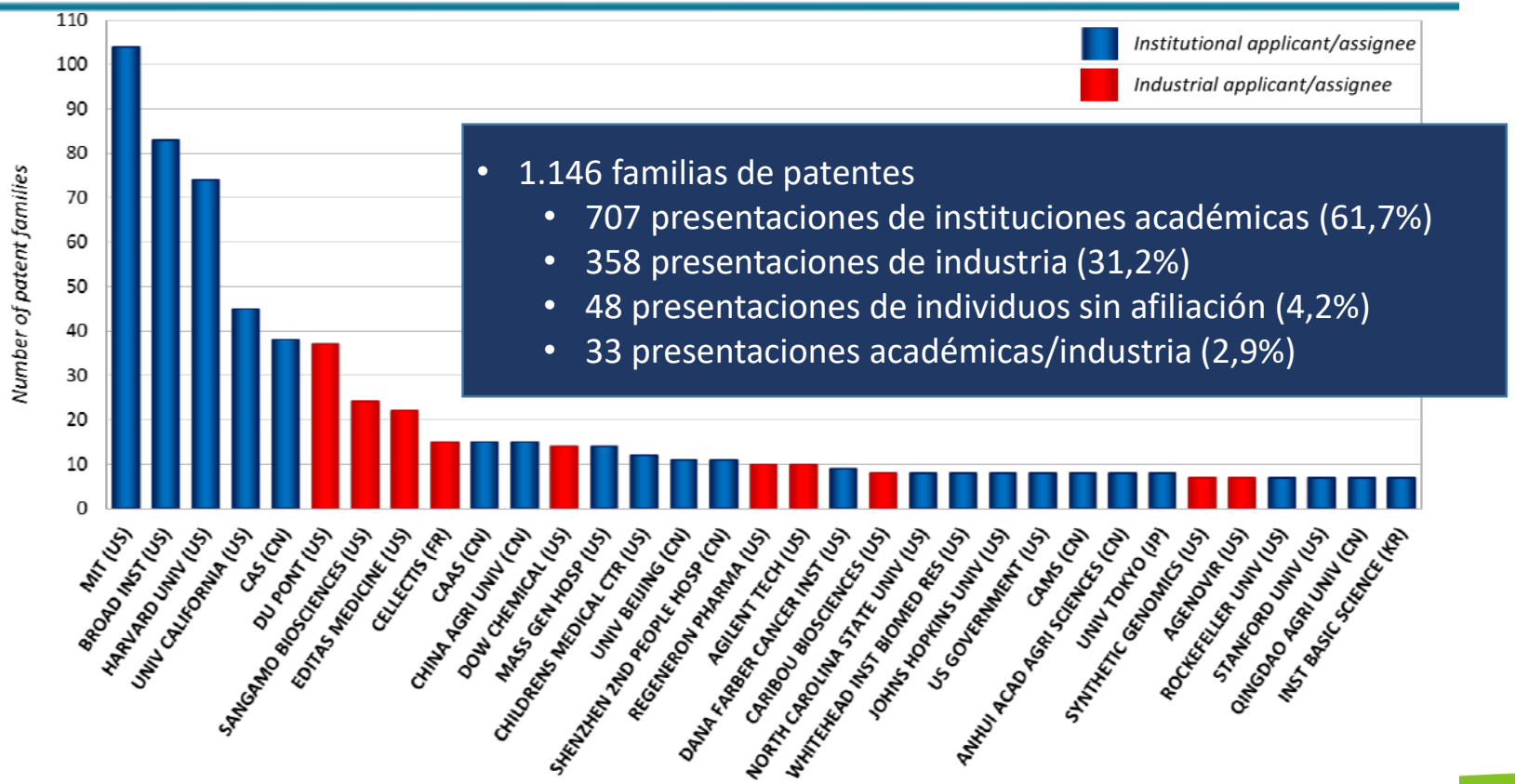
August 4, 2017

Cellectis Wins CRISPR Patent in Europe

Jonathan Wosen, GEN News Highlights, 25 July 2017, http://www.genengnews.com/gen-news-highlights/cellectis-granted-t-cell-crispr-patent-in-europe/81254707

French biotech company Cellectis has been granted a European patent to use CRISPR in T cells valid until 2034. Cellectis hopes to use this technology to edit T cells for cancer therapy. While other companies are pursuing similar treatments, Cellectis hopes to develop a universal CAR-T cell line that can be widely used without tailoring treatment to individuals.

Principales solicitantes



- 1.146 familias de patentes
  - 707 presentaciones de instituciones académicas (61,7%)
  - 358 presentaciones de industria (31,2%)
  - 48 presentaciones de individuos sin afiliación (4,2%)
  - 33 presentaciones académicas/industria (2,9%)

Antecedentes

Harvard Oncomouse

Tecnología PCR – PCR/Taq patent war

Plataforma Global de Licencias Conjuntas

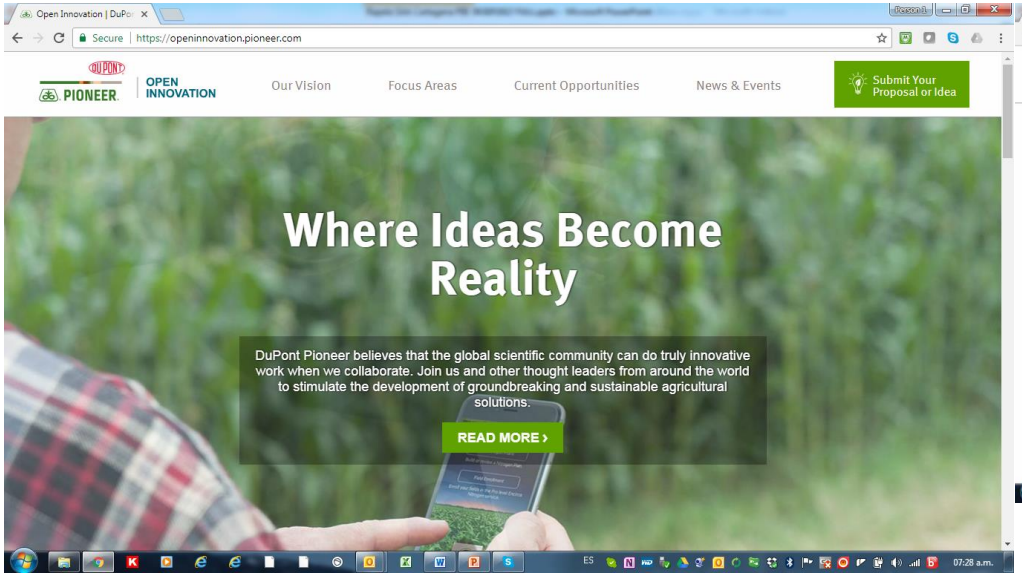
- **Broad Institute**
- **MIT**
- **Harvard University**
- **Rockefeller University**

Plataforma Global de Licencias Conjuntas

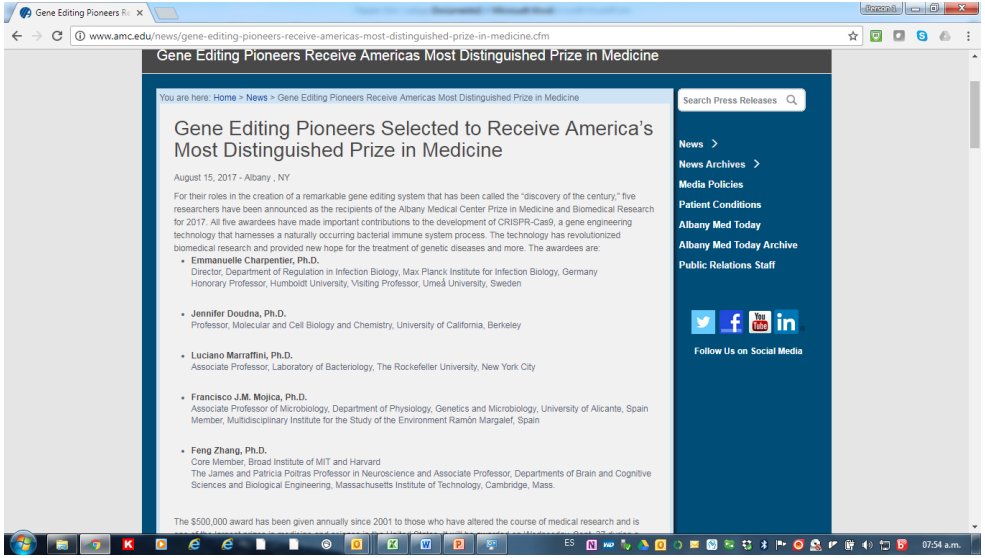
MPEG LA

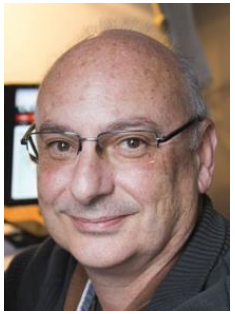
Mecanismo de licencias no exclusivo mantenido y manejado por una entidad independiente de los poseedores de las patentes

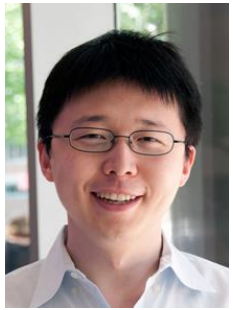
Iniciativas de Open Innovation



Reconocimiento







17 de Agosto 2017

Albany Medical Center Prize in Medicine and Biomedical Research for 2017

PBI: factores claves en el mejoraniento vegetal

1. Técnica / Conocimiento
2. Acceso
3. **Ambiente Regulatorio**

Ambiente regulatorio

- Los productos editados, ¿son organismos genéticamente modificados?
- ¿Regular por proceso o por producto?
- ¿Es necesario un marco regulatorio especial para los productos editados?
- ¿Es necesario crear una nueva categoría de producto regulado?
- ¿Es necesario mencionar las técnicas?
- Si las modificaciones también pueden ser logradas mediante mejoramiento convencional, ¿el producto debe ser regulado?
- ¿La cantidad de nucleótidos modificada es el criterio central? ¿Es un criterio secundario? ¿No es un criterio?
- ¿Cuál es entonces el criterio?

Ambiente regulatorio

- Canadá

- Argentina (2015)
- Israel (2016)
- Chile (2017)

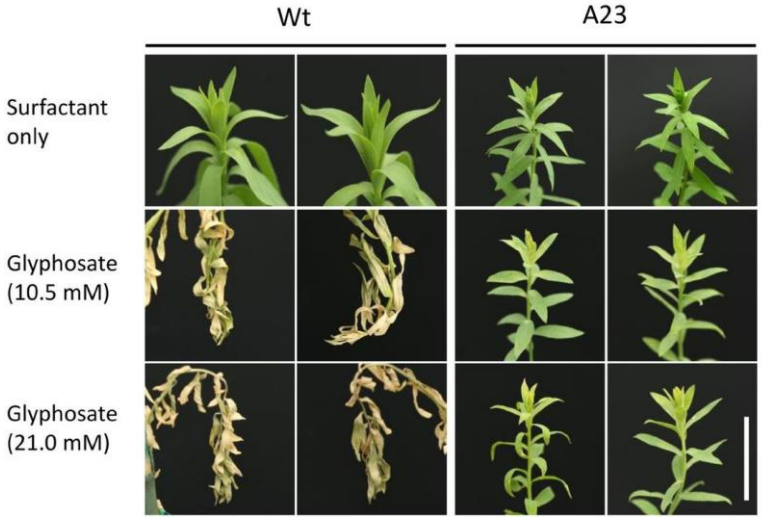
- US (2017 – propuesta)

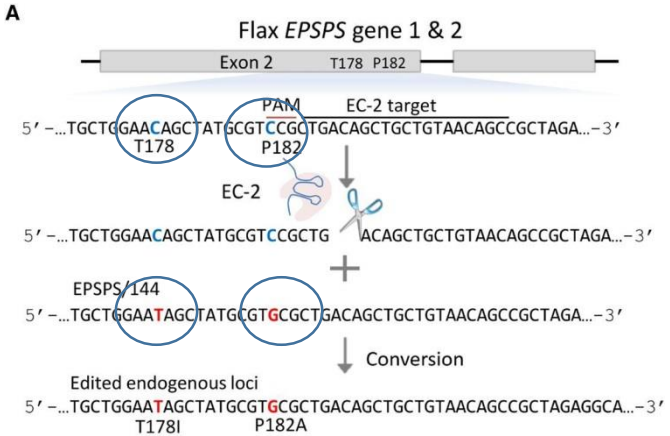
- Regulación por producto

- Caso a caso
- No crear una 3ª categoría de producto
- El producto final está fuera del alcance del marco regulatorio si NO contiene una nueva combinación de material genético *(= la inserción en el genoma en forma estable y conjunta de uno o más genes o secuencias de ADN que forman parte de una construcción genética definida).*

Y los productos, ¿cómo se protegen?

Caso 1





Oligonucleotide-mediated genome editing provides precision and function to engineered nucleases and antibiotics in plants

Noel J Sauer (nsauer@cibus.com), Javier Narváez-Vásquez (jnarvaez@cibus.com), Jerry Mozoruk (jmozoruk@cibus.com), Ryan B Miller (rmiller@cibus.com), Zachary J Warburg (zwarburg@cibus.com), Melody J Woodward (mwoodward@cibus.com), Yohannes A Mihiret (ymihiret@cibus.com), Tracey A Lincoln (tlincoln@cibus.com), Rosa E Segami (rsegami@cibus.com), Steven L Sanders (ssanders@cibus.com), Keith A Walker (kwalker@cibus.com), Peter R Beetham (pbeetham@cibus.com), Christian R Schöpke (cschopke@cibus.com) and Greg FW Gocal (ggocal@cibus.com)

Plant Physiology. February 10, 2016

Caso 1

Compañía A

Compañía C

Variedad 1
Convencional

Compañía B

¿Definición de Variedad?

Ley 20147/73
Ley 24376/94

Variedad 3
No Transgénica
CRISPR-Cas9
Tol. glfosato

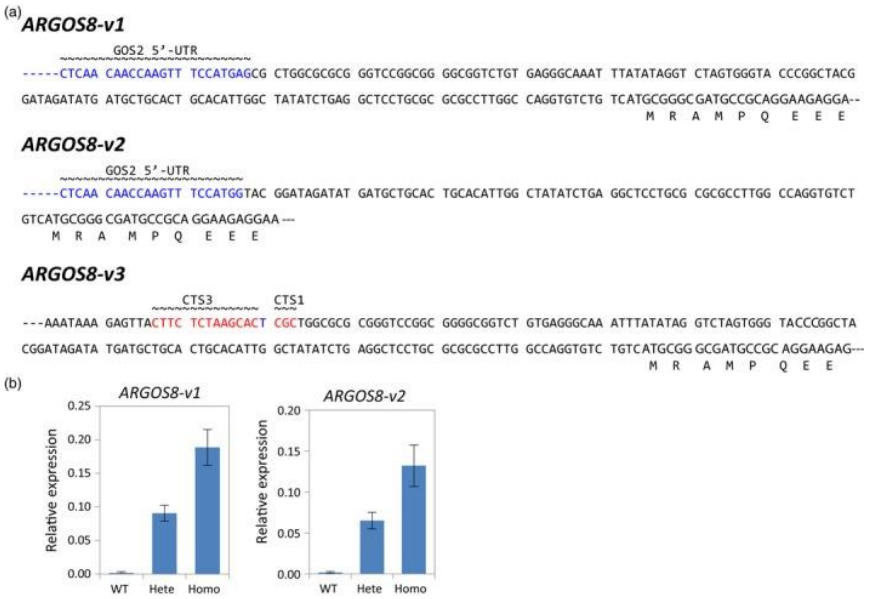
Variedad 2
Transgénica
Tol. glfosato

Caso 2

En maíz, el gen ARGOS8 es un regulador negativo de la respuesta al etileno. Las plantas con sobreexpresión de ARGOs8 muestran una reducida sensibilidad al etileno y mejoran la producción de grano bajo condiciones de stress hídrico.

En el año 2016 científicos de la compañía Pioneer utilizaron CRSPR-Cas9 tanto para editar el promotor nativo del gen ARGOS8 como para reemplazar al promotor nativo de este gen.

Las plantas regeneradas presentaron una alta expresión de ARGOS8, lo cual fue detectable en todos los tejidos de la planta, y en ensayos a campo incrementaron significativamente su producción de grano bajo condiciones de stress hídrico en floración, no mostrando a la par ninguna disminución de rendimiento en condiciones de adecuada humedad. Las nuevas variedades no son transgénicas.



Shi j, Gao H, Wang H, Lafitte HR, Archibald RL, Yang M, Hakimi SM, Mo H, Habben JE (2016). ARGOS8 variants generated by CRISPR-Cas9 improve maize grain yield under field drought stress conditions. Plant Biotechnol. J., doi: 10.1111/pbi.12603

Caso 2

Variedad 1

Variedad 2
Tolerante stress hídrico por modificación de un gen promotor nativo

¿Patente sobre un gen nativo modificado?

¿DOV sobre el híbrido?

¿DOV sobre la línea paterna?

Caso 3

El tomate tiene su origen en los Andes sudamericanos. Un equipo de investigadores liderado por Zachary Lippman en el Cold Spring Harbor Laboratory de los Estados Unidos analizó una colección de 4.193 variedades silvestres de tomate, buscando aquellos con patrones de ramificación inusuales, identificando dos genes de elevada aptitud comercial (Lippman y col, 2008).

Con estos genes descubiertos, su equipo utilizó la edición génica de CRISPR-Cas9 para eliminar su actividad en una variedad de tomate comercial, así como la de un tercer gen que también afecta el número de flores, en varias combinaciones. Esto generó una gama de arquitecturas en la planta, desde largas y delgadas ramas con racimos de flores, hasta tupidos ramitos de flores con una arquitectura similar a la coliflor; incluyendo algunos con rendimientos mejorados (Soyk y col, 2017). En otros términos, para este desarrollo, no se hizo uso ni se tomó acceso físico al material que conforma el recurso genético, sino solo información del mismo. DEMATERIALIZACIÓN

GENETICS

CRISPR editing seeks the perfect tomato

Geneticists correct harmful interaction of two desirable plant mutations.

BY HEIDI LEDFORD

From giant fruit to compact plants, today's tomatoes have been sculpted by thousands of years of breeding. But mutations linked to prized traits — including one that made the fruit easier to harvest — yield an undesirable plant when combined, geneticists have found.

It is a rare example of a gene harnessed during domestication that later hampered crop-improvement efforts, says geneticist Zachary Lippman of Cold Spring Harbor Laboratory in New York. After identifying the mutations, he and his colleagues used CRISPR gene editing to engineer more-productive plants — a strategy that plant breeders are eager to adopt.

"It's pretty exciting," says Rod Wing, a plant geneticist at the University of Arizona in Tucson. "The approach can be applied to crop improvement, not just in tomato, but in all crops."

PHILIPPE HUGUEN/AFP/GETTY

Tomatoes have been bred for thousands of years.

Lippman knows his way around a tomato farm. As a teenager, he spent his summers picking the fruit by hand — a chore he hated. "Rotten tomatoes. The smell lasts all day long," he says. "I would always pray for rain on tomato-harvest day."

But years later, his interest in the genetics that control a plant's shape led him back to tomato fields, to untangle the genetic changes that breeders had unknowingly made.

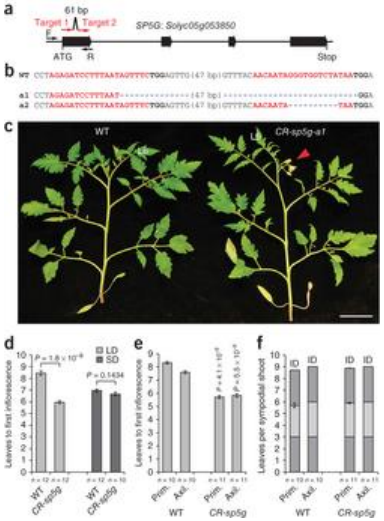
In the 1950s, researchers found a new trait in a wild relative of tomatoes growing in the Galapagos Islands: it lacked the swollen part of the stem called the joint.

Joints are weak regions of the stem that allow fruit to drop off the plant. Wild plants benefit from dropping fruit because it helps seed dispersal. But with the advent of mechanical tomato pickers, farmers wanted their fruit

Lippman ZB, Cohen O, Alvarez JP, Abu-Abied M, Pekker I, Paran I, et al. (2008) The Making of a Compound Inflorescence in Tomato and Related Nightshades. PLoS Biol 6(11): e288. https://doi.org/10.1371/journal.pbio.0060288

Soyk S, Lemmon ZH, Oved M, Fisher J, Liberatore KL, Park SJ, Goren A, Jiang K, Ramos A, van der Knaap E, van Eck J, Zamir D, Eshed Y, Lippman ZB (2017). Bypassing Negative Epistasis on Yield in Tomato Imposed by a Domestication Gene. Cell DOI: http://dx.doi.org/10.1016/j.cell.2017.04.032

Caso 3



Información genética

Silvestre

Variedad 1

Edición génica a partir de información sobre un RRGG

¿Se hizo utilización del recurso genético?

Ley 27182/15 TIRFAA
Ley 27246/15 PN

Conclusiones

- **CRISPR-Cas**
  - **Es una plataforma multifuncional para la edición génica de todo tipo de organismo procariota o eucariota;**
  - **Es el avance tecnológico en mejoramiento vegetal más significativo desde la transgénesis;**
  - **Es una técnica versátil, sencilla, económica, rápida, precisa, muy eficiente y predecible;**
  - **Podría reemplazar a varias de las técnicas de mejoramiento convencional (ej, back cross);**
  - **Podría reemplazar a toda la transgénesis en tanto el carácter a modificar esté presente en la especie;**
  - **Permite transgénesis a sitios definidos.**

Conclusiones

- Marco Regulatorios
  - Probable: productos SDN-1 y SDN-2, no serán regulados
    productos SDN-3, regulados, aunque no en todos los casos (¿tipos particulares de cisgénesis, reemplazo alélico?)
  - ¿Cómo generar doctrina?

- Marco Propiedad Intelectual – Recursos Genéticos
  - Cuestionamientos sobre la utilidad del alcance de los sistemas vigentes

Conclusiones

Potencial futuro y desafíos de la industria semillera argentina

- **Las técnicas de edición génica constituyen un nuevo punto de ruptura y plantean la necesidad de un profundo ejercicio de armonización de la biotecnología, con aspectos regulatorios y de propiedad intelectual.**

Thank you for your attention!