FACULTAD DE CIENCIAS QUÍMICAS Y FARMACÉUTICAS UNIVERSIDAD DE CHILE

20. Biotecnología y Biología Sintética. Aplicaciones modernas de la biología molecular

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¿Qué es la biotecnología?

La biotecnología es la disciplina que utiliza sistemas biológicos (como células), organismos vivos (como bacterias) o sus componentes (como enzimas o genes) para desarrollar nuevos productos y procesos

Ejemplos del uso de la biotecnología

TABLE 21.1

Common Uses of Microorganisms

Application	Examples
Production of medicines	Antibiotics, vitamins
	Synthesis of human insulin in recombinant *E. coli*
Food and beverage production via fermentation	Cheese, yogurt, vinegar, wine, and beer
Biological control	Control of plant diseases, insect pests, and weeds
	Symbiotic nitrogen fixation
	Prevention of frost formation
Bioremediation	Cleanup of environmental pollutants such as petroleum hydrocarbons and synthetics that are difficult to degrade

TABLE 21.2

Examples of Medical Agents Produced by Recombinant Microorganisms

Drug	Action	Condition Treated
Insulin	A hormone that promotes glucose uptake	Diabetes
Tissue plasminogen activator (TPA)	Dissolves blood clots	Heart attacks and other vascular occlusions
Superoxide dismutase	Antioxidant	Heart attacks and tissue damage
Factor VIII	Blood-clotting factor	Certain types of hemophilias
Renin inhibitor	Lowers blood pressure	Hypertension
Erythropoietin	Stimulates the production of red blood cells	Anemia

Insulina

Humulin, una forma recombinante de la insulina humana, fue la primera proteína terapéutica producida mediante tecnología de ADN recombinante aprobada para uso en humanos

1982

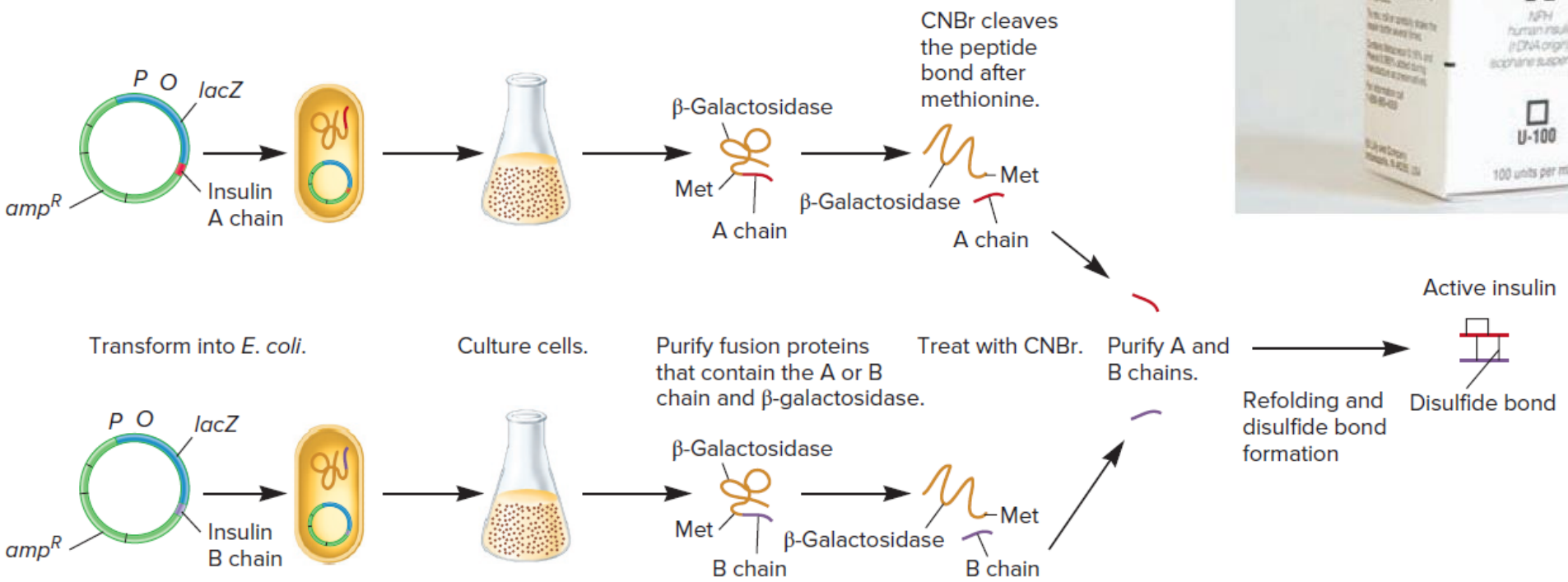

FIGURE 21.1 The use of bacteria to make human insulin. In recent forms of manufactured insulin, slight changes have been made to the insulin amino acid sequence. These changes prevent insulin molecules from clumping together, and thereby improve the manufactured insulin's biological properties.

Cyanogen bromide (CNBr) cleaves at methionine (Met) residues

En la actualidad la insulina de acción rápida para tratamiento humano es producida por Novo Nordisk en el sistema de expresión de S. cerevisiae

Producción de proteínas recombinantes

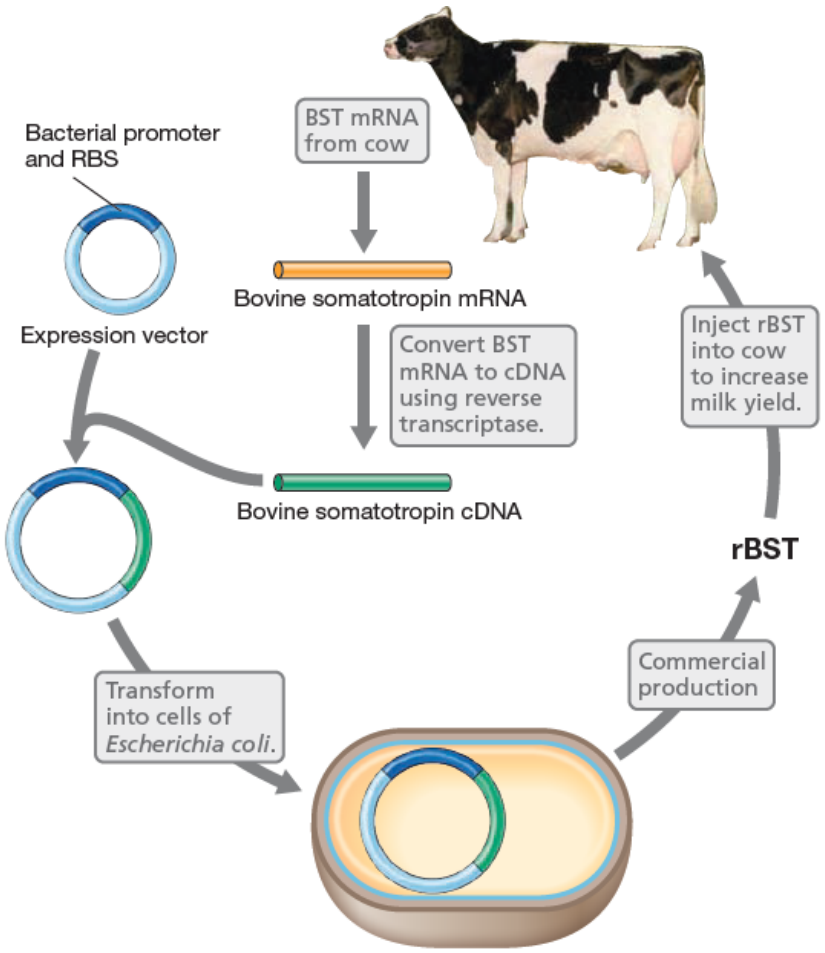

Figure 11.26 **Cloning and expression of bovine somatotropin.** The mRNA for bovine somatotropin (BST) is obtained from an animal. The mRNA is converted to cDNA by reverse transcriptase. The cDNA version of the somatotropin gene is then cloned into a bacterial expression vector that has a bacterial promoter and ribosome-binding site (RBS). The construct is transformed into cells of *Escherichia coli*, and recombinant bovine somatotropin (rBST) is produced. Milk production increases in cows treated with rBST.

Table 11.2 A few human medical products made by genetic engineering

Product	*Function*
Blood proteins	
Erythropoietin	Treats certain types of anemia
Factors VII, VIII, IX	Promotes blood clotting
Tissue plasminogen activator	Dissolves blood clots
Urokinase	Promotes blood clotting
Human hormones	
Epidermal growth factor	Wound healing
Follicle-stimulating hormone	Treatment of reproductive disorders
Insulin	Treatment of diabetes
Nerve growth factor	Treatment of degenerative neurological disorders and stroke
Relaxin	Facilitates childbirth
Somatotropin (growth hormone)	Treatment of some growth abnormalities
Immune modulators	
α-Interferon	Antiviral, antitumor agent
β-Interferon	Treatment of multiple sclerosis
Colony-stimulating factor	Treatment of infections and cancer
Interleukin-2	Treatment of certain cancers
Lysozyme	Anti-inflammatory
Tumor necrosis factor	Antitumor agent, potential treatment of arthritis
Replacement enzymes	
β-Glucocerebrosidase	Treatment of Gaucher disease, an inherited neurological disease
Therapeutic enzymes	
Human DNase I	Treatment of cystic fibrosis
Alginate lyase	Treatment of cystic fibrosis

Genetically modified crops

https://www.fda.gov/food/agricultural-biotechnology/gmo-crops-animal-food-and-beyond

TABLE ST 4.1 Some GM Crops Approved for Food, Feed, or Cultivation in the United States*

Crop	Number of Varieties	GM Characteristics
Soybeans	19	Tolerance to glyphosate herbicide Tolerance to glufosinate herbicide Reduced saturated fats Enhanced oleic acid Enhanced omega-3 fatty acid
Maize	68	Tolerance to glyphosate herbicide Tolerance to glufosinate herbicide Bt insect resistance Enhanced ethanol production
Cotton	30	Tolerance to glyphosate herbicide Bt insect resistance
Potatoes	28	Bt insect resistance
Canola	23	Tolerance to glyphosate herbicide Tolerance to glufosinate herbicide Enhanced lauric acid
Papaya	4	Resistance to papaya ringspot virus
Sugar beets	3	Tolerance to glyphosate herbicide
Rice	3	Tolerance to glufosinate herbicide
Zucchini squash	2	Resistance to zucchini, watermelon, and cucumber mosaic viruses
Alfalfa	2	Tolerance to glyphosate herbicide
Plum	1	Resistance to plum pox virus

*Information from the International Service for the Acquisition of Agri-Biotech Applications, www.isaaa.org.

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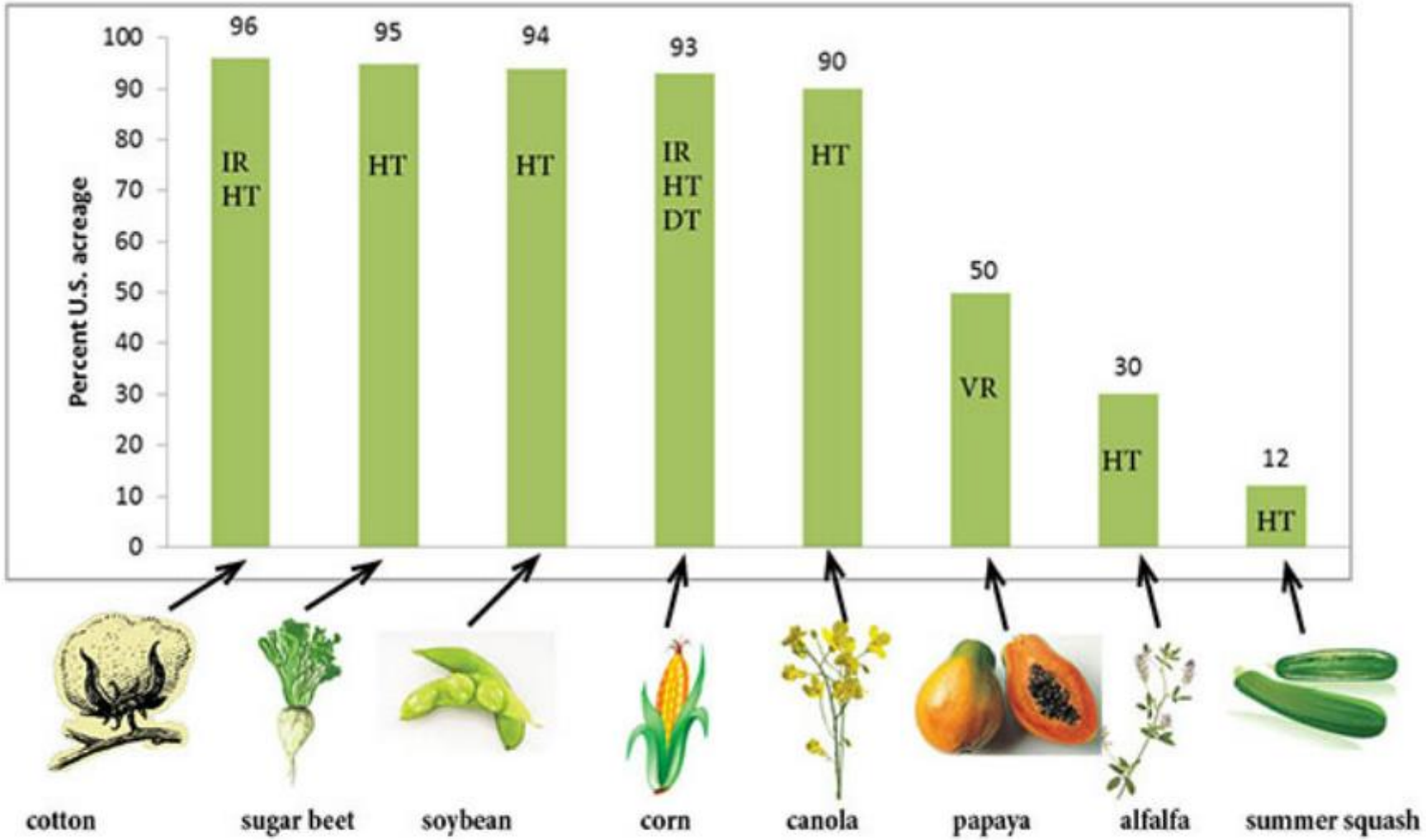

Figure 1. Currently grown GM crops in the U.S., traits for which they are modified, and percent of total acreage of the crop that is planted to GM varieties. IR=insect resistant, HT=herbicide tolerant, DT=drought tolerant, VR=virus resistant.

https://extension.colostate.edu/topic-areas/agriculture/genetically-modified-gm-crops-techniques-and-applications-0-710/

Arroz Dorado: Una solución biotecnológica a la deficiencia de vitamina A

- **250,000-500,000 niños pierden la vista anualmente por falta de vitamina A**
- La deficiencia también causa:
  - Debilitamiento del sistema inmune
  - Mayor riesgo de diarrea
  - Aumento de infecciones virales

FIGURE ST 4.3 Non-GM and Golden Rice 2. Golden Rice 2 contains high levels of beta-carotene, giving the rice endosperm a yellow color. The intensity of the color reflects the amount of beta-carotene in the endosperm.

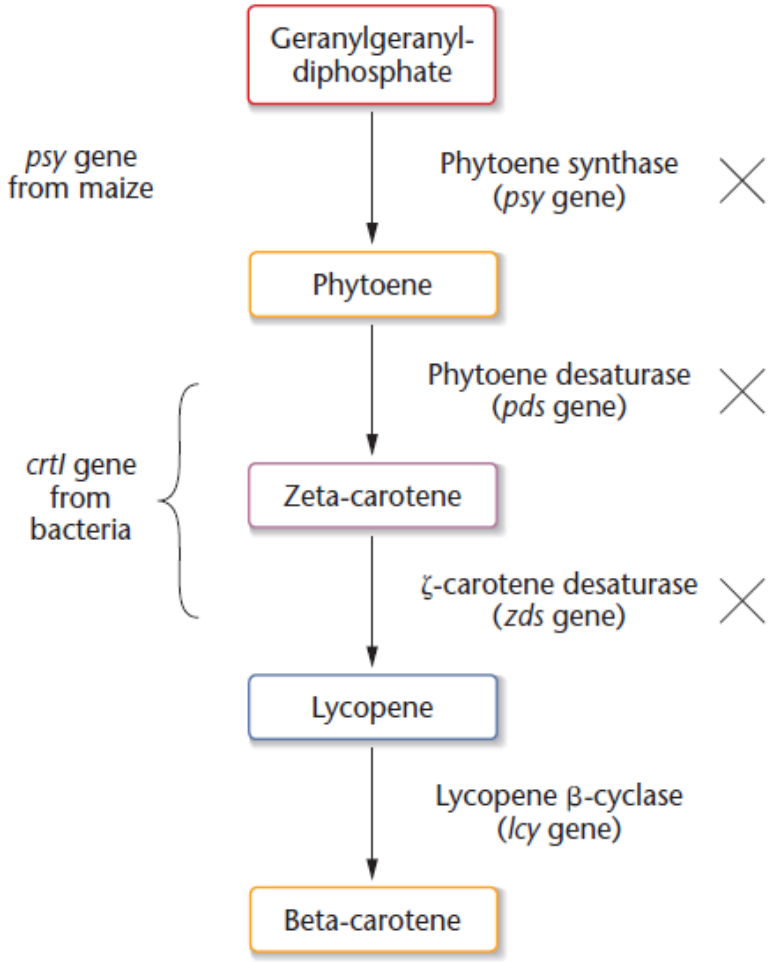

FIGURE ST 4.2 Beta-carotene pathway in Golden Rice 2. Rice plant enzymes and genes involved in beta-carotene synthesis are shown on the right. The enzymes that are not expressed in rice endosperm are indicated with an "X." The genes inserted into Golden Rice 2 are shown on the left.

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Resistance of Roundup Ready crops

El **glifosato** es un herbicida de amplio espectro

Actúa inhibiendo la enzima **EPSPS** (5-enolpiruvilshikimato-3-fosfato sintasa)

Figure 11.29 **Transgenic plants: herbicide resistance.** The photograph shows a portion of a field of soybeans that has been treated with Roundup™, a glyphosate-based herbicide manufactured by Monsanto Company (St. Louis, Missouri, USA). The plants on the right are normal soybeans; those on the left have been genetically engineered to be glyphosate resistant.

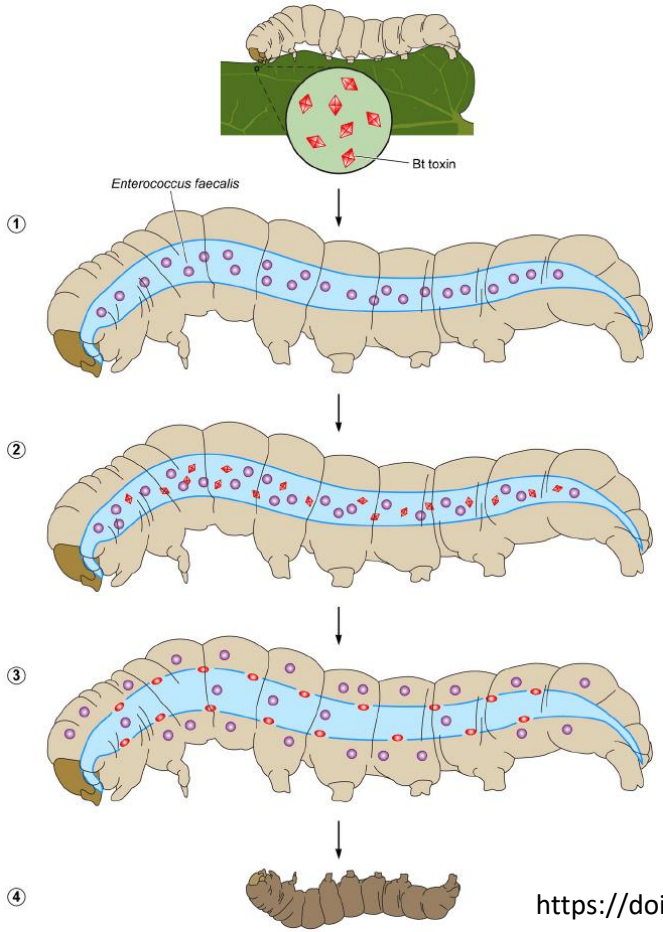
FIGURE ST 4.5 Portion of plasmid pV-GMGT04 used to create Roundup-Ready soybeans. A 1365-bp fragment encoding the EPSPS enzyme from *Agrobacterium CP4* was cloned downstream from the cauliflower mosaic virus *E35S* promoter and the petunia chloroplast transit peptide signal sequence (*ctp4*). CTP4 signal sequences direct the EPSPS protein into chloroplasts, where aromatic amino acids are synthesized. The *CP4 epsps* coding region was cloned upstream of the nopaline synthase (*nos*) transcription termination and polyadenylation sequences. The *CP4 epsps* sequences encode a 455-amino-acid 46-kDa ESPSP protein.

Gen **CP4 EPSPS** aislado de Agrobacterium sp. cepa CP4
Bacteria naturalmente resistente al glifosato

Klug, W (2019) Concepts of Genetics 12th Edition

Transgenic Bt crops

- *Bacillus thuringiensis (Bt):* Bacteria natural del suelo
- Produce proteínas cristalinas (proteínas Cry)
- Estas proteínas son tóxicas para grupos específicos de insecto
- Se ha usado como pesticida orgánico por más de 50 años



https://doi.org/10.1128/mbio.00161-11

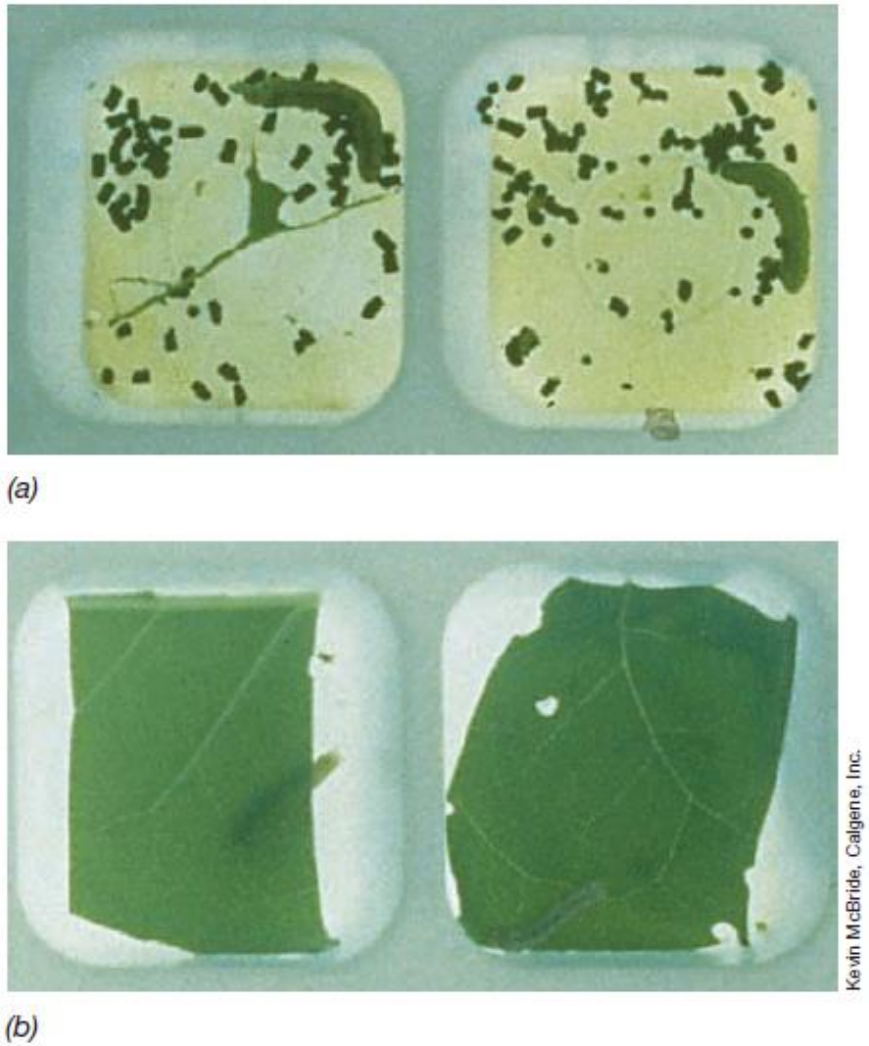
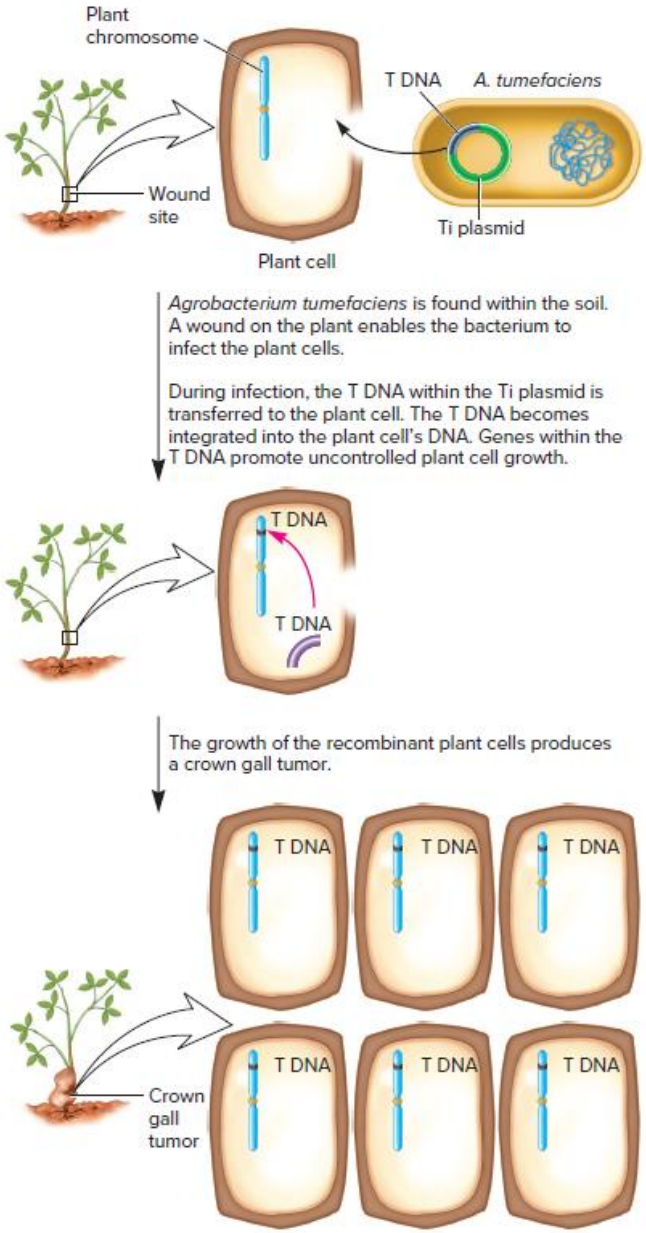


Figure 11.30 **Transgenic plants: insect resistance.** *(a)* The results of two different assays to determine the effect of beet armyworm larvae on tobacco leaves from normal plants. *(b)* The results of similar assays using tobacco leaves from transgenic plants that express Bt toxin in their chloroplasts.

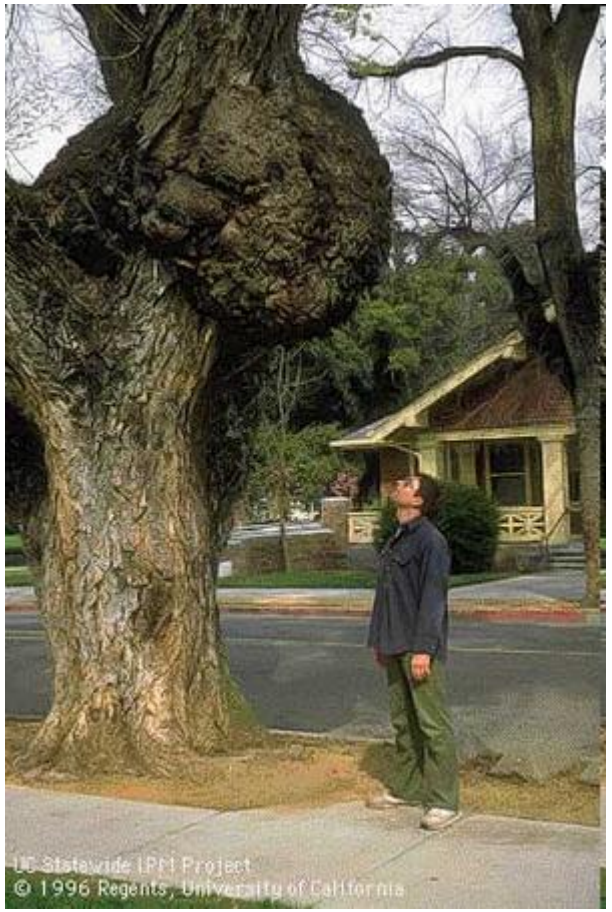


(a) The production of a crown gall tumor by *A. tumefaciens* infection

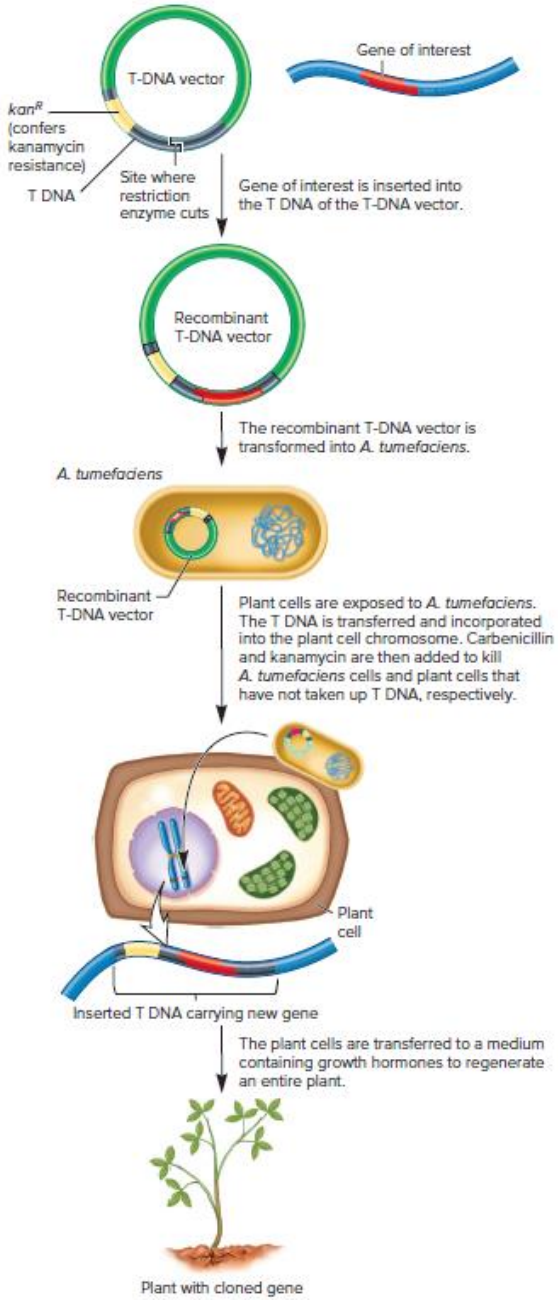
FIGURE 21.13 ***Agrobacterium tumefaciens*** **infecting a plant and causing a crown gall tumor.**

(b): ©Nigel Cattlin/Alamy

Agrobacterium tumefaciens



The Ti Plasmid and Transgenic Plants



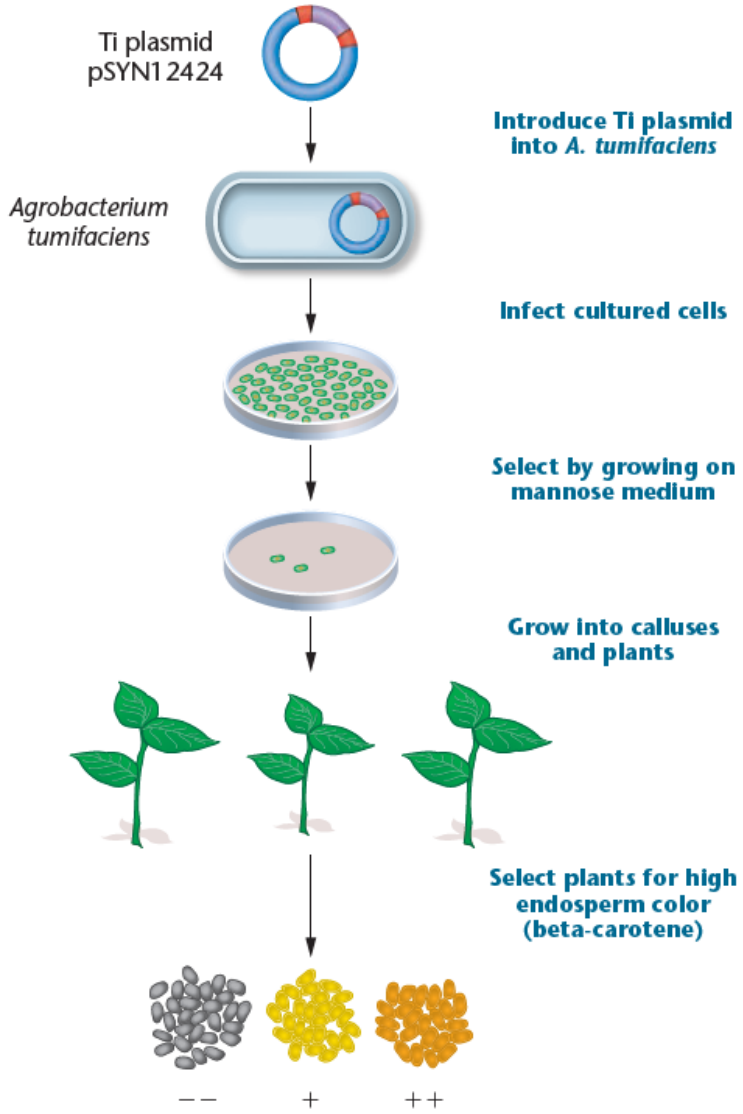
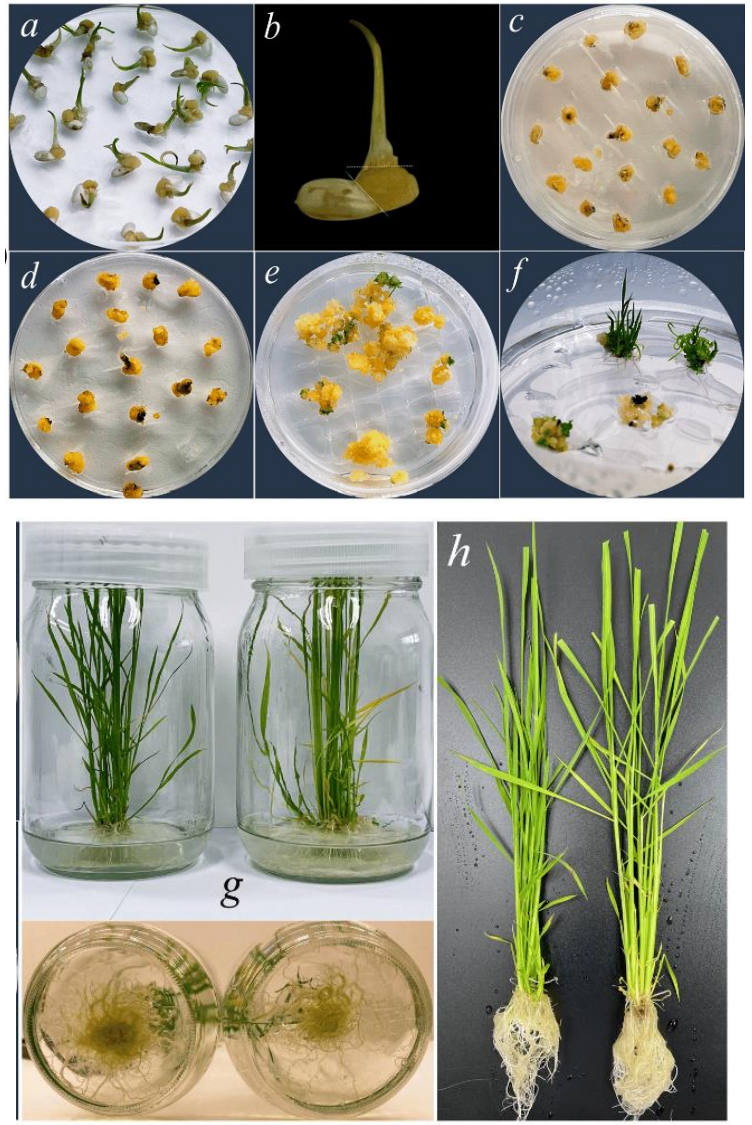


FIGURE ST 4.8 Method for creating Golden Rice 2. Rice plant cells were transformed by pSYN12424 and selected on mannose-containing medium, as described in the text. Plants that produced high levels of beta-carotene in rice grain endosperm (+ +), based on the intensity of the grain's yellow color, were selected for further analysis.



https://doi.org/10.3390/ijms241210365

Gen gun

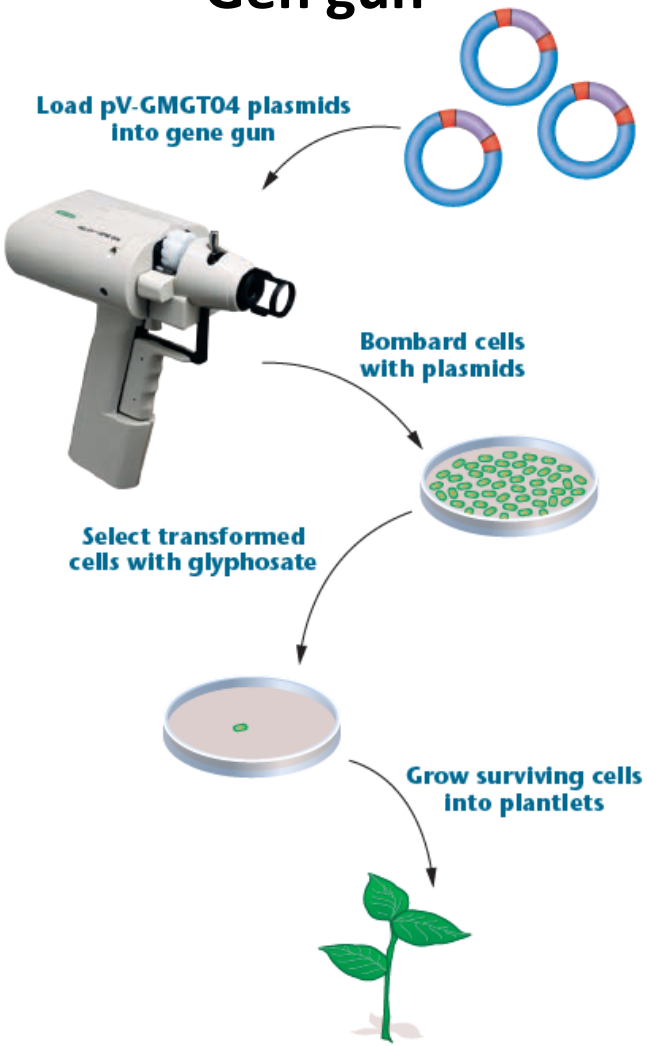


FIGURE ST 4.6 Method for creating Roundup-Ready soybeans. Plasmids were loaded into the gene gun and fired at high pressure into cells growing in tissue cultures. Cells were grown in the presence of glyphosate to select those that had integrated and expressed the *epsps* gene. Surviving cells were stimulated to form calluses and to grow into plantlets.

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GloFish

FIGURE 22.4 GloFish, marketed as the world's first GM pet, are a controversial product of genetic engineering.

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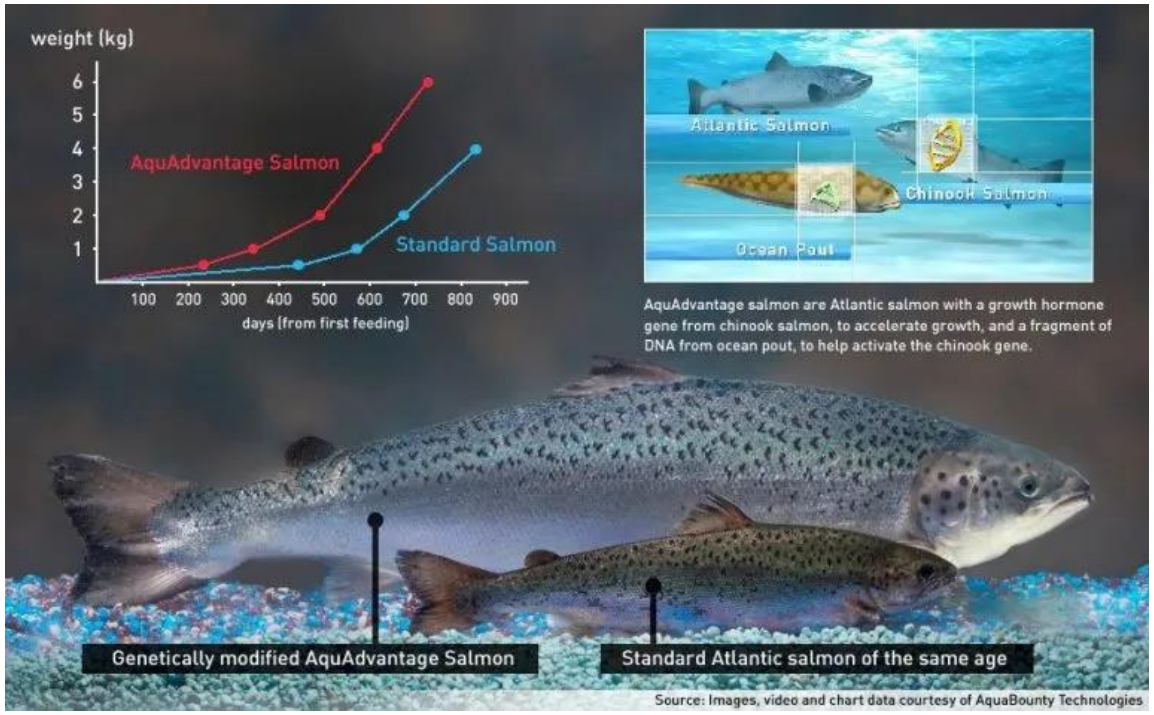
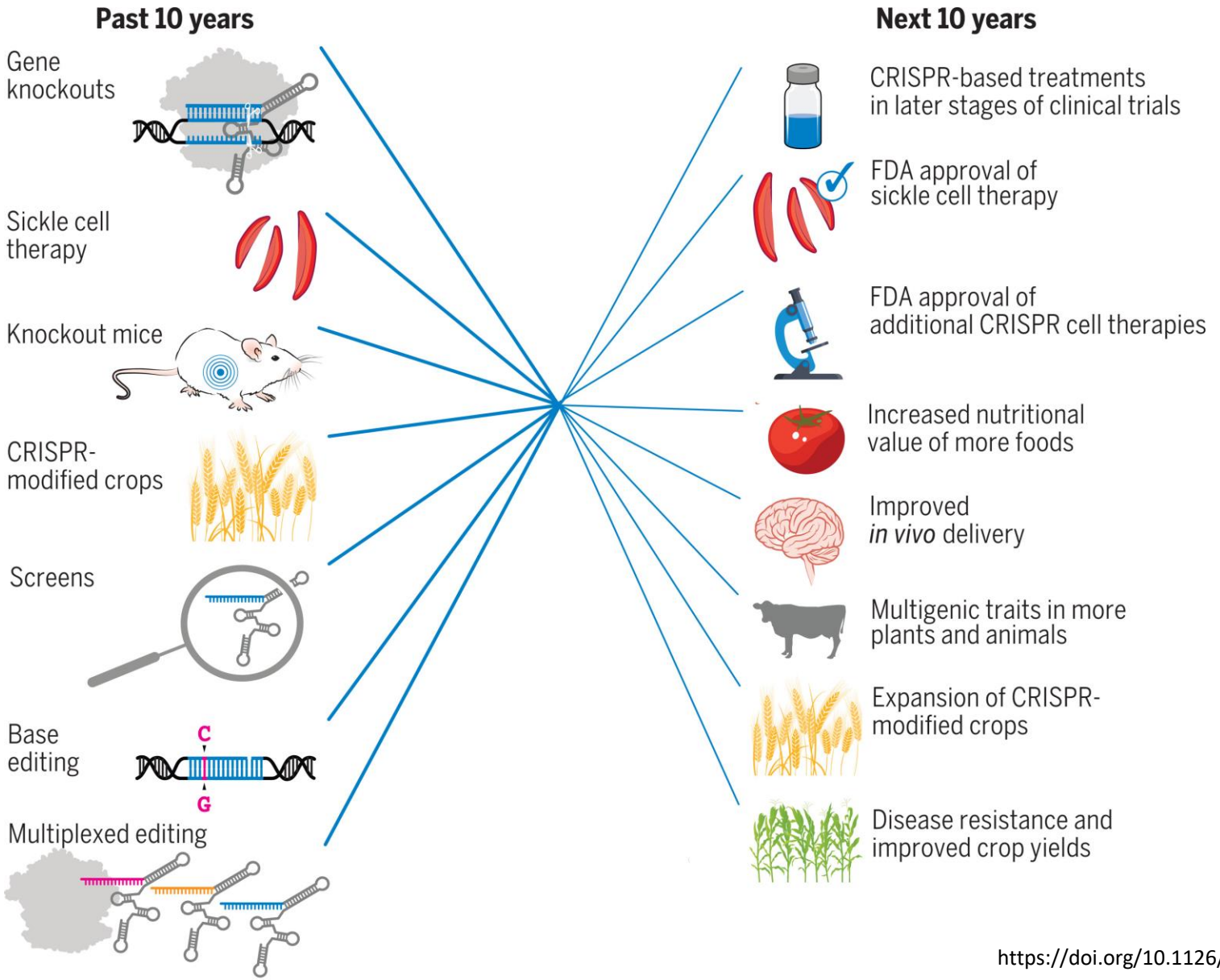
En 2015, el salmón AquAdvantage se convirtió en el primer animal genéticamente modificado aprobado para consumo humano



Salmón del Atlántico con un único **gen que codifica la hormona del crecimiento del salmón Chinook**. El gen fue **clonado después del promotor del gen de la proteína anticongelante de una anguila.** Este **promotor estimula la síntesis de la hormona del crecimiento en invierno**, una época en la que el gen de la hormona del crecimiento propio del pez no se expresa. El rápido crecimiento del salmón GM permite a los piscicultores duplicar su productividad.

https://www.chilebio.cl/2021/05/14/otro-exito-biotecnologico-finalmente-el-salmon-transgenico-aquadvantge-sale-a-la-venta-en-ee-uu/

El Descubrimiento de CRISPR: Del Yogur a la Ingeniería Genética

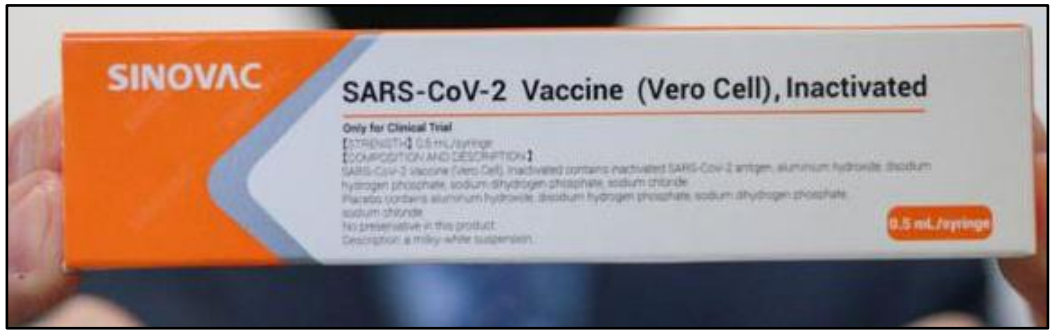


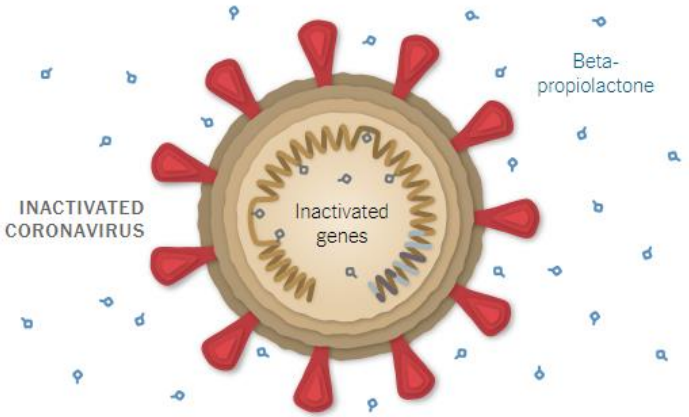
https://doi.org/10.1126/science.add8643

Tipos de vacunas

Atenuadas
Sarampión, Paperas, Rubeola, Varicela, etc

Inactivadas
Hepatitis A, Rabia, Polio (Salk)





- Virus aislados de un paciente Chino
- El virus se produce en células Vero
- Como inactivante se usa beta-propiolactona
- Como adjuvante se utiliza hidróxido de aluminio

El Desarrollo de vacunas modernas

Atenuadas
Sarampión, Paperas, Rubeola, Varicela, etc

Inactivadas
Hepatitis A, Rabia, Polio (Salk)

Subunidad
Hepatitis B, HPV, etc

Nature Vol. 298 22 July 1982

Synthesis and assembly of hepatitis B virus surface antigen particles in yeast

Pablo Valenzuela*†, Angelica Medina* & William J. Rutter*

* Department of Biochemistry and Biophysics, University of California, San Francisco, California 94143, and † Chiron Corporation, 4560 Horton, Emeryville, California 94608, USA

Gustav Ammerer & Benjamin D. Hall

Department of Genetics, SK-50, University of Washington, Seattle, Washington 98195, USA

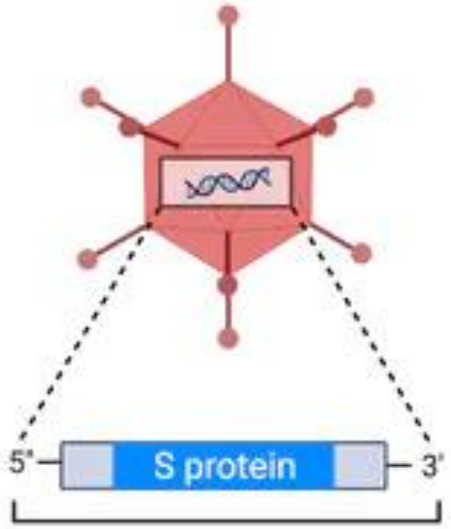
The surface antigen of hepatitis B virus (HBsAg) has been synthesized in the yeast Saccharomyces cerevisiae *by using an expression vector that employs the 5′-flanking region of yeast alcohol dehydrogenase I as a promoter to transcribe surface antigen coding sequences. The protein synthesized in yeast is assembled into particles having properties similar to the 22-nm particles secreted by human cells.*

El Desarrollo de vacunas modernas

Adenoviral
Oxford-AstraZeneca, CanSinoBIO, Sputnik and J&J

mRNA
Pfizer/Biontech and Moderna

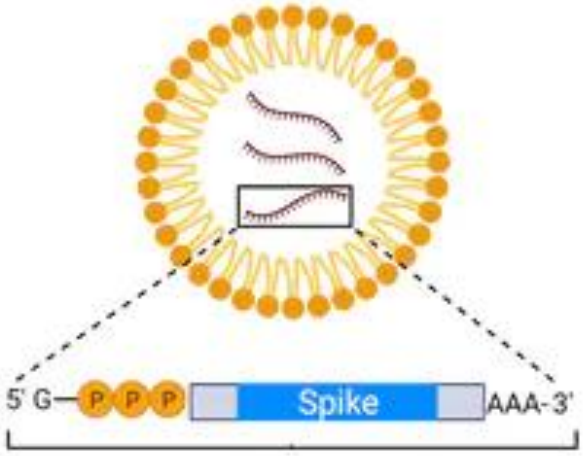
Vaccine: University of Oxford/ AstraZeneca



DNA

Platform: Adenovirus with gene for the SARS-CoV-2 spike (S) protein

BioNTech/Pfizer



Platform: lipid nanoparticle-encapsulated mRNA vaccines encoding Spike protein

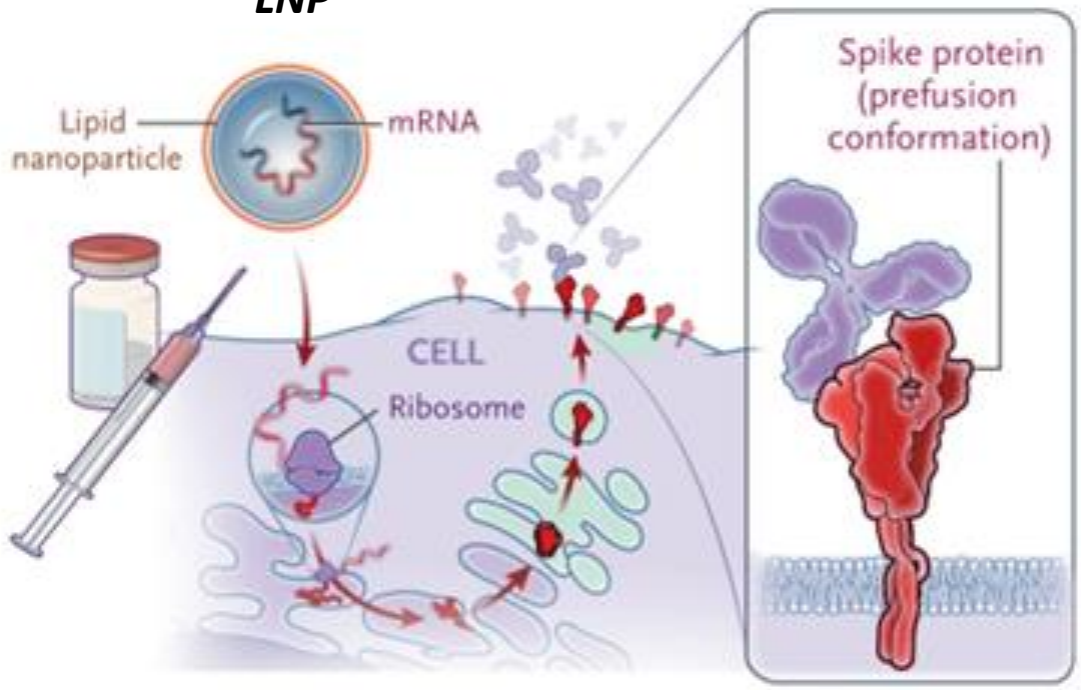
Vacunas de mRNA

- **Concepto**
  Inyectar mRNAs para que nuestras propias células expresen el antígeno

- **Problemas**
  1. ¿Cómo lograr que el mRNA ”entre” a las células y protegerlo de las ”RNAsas”?
  2. Cómo evitar la activación del sistema inmune innato?

- **Soluciones**
  1. Desarrollo de nanoparticulas lipídicas
  2. Utilización de mRNA ”modificado”

LNP



Pieter Cullis

Ian MacLachlan

Vacunas de mRNA

¿Qué significa que la vacuna de Pfizer y moderna un mRNA con nucleosidos "modificados"?

El RNA está compuesto principalmente por 4 nucleótidos: A, G, C y U (uracilo).

WHO
International Nonproprietary Names Programme

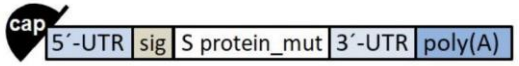
9/2020

11889

Description

Messenger RNA encoding the full-length SARS-CoV-2 spike glycoprotein.

Schematic



Sequence / Séquence / Secuencia

```
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ΨGAACCWGAC CACCAGAACA CAGCWGCCWC CAGCCWACAC CAACAGCWWW   150
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GGACGWGGWC AACCAGAAWG CCCAGGCACW GAACACCCWG GWCAAGCAGC  2950
WGWCCWCCAA CWWCGGCGCC AWCAGCWCWG WGCWGAACGA WAWCCWGAGC  3000
AGACWGGACC CWCCWGAGGC CGAGGWGCAG AWCGACAGAC WGAWCACAGG  3050
CAGACWGCAG AGCCWCCAGA CAWACGWGAC CCAGCAGCWG AWCAGAGCCG  3100
CCGAGAWWAG AGCCWCWGCC AAWCWGGCCG CCACCAAGAW GWCWGAGWGW  3150
GWGCWGGGCC AGAGCAAGAG AGWGGACWWW WGCGGCAAGG GCWACCACCW  3200
GAWGAGCWWC CCWCAGWCWG CCCCWCACGG CGWGGWGWWW CWGCACGWGA  3250
CAWAWGWGCC CGCWCAAGAG AAGAAWWWCA CCACCGCWCC AGCCAWCWGC  3300
CACGACGGCA AAGCCCACWW WCCWAGAGAA GGCGWGWWCG WGWCCAACGG  3350
CACCCAWWGG WWCGWGACAC AGCGGAACWW CWACGAGCCC CAGAWCAWCA  3400
CCACCGACAA CACCWWCGWG WCWGGCAACW GCGACGWCGW GAWCGGCAWW  3450
GWGAACAAWA CCGWGWACGA CCCWCWGCAG CCCGAGCWGG ACAGCWWCAA  3500
AGAGGAACWG GACAAGWACW WWAAGAACCA CACAAGCCCC GACGWGGACC  3550
WGGGCGAWAW CAGCGGAAWC AAWGCCAGCG WCGWGAACAW CCAGAAAGAG  3600
AWCGACCGGC WGAACGAGGW GGCCAAGAAW CWGAACGAGA GCCWGAWCGA  3650
CCWGCAAGAA CWGGGGAAGW ACGAGCAGWA CAWCAAGWGG CCCWGGWACA  3700
WCWGGCWGGG CWWWAWCGCC GGACWGAWWG CCAWCGWGAW GGWCACAAWC  3750
AWGCWGWGWW GCAWGACCAG CWGCWGWAGC WGCCWGAAGG GCWGWWGWAG  3800
CWGWGGCAGC WGCWGCAAGW WCGACGAGGA CGAWWCWGAG CCCGWGCWGA  3850
AGGGCGWGAA ACWGCACWAC ACAWGAWGAC WCGAGCWGGW ACWGCAWGCA  3900
CGCAAWGCWA GCWGCCCCWW WCCCGWCCWG GGWACCCCGA GWCWCCCCCG  3950
ACCWCGGGWC CCAGGWAWGC WCCCACCWCC ACCWGCCCCA CWCACCACCW  4000
CWGCWAGWWC CAGACACCWC CCAAGCACGC AGCAAWGCAG CWCAAAACGC  4050
WWAGCCWAGC CACACCCCCA CGGGAAACAG CAGWGAWWAA CCWWWAGCAA  4100
WAAACGAAAG WWWAACWAAG CWAWACWAAC CCCAGGGWWG GWCAAWWWCG  4150
WGCCAGCCAC ACCCWGGAGC WAGCAAAAAA AAAAAAAAAA AAAAAAAAAA  4200
AAAAGCAWAW GACWAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA  4250
AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAA                    4284
```
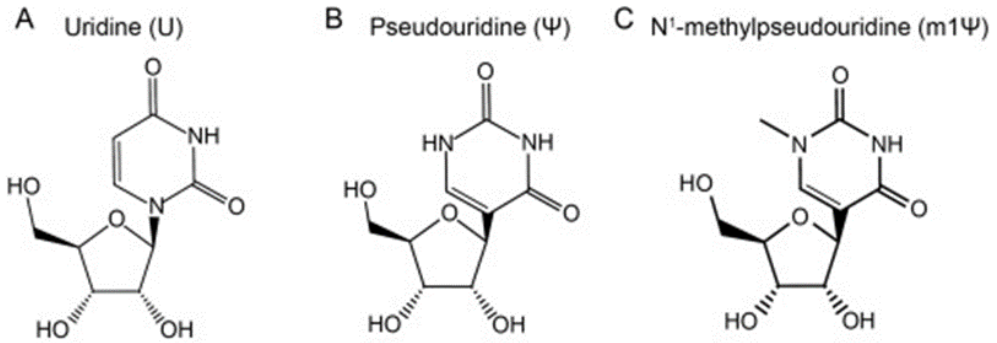
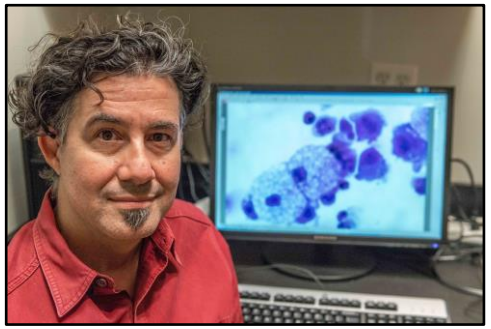

Ψ = 1-methyl-3'-pseudouridylyl

Vacunas de mRNA

En 2005, Katalin Karikó y Drew Weissman mostraron que al reemplazar las uridinas por pseudouridinas (Ψ) podían disminuir la activación del sistema inmune innato y aumentar la traducción y estabilidad del mRNA.

Ψ es una modificacion del RNA que existe desde bacterias hasta humanos y es la modificacion más abundante en el RNA de las células incluso ha sido llamada el quinto nucleótido.

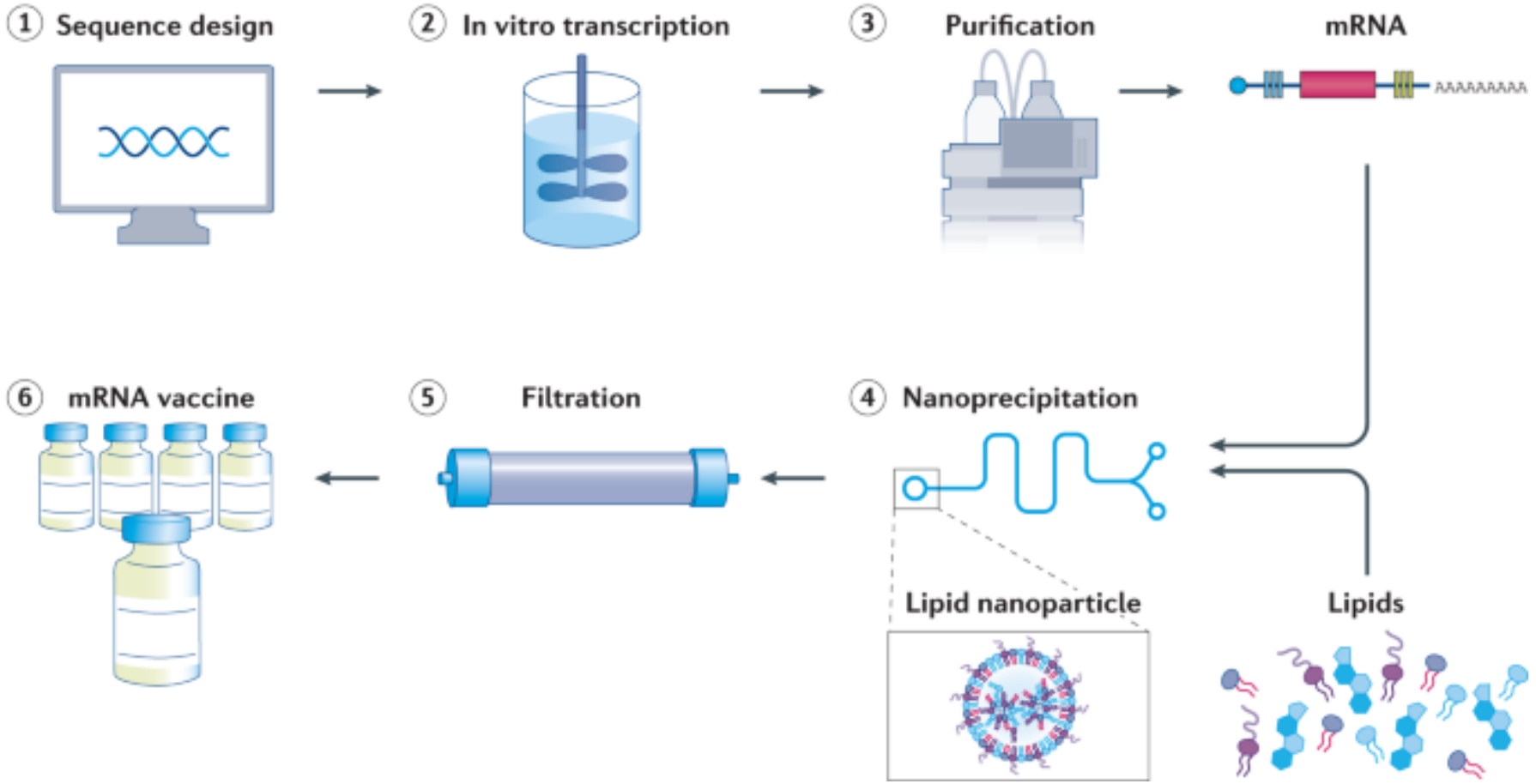




Derrick Rossi

moderna

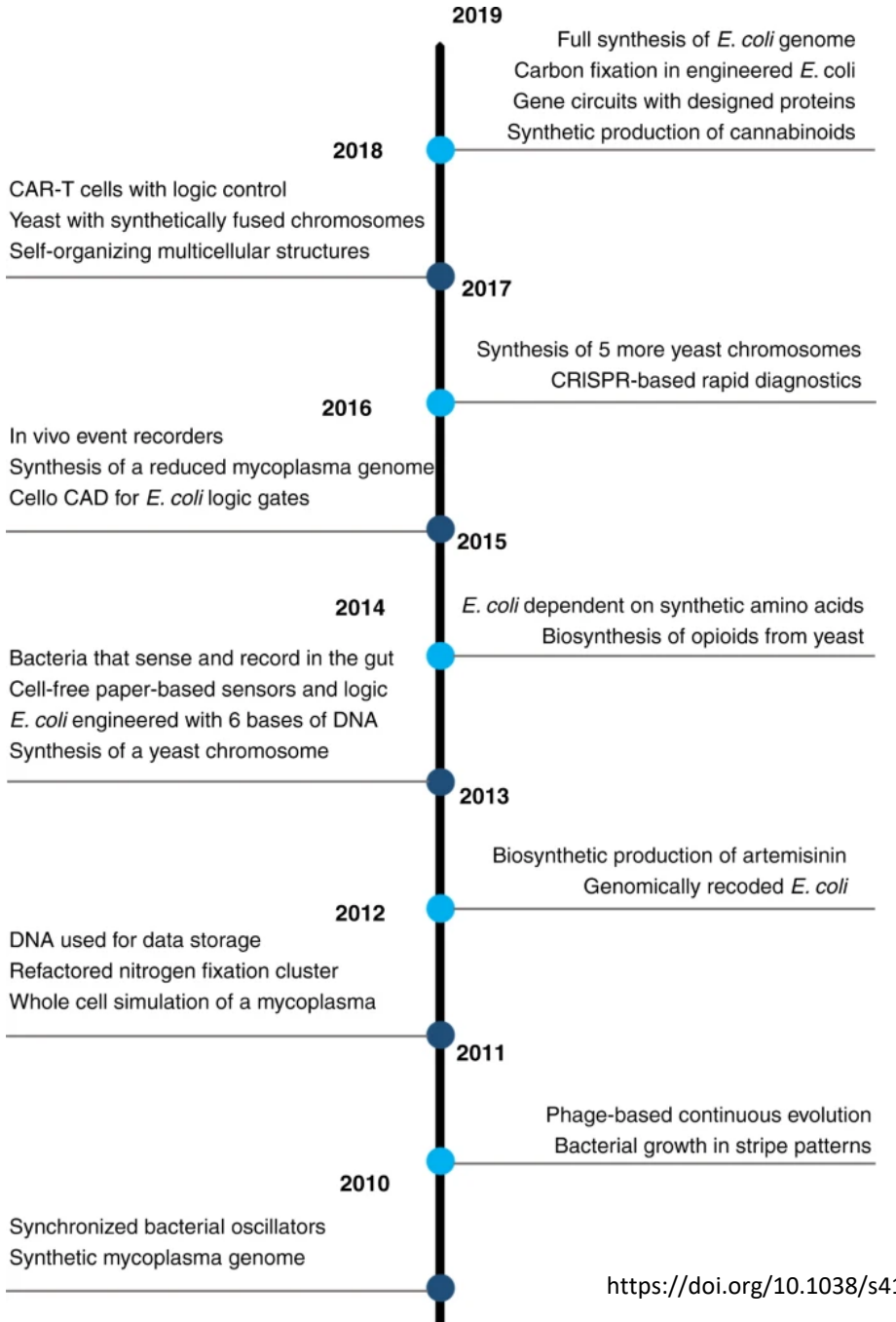
Producción de vacunas de mRNA



Biología sintética

La biología sintética es un campo interdisciplinario que combina principios de biología, ingeniería, genética, química y ciencias de la computación para diseñar y construir nuevas partes biológicas, dispositivos y sistemas, o para rediseñar sistemas biológicos existentes. Implica la manipulación y fabricación de componentes y sistemas biológicos que no existen en el mundo natural, con el objetivo de comprender los sistemas biológicos y crear nuevas funcionalidades.

The second decade of synthetic biology: 2010–2020



https://doi.org/10.1038/s41467-020-19092-2

El Genoma Mínimo: ¿Cuántos Genes Esenciales Requiere una Célula Viva?

En 1984, Morowitz propuso a las células más simples capaces de crecimiento autónomo, los micoplasmas, como modelos para entender los principios básicos de la vida.

En **1995, el Instituto J. Craig Venter** reportó las primeras secuencias completas de genomas celulares (**Haemophilus influenza, 1815 genes, y Mycoplasma genitalium, 525 genes**). La comparación de estas secuencias reveló un núcleo conservado de 256 genes esenciales, mucho menor que cualquiera de los dos genomas..

Mycoplasma genitalium tiene el genoma más pequeño de cualquier organismo que puede ser cultivado en cultivo puro (580 kb).

www.sciencemag.org SCIENCE VOL 286 10 DECEMBER 1999

Global Transposon Mutagenesis and a Minimal Mycoplasma Genome

Clyde A. Hutchison III,[1,2]* Scott N. Peterson,[1]*† Steven R. Gill,[1] Robin T. Cline,[1] Owen White,[1] Claire M. Fraser,[1] Hamilton O. Smith,[1]‡ J. Craig Venter[1]‡§

Mycoplasma genitalium with 517 genes has the smallest gene complement of any independently replicating cell so far identified. Global transposon mutagenesis was used to identify nonessential genes in an effort to learn whether the naturally occurring gene complement is a true minimal genome under laboratory growth conditions. The positions of 2209 transposon insertions in the completely sequenced genomes of *M. genitalium* and its close relative *M. pneumoniae* were determined by sequencing across the junction of the transposon and the genomic DNA. These junctions defined 1354 distinct sites of insertion that were not lethal. The analysis suggests that 265 to 350 of the 480 protein-coding genes of *M. genitalium* are essential under laboratory growth conditions, including about 100 genes of unknown function.

Predicen 375 genes como esenciales

PNAS | January 10, 2006 | vol. 103 | no. 2 | 425–430

Essential genes of a minimal bacterium

John I. Glass, Nacyra Assad-Garcia, Nina Alperovich, Shibu Yooseph, Matthew R. Lewis, Mahir Maruf, Clyde A. Hutchison III, Hamilton O. Smith*, and J. Craig Venter

Synthetic Biology Group, J. Craig Venter Institute, 9704 Medical Center Drive, Rockville, MD 20850

Contributed by Hamilton O. Smith, November 18, 2005

Mycoplasma genitalium **has the smallest genome of any organism that can be grown in pure culture. It has a minimal metabolism and little genomic redundancy. Consequently, its genome is expected to be a close approximation to the minimal set of genes needed to sustain bacterial life. Using global transposon mutagenesis, we isolated and characterized gene disruption mutants for 100 different nonessential protein-coding genes. None of the 43 RNA-coding genes were disrupted. Herein, we identify 382 of the 482 *M. genitalium* protein-coding genes as essential, plus five sets of disrupted genes that encode proteins with potentially redundant essential functions, such as phosphate transport. Genes encoding proteins of unknown function constitute 28% of the essential protein-coding genes set. Disruption of some genes accelerated *M. genitalium* growth.**

382 de los 482 genes codificantes de proteínas son esenciales

Genomas Sintéticos y el Surgimiento de la Biología Sintética

2 JULY 2010 VOL 329 **SCIENCE** www.sciencemag.org

RESEARCH ARTICLE

Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome

Daniel G. Gibson,[1] John I. Glass,[1] Carole Lartigue,[1] Vladimir N. Noskov,[1] Ray-Yuan Chuang,[1] Mikkel A. Algire,[1] Gwynedd A. Benders,[2] Michael G. Montague,[1] Li Ma,[1] Monzia M. Moodie,[1] Chuck Merryman,[1] Sanjay Vashee,[1] Radha Krishnakumar,[1] Nacyra Assad-Garcia,[1] Cynthia Andrews-Pfannkoch,[1] Evgeniya A. Denisova,[1] Lei Young,[1] Zhi-Qing Qi,[1] Thomas H. Segall-Shapiro,[1] Christopher H. Calvey,[1] Prashanth P. Parmar,[1] Clyde A. Hutchison III,[2] Hamilton O. Smith,[2] J. Craig Venter[1,2]*

We report the design, synthesis, and assembly of the 1.08–mega–base pair *Mycoplasma mycoides* JCVI-syn1.0 genome starting from digitized genome sequence information and its transplantation into a *M. capricolum* recipient cell to create new *M. mycoides* cells that are controlled only by the synthetic chromosome. The only DNA in the cells is the designed synthetic DNA sequence, including "watermark" sequences and other designed gene deletions and polymorphisms, and mutations acquired during the building process. The new cells have expected phenotypic properties and are capable of continuous self-replication.

nome. Because *M. genitalium* has an extremely slow growth rate, we turned to two faster-growing mycoplasma species, *M. mycoides* subspecies *capri* (GM12) as donor, and *M. capricolum* subspecies *capricolum* (CK) as recipient.

Genome transplantation

Mycoplasma mycoides JCVI-syn1.0

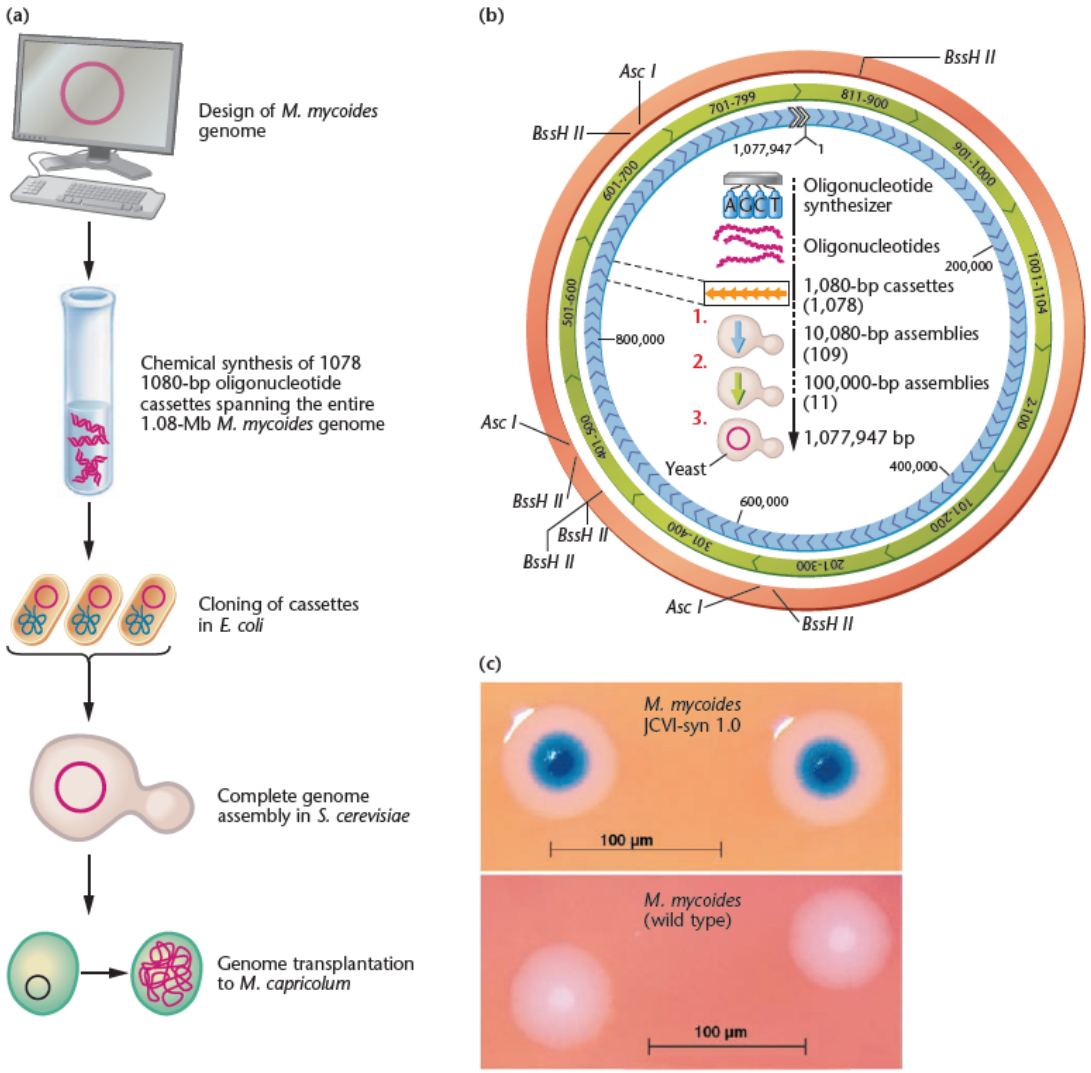


FIGURE 22.14 Building a synthetic version of the 1.08-Mb *Mycoplasma mycoides* genome. (a) Overview of the approach used to produce *M. mycoides* JCVI-syn1.0. (b) Assembly of JCVI-syn1.0 genome occurred in three steps: (1) 1080-bp segments (cassettes; orange arrows), produced from overlapping synthetic oligonucleotides, were recombined in sets of 10 to produce 109 ~10-kb assemblies (blue arrows). (2) The 109 were then combined in sets of 10 to produce 11 ~100-kb assemblies (green arrows). (3) In the final step, the 11 segments were recombined to create the entire synthetic genome (red circle; the locations of *Asc I* and *BssH II* restriction sites are shown). All recombination steps were carried out in yeast. (c) Colonies of *M. mycoides* JCVI-syn1.0 (top) and wild-type *M. mycoides* (bottom). Cells were cultured on agar containing the compound X-gal. Colonies with the synthetic genome are blue because their cells contain the *lacZ* gene and express β-galactosidase, which metabolized X-gal to a blue compound (see Chapter 20). Wild-type cells do not express the *lacZ* gene and therefore remained white in color.

Klug, W (2019) Concepts of Genetics 12th Edition

Diseño y Trasplante de un Genoma Sintético: Definiendo el Genoma Bacteriano Mínimo

SCIENCE sciencemag.org 25 MARCH 2016 • VOL 351 ISSUE 6280

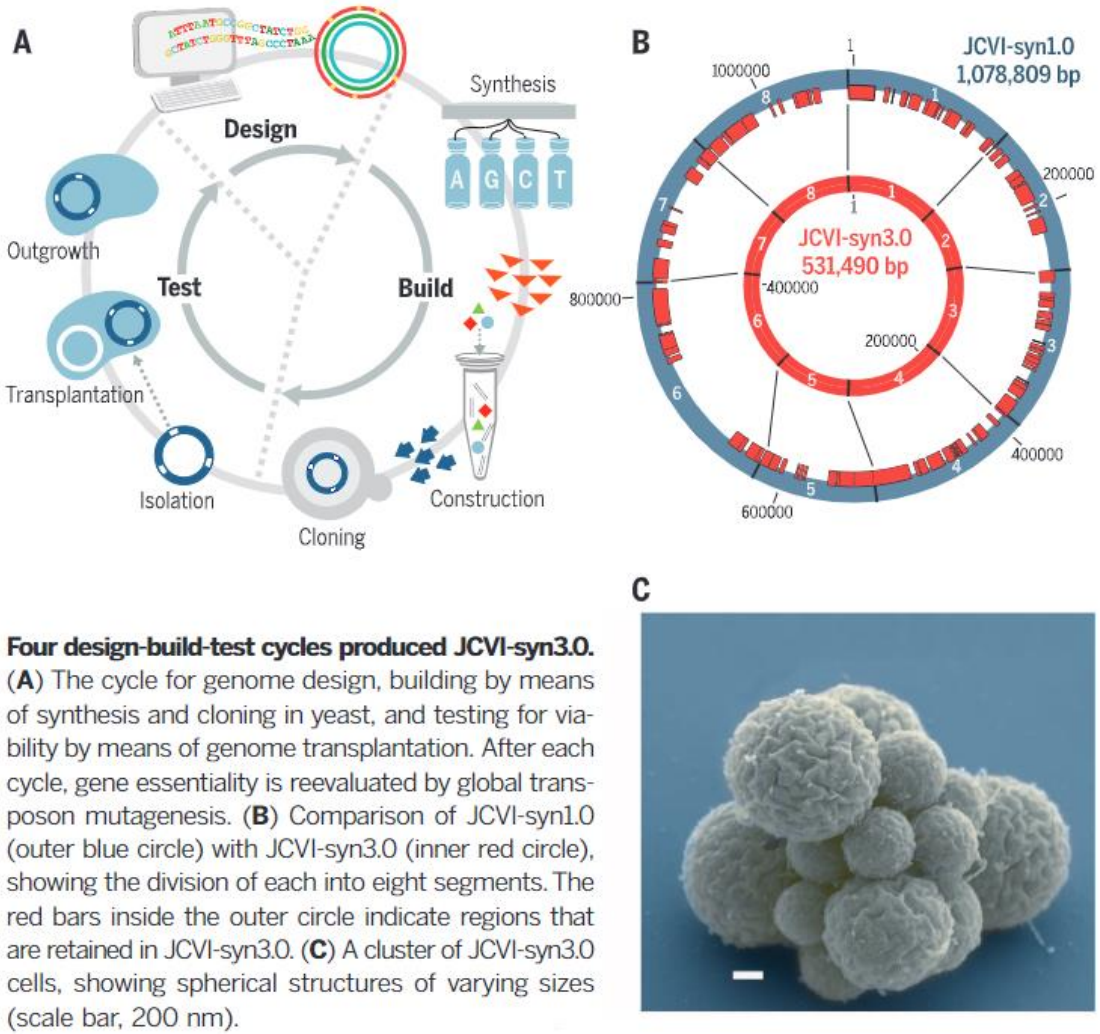
RESEARCH ARTICLE

SYNTHETIC BIOLOGY

Design and synthesis of a minimal bacterial genome

Clyde A. Hutchison III,[1]*† Ray-Yuan Chuang,[1]†‡ Vladimir N. Noskov,[1] Nacyra Assad-Garcia,[1] Thomas J. Deerinck,[2] Mark H. Ellisman,[2] John Gill,[3] Krishna Kannan,[3] Bogumil J. Karas,[1] Li Ma,[1] James F. Pelletier,[4]§ Zhi-Qing Qi,[3] R. Alexander Richter,[1] Elizabeth A. Strychalski,[4] Lijie Sun,[1]|| Yo Suzuki,[1] Billyana Tsvetanova,[3] Kim S. Wise,[1] Hamilton O. Smith,[1,3] John I. Glass,[1] Chuck Merryman,[1] Daniel G. Gibson,[1,3] J. Craig Venter[1,3]*

We used whole-genome design and complete chemical synthesis to minimize the 1079–kilobase pair synthetic genome of *Mycoplasma mycoides* JCVI-syn1.0. An initial design, based on collective knowledge of molecular biology combined with limited transposon mutagenesis data, failed to produce a viable cell. Improved transposon mutagenesis methods revealed a class of quasi-essential genes that are needed for robust growth, explaining the failure of our initial design. Three cycles of design, synthesis, and testing, with retention of quasi-essential genes, produced JCVI-syn3.0 (531 kilobase pairs, 473 genes), which has a genome smaller than that of any autonomously replicating cell found in nature. JCVI-syn3.0 retains almost all genes involved in the synthesis and processing of macromolecules. Unexpectedly, it also contains 149 genes with unknown biological functions. JCVI-syn3.0 is a versatile platform for investigating the core functions of life and for exploring whole-genome design.



Four design-build-test cycles produced JCVI-syn3.0. (**A**) The cycle for genome design, building by means of synthesis and cloning in yeast, and testing for viability by means of genome transplantation. After each cycle, gene essentiality is reevaluated by global transposon mutagenesis. (**B**) Comparison of JCVI-syn1.0 (outer blue circle) with JCVI-syn3.0 (inner red circle), showing the division of each into eight segments. The red bars inside the outer circle indicate regions that are retained in JCVI-syn3.0. (**C**) A cluster of JCVI-syn3.0 cells, showing spherical structures of varying sizes (scale bar, 200 nm).

473 genes que codifican 438 proteínas y 35 RNAs

Organismos con genoma recodificado

www.sciencemag.org SCIENCE VOL 342 18 OCTOBER 2013

Genomically Recoded Organisms Expand Biological Functions

Marc J. Lajoie,[1,2] Alexis J. Rovner,[3,4] Daniel B. Goodman,[1,5] Hans-Rudolf Aerni,[4,6] Adrian D. Haimovich,[3,4] Gleb Kuznetsov,[1] Jaron A. Mercer,[7] Harris H. Wang,[8] Peter A. Carr,[9] Joshua A. Mosberg,[1,2] Nadin Rohland,[1] Peter G. Schultz,[10] Joseph M. Jacobson,[11,12] Jesse Rinehart,[4,6] George M. Church,[1,13*] Farren J. Isaacs[3,4*]

We describe the construction and characterization of a genomically recoded organism (GRO). We replaced all known UAG stop codons in *Escherichia coli* MG1655 with synonymous UAA codons, which permitted the deletion of release factor 1 and reassignment of UAG translation function. This GRO exhibited improved properties for incorporation of nonstandard amino acids that expand the chemical diversity of proteins in vivo. The GRO also exhibited increased resistance to T7 bacteriophage, demonstrating that new genetic codes could enable increased viral resistance.

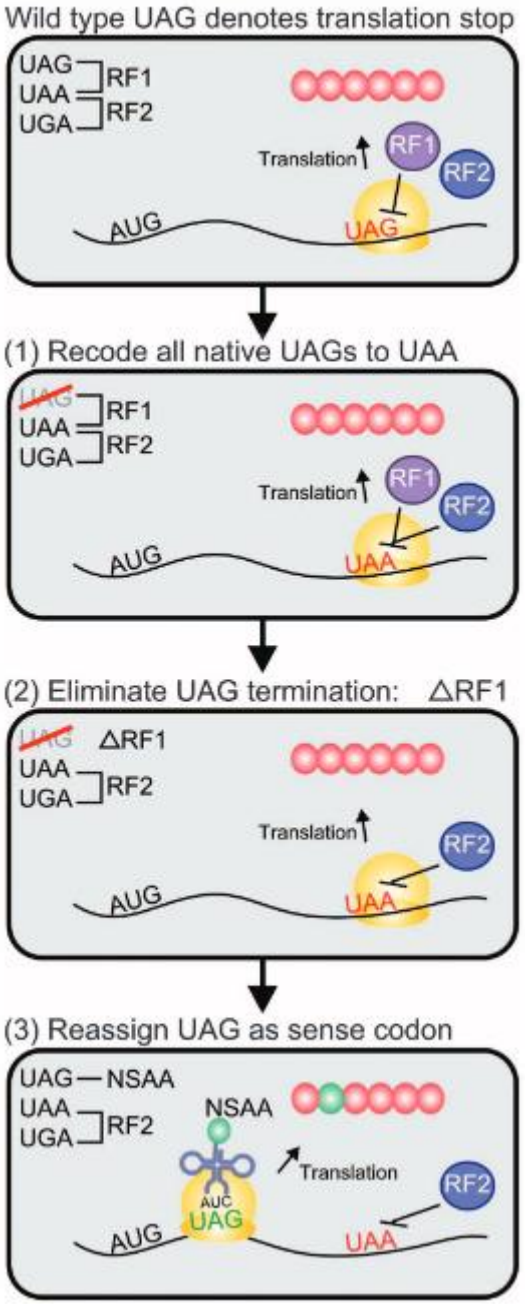


Fig. 1. Engineering a GRO with a reassigned UAG codon. Wild-type *E. coli* MG1655 has 321 known UAG codons that are decoded as translation stops by RF1 (for UAG and UAA). (1) Remove codons: converted all known UAG codons to UAA, relieving dependence on RF1 for termination. (2) Eliminate natural codon function: abolished UAG translational termination by deleting RF1, creating a blank codon. (3) Expand the genetic code: introduced an orthogonal aminoacyl–tRNA synthetase (aaRS) and tRNA to reassign UAG as a dedicated sense codon capable of incorporating nonstandard amino acids (NSAAs) with new chemical properties.

19 AUGUST 2016 • VOL 353 ISSUE 6301

SYNTHETIC GENOMICS

Design, synthesis, and testing toward a 57-codon genome

Nili Ostrov,[1*] Matthieu Landon,[1,2,3*] Marc Guell,[1,4*] Gleb Kuznetsov,[1,5*] Jun Teramoto,[1,6] Natalie Cervantes,[1] Minerva Zhou,[7] Kerry Singh,[7] Michael G. Napolitano,[1,8] Mark Moosburner,[1] Ellen Shrock,[1] Benjamin W. Pruitt,[4] Nicholas Conway,[4] Daniel B. Goodman,[1,4] Cameron L. Gardner,[1] Gary Tyree,[1] Alexandra Gonzales,[1] Barry L. Wanner,[1,9] Julie E. Norville,[1] Marc J. Lajoie,[1†] George M. Church[1,4†]

Recoding—the repurposing of genetic codons—is a powerful strategy for enhancing genomes with functions not commonly found in nature. Here, we report computational design, synthesis, and progress toward assembly of a 3.97-megabase, 57-codon *Escherichia coli* genome in which all 62,214 instances of seven codons were replaced with synonymous alternatives across all protein-coding genes. We have validated 63% of recoded genes by individually testing 55 segments of 50 kilobases each. We observed that 91% of tested essential genes retained functionality with limited fitness effect. We demonstrate identification and correction of lethal design exceptions, only 13 of which were found in 2229 genes. This work underscores the feasibility of rewriting genomes and establishes a framework for large-scale design, assembly, troubleshooting, and phenotypic analysis of synthetic organisms.

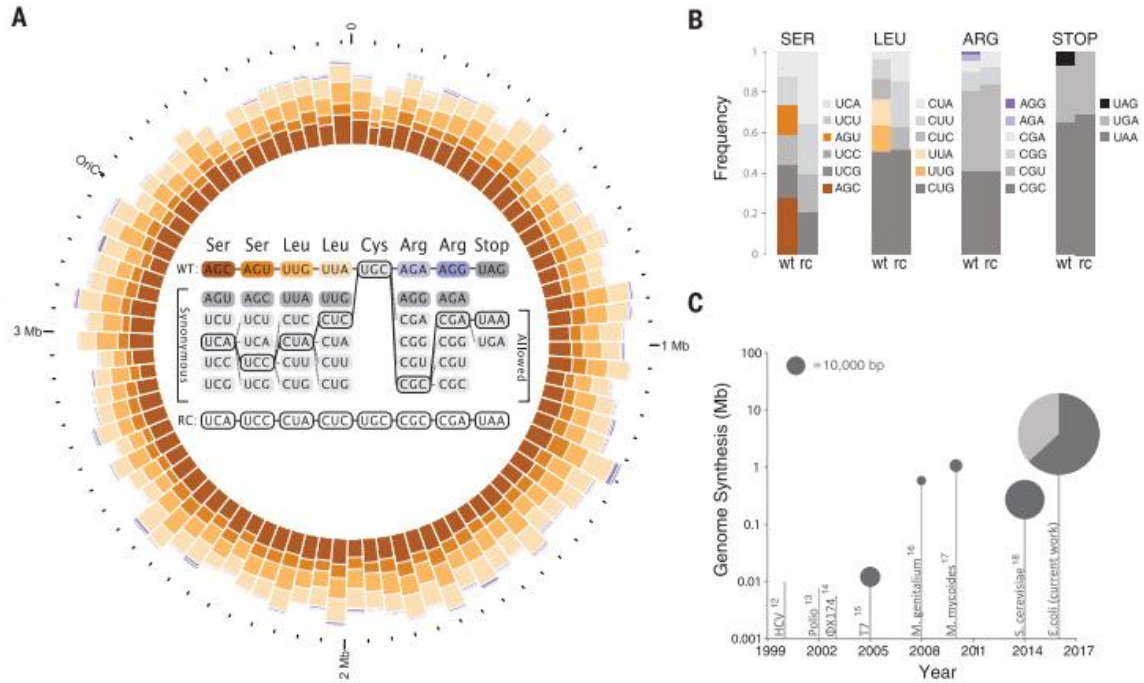


Fig. 1. A 57-codon *E. coli* genome. (**A**) The recoded genome was divided into 87 segments of ~50 kb. Codons AGA, AGG, AGC, AGU, UUA, UUG, and UAG were computationally replaced by synonymous alternatives (center). Other codons (e.g., UGC) remain unchanged. Color-coded histograms represent the abundance of the seven forbidden codons in each segment. (**B**) Codon frequencies in nonrecoded [wild-type (wt), *E. coli* MDS42] versus recoded [(rc), *rE.coli-57*] genome. Forbidden codons are colored. (**C**) The scale of DNA editing in genomes constructed by de novo synthesis. Plot area represents the number of modified base pairs compared with the parent genome. For the current work, dark gray represents percent of genome validated in vivo at time of publication (63%). HCV, hepatitis C virus; T7, bacteriophage T7; *M. genitalium*, *Mycoplasma genitalium*; and *M. mycoides*, *Mycoplasma mycoides*.

E. coli con un genoma que funciona con 61 codones

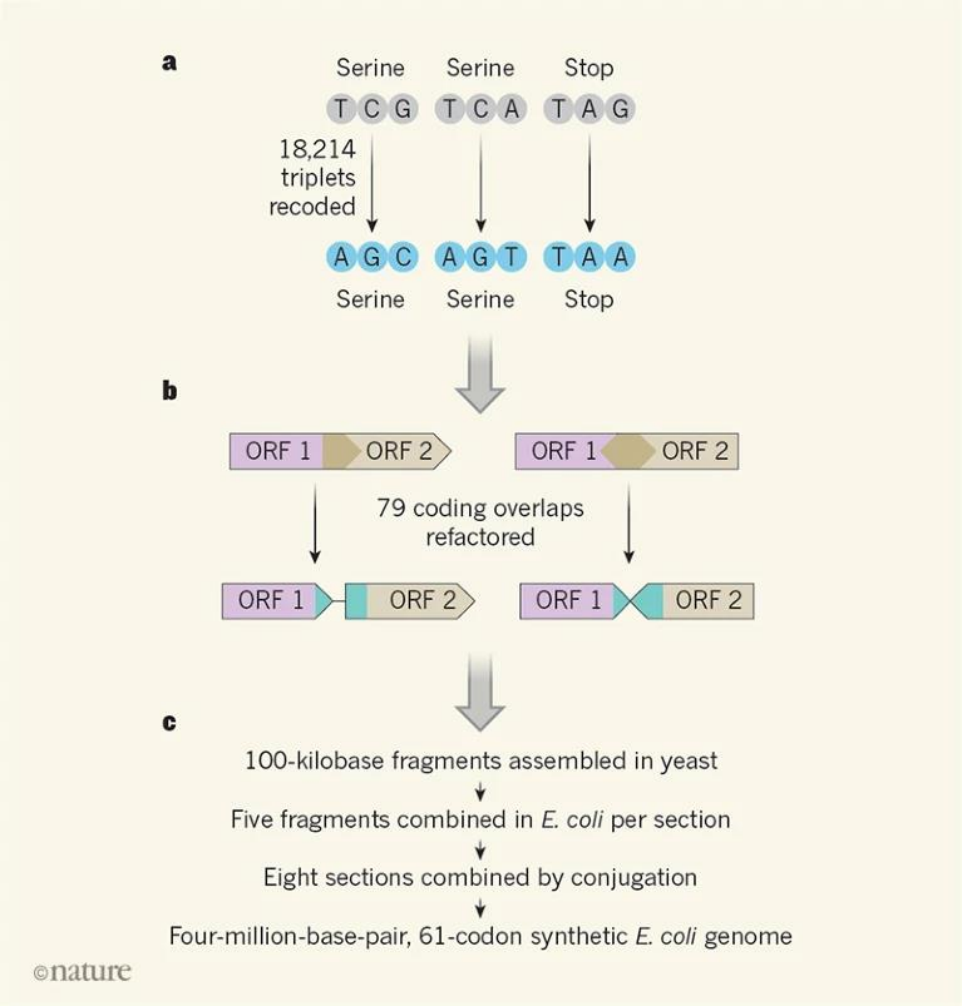
ARTICLE 514 | NATURE | VOL 569 | 23 MAY 2019

https://doi.org/10.1038/s41586-019-1192-5

Total synthesis of *Escherichia coli* with a recoded genome

Julius Fredens[1,4], Kaihang Wang[1,2,4], Daniel de la Torre[1,4], Louise F. H. Funke[1,4], Wesley E. Robertson[1,4], Yonka Christova[1], Tiongsun Chia[1], Wolfgang H. Schmied[1], Daniel L. Dunkelmann[1], Václav Beránek[1], Chayasith Uttamapinant[1,3], Andres Gonzalez Llamazares[1], Thomas S. Elliott[1] & Jason W. Chin[1*]

Nature uses 64 codons to encode the synthesis of proteins from the genome, and chooses 1 sense codon—out of up to 6 synonyms—to encode each amino acid. Synonymous codon choice has diverse and important roles, and many synonymous substitutions are detrimental. Here we demonstrate that the number of codons used to encode the canonical amino acids can be reduced, through the genome-wide substitution of target codons by defined synonyms. We create a variant of *Escherichia coli* with a four-megabase synthetic genome through a high-fidelity convergent total synthesis. Our synthetic genome implements a defined recoding and refactoring scheme—with simple corrections at just seven positions—to replace every known occurrence of two sense codons and a stop codon in the genome. Thus, we recode 18,214 codons to create an organism with a 61-codon genome; this organism uses 59 codons to encode the 20 amino acids, and enables the deletion of a previously essential transfer RNA.



Ya no utiliza el codón de terminación TAG ni los dos codones de serina TCG y TCA, por lo que la maquinaria celular que reconoce estos codones puede ahora ser eliminada o reasignada para incorporar aminoácidos 'no canónicos' más allá de los 20 usuales utilizados por la mayoría de las células vivas.

Figure 1 | Design and construction of a recoded genome. a, Fredens et al.3 recoded three base triplets (codons) — TCG and TCA, which encode the amino acid serine, and TAG, a stop codon that marks the end of a protein-coding sequence — to alternatives that have the same functions (AGC, AGT and TAA respectively) in the genome of the bacterium Escherichia coli. b, In some genomic locations, open reading frames (ORFs; protein-coding regions) overlap, and a change in the codons of one ORF might produce an unwanted change in the overlapping region. Fredens et al. 'refactored' these ORFs to separate them, as illustrated for ORF1 and ORF2 (the two ORFs on the left are 'read' in the same direction; the two on the right are read in opposite directions)

Ingeniería de Rutas Metabólicas

528 | NATURE | VOL 496 | 25 APRIL 2013

LETTER

doi:10.1038/nature12051

High-level semi-synthetic production of the potent antimalarial artemisinin

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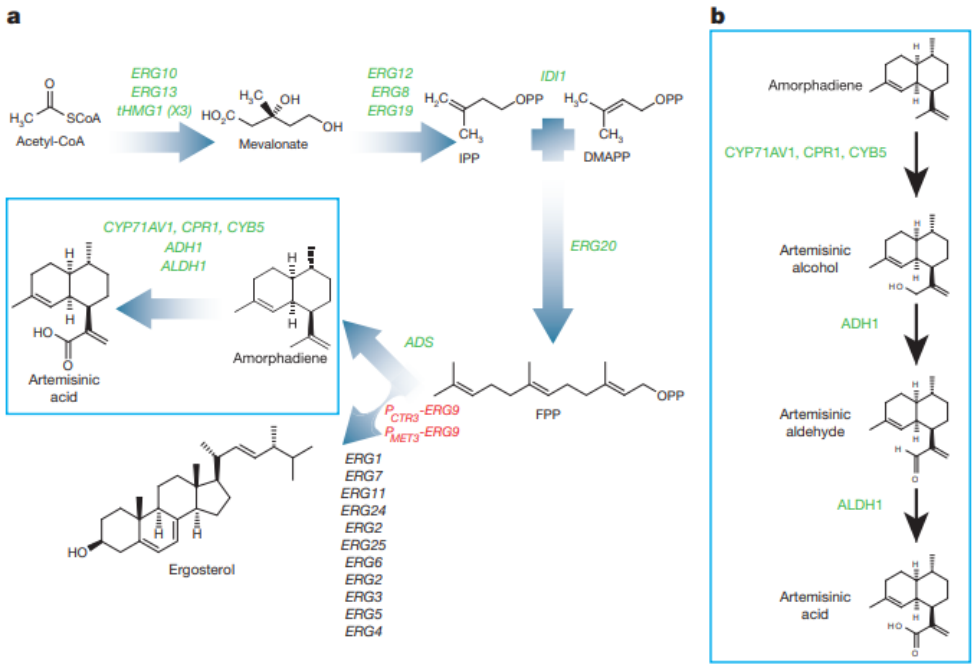

In 2010 there were more than 200 million cases of malaria, and at least 655,000 deaths[1]. The World Health Organization has recommended artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated malaria caused by the parasite *Plasmodium falciparum*. Artemisinin is a sesquiterpene endoperoxide with potent antimalarial properties, produced by the plant *Artemisia annua*. However, the supply of plant-derived artemisinin is unstable, resulting in shortages and price fluctuations, complicating production planning by ACT manufacturers[2]. A stable source of affordable artemisinin is required. Here we use synthetic biology to develop strains of *Saccharomyces cerevisiae* (baker's yeast) for high-yielding biological production of artemisinic acid, a precursor of artemisinin. Previous attempts to produce commercially relevant concentrations of artemisinic acid were unsuccessful, allowing production of only 1.6 grams per litre of artemisinic acid[3]. Here we demonstrate the complete biosynthetic pathway, including the discovery of a plant dehydrogenase and a second cytochrome that provide an efficient biosynthetic route to artemisinic acid, with fermentation titres of 25 grams per litre of artemisinic acid. Furthermore, we have developed a practical, efficient and scalable chemical process for the conversion of artemisinic acid to artemisinin using a chemical source of singlet oxygen, thus avoiding the need for specialized photochemical equipment. The strains and processes described here form the basis of a viable industrial process for the production of semi-synthetic artemisinin to stabilize the supply of artemisinin for derivatization into active pharmaceutical ingredients (for example, artesunate) for incorporation into ACTs. Because all intellectual property rights have been provided free of charge, this technology has the potential to increase provision of first-line antimalarial treatments to the developing world at a reduced average annual price.

4 SEPTEMBER 2015 • VOL 349 ISSUE 6252

SYNTHETIC BIOLOGY

Complete biosynthesis of opioids in yeast

Stephanie Galanie,[1] Kate Thodey,[2] Isis J. Trenchard,[2] Maria Filsinger Interrante,[2] Christina D. Smolke[2]*

Opioids are the primary drugs used in Western medicine for pain management and palliative care. Farming of opium poppies remains the sole source of these essential medicines, despite diverse market demands and uncertainty in crop yields due to weather, climate change, and pests. We engineered yeast to produce the selected opioid compounds thebaine and hydrocodone starting from sugar. All work was conducted in a laboratory that is permitted and secured for work with controlled substances. We combined enzyme discovery, enzyme engineering, and pathway and strain optimization to realize full opiate biosynthesis in yeast. The resulting opioid biosynthesis strains required the expression of 21 (thebaine) and 23 (hydrocodone) enzyme activities from plants, mammals, bacteria, and yeast itself. This is a proof of principle, and major hurdles remain before optimization and scale-up could be achieved. Open discussions of options for governing this technology are also needed in order to responsibly realize alternative supplies for these medically relevant compounds.

BioBricks y Estandarización en Biología Sintética

BioBricks Concept: Los BioBricks son secuencias estandarizadas de ADN utilizadas en biología sintética. Son análogos a los bloques de construcción en la arquitectura, donde cada 'ladrillo' cumple una función específica y puede combinarse con otros ladrillos para construir sistemas biológicos complejos.

International Genetically Engineered Machine

https://parts.igem.org/Main_Page

354 | VOL.10 NO.4 | APRIL 2013 | NATURE METHODS

Precise and reliable gene expression via standard transcription and translation initiation elements

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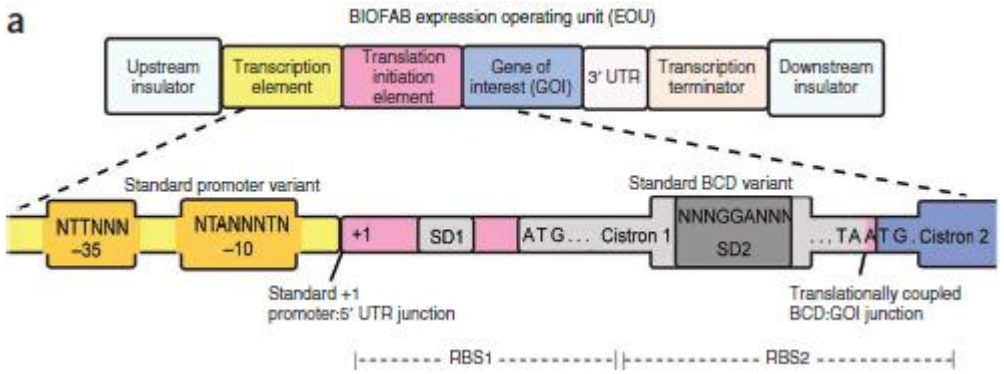

Figure 1 | Rules for regularizing gene expression. (**a**) We defined an expression operating unit (EOU) to set boundaries and junctions of functional genetic elements underlying the expression of heterologous genes (**Supplementary Note**). The variable regions within each element type (wider icons) and the standard junctions (labeled lines) between elements that best enable reliable reuse of elements in novel combinations are detailed. The bicistronic design (BCD) with its two Shine-Dalgarno motifs (SD1 and SD2)

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Engineering modular and orthogonal genetic logic gates for robust digital-like synthetic biology

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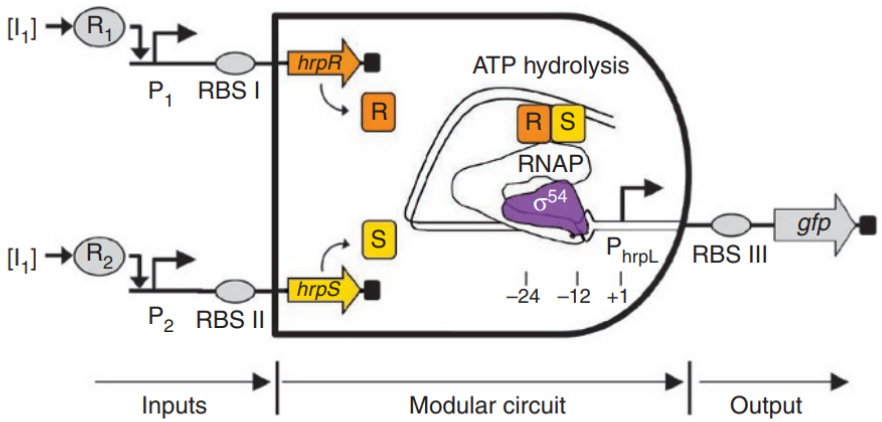
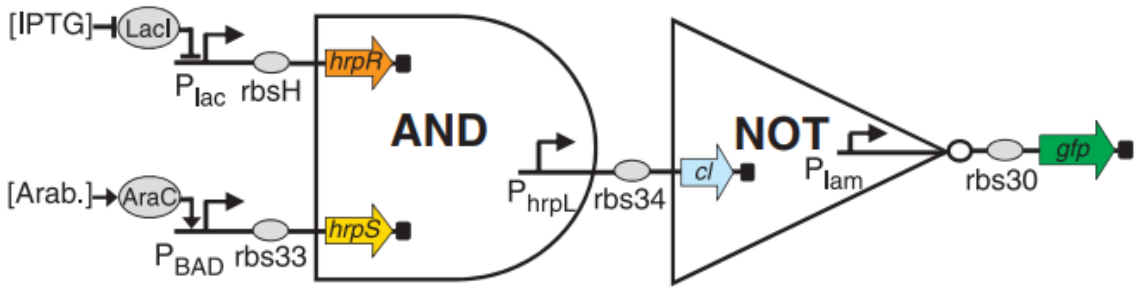


Figure 1 | A modular and orthogonal genetic AND gate design. The AND gate is designed on the basis of the σ^{54}-dependent *hrpR/hrpS* hetero-regulation module. Two environment-responsive promoters, P_1 and P_2, act as the inputs to drive the transcriptions of *hrpR* and *hrpS*, and respond to the small molecules I_1 and I_2, respectively. The transcription of the output *hrpL* promoter is turned on only when both proteins HrpR and HrpS are present and bind the upstream activator sequence to remodel the closed σ^{54}-RNAP-*hrpL* transcription complex to an open one through ATP hydrolysis. The output shown is a *gfp* reporter. The RBS is used for

Genetic circuits



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RESEARCH ARTICLE

SYNTHETIC BIOLOGY

Genetic circuit design automation

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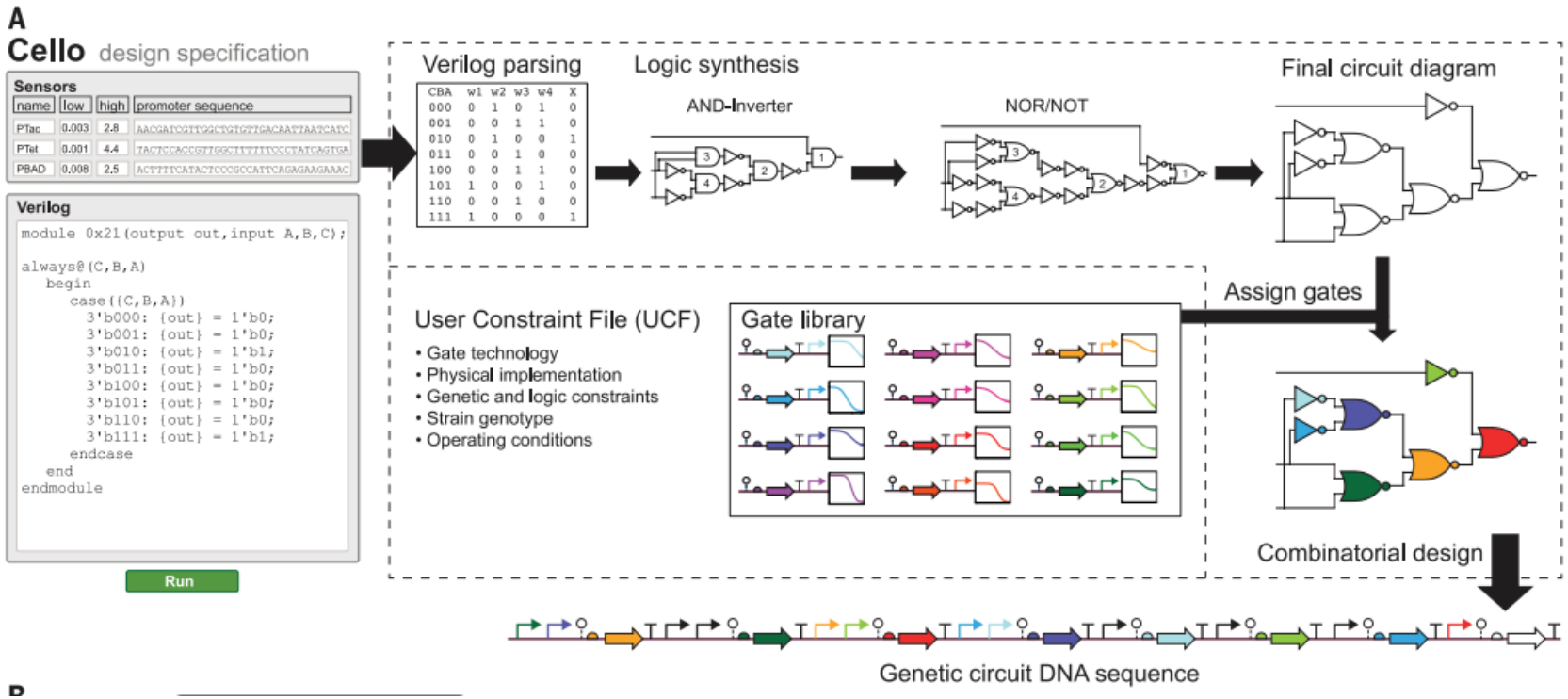
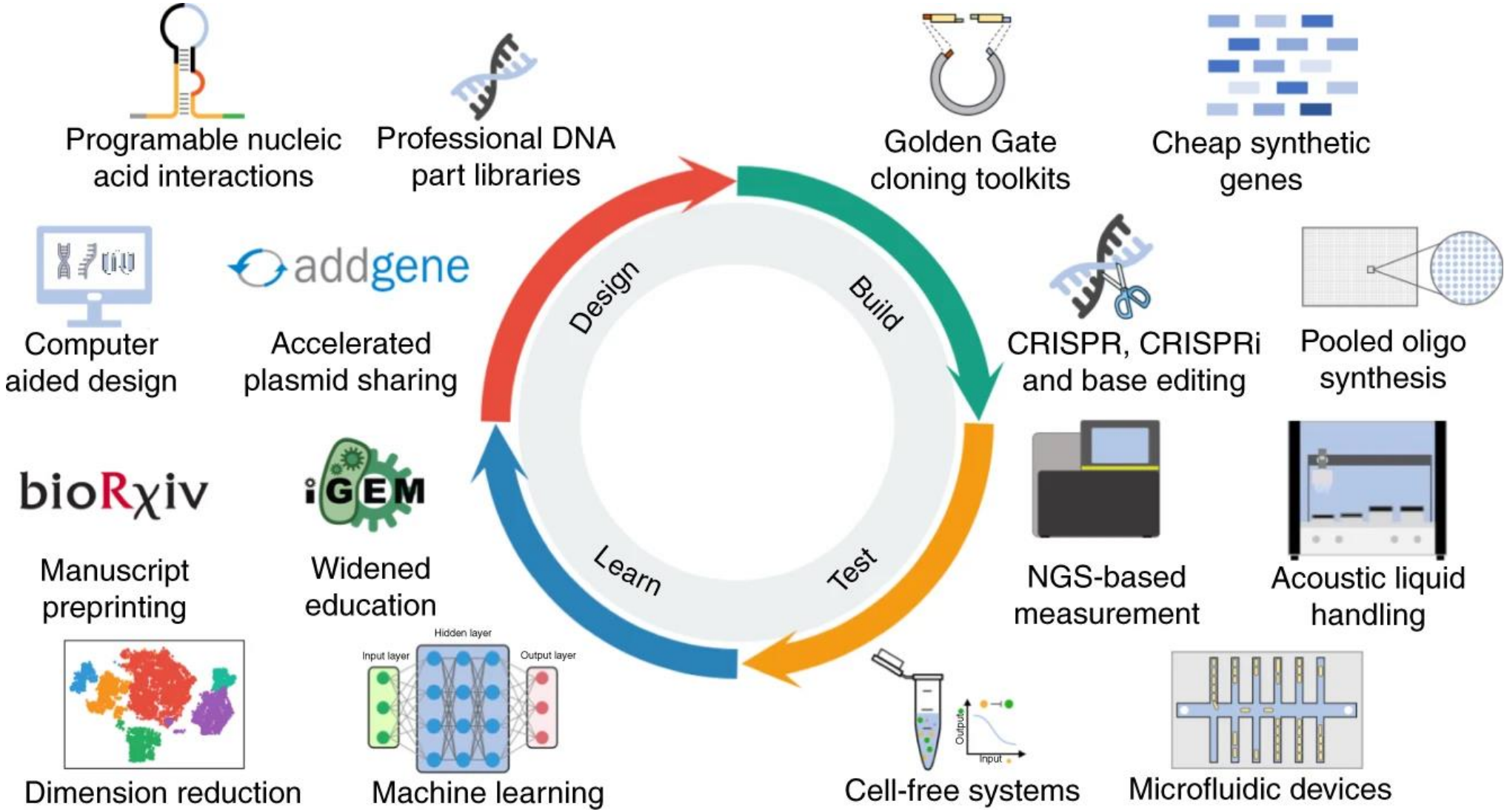
Computation can be performed in living cells by DNA-encoded circuits that process sensory information and control biological functions. Their construction is time-intensive, requiring manual part assembly and balancing of regulator expression. We describe a design environment, Cello, in which a user writes Verilog code that is automatically transformed into a DNA sequence. Algorithms build a circuit diagram, assign and connect gates, and simulate performance. Reliable circuit design requires the insulation of gates from genetic context, so that they function identically when used in different circuits. We used Cello to design 60 circuits for *Escherichia coli* (880,000 base pairs of DNA), for which each DNA sequence was built as predicted by the software with no additional tuning. Of these, 45 circuits performed correctly in every output state (up to 10 regulators and 55 parts), and across all circuits 92% of the output states functioned as predicted. Design automation simplifies the incorporation of genetic circuits into biotechnology projects that require decision-making, control, sensing, or spatial organization.



Tecnologías emergentes y metodologías que han potenciado la aceleración del ciclo DCPA (diseño-construcción-prueba-aprendizaje) en biología sintética durante la última década



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