# Evaluación del marco regulatorio e institucional de la edición génica en agricultura mediante tecnologías basadas en el CRISPR en América Latina y el Caribe

Presentación Final

24 agosto 2022

# Traducción simultánea

- La reunión se desarrollará en español, inglés, y portugués
- Hay traducción simultánea para el inglés y español
- Para escuchar las traducciones:
  - **En los controles de su reunión/webinar, haga clic en Interpretación** 
  - Haga clic en el idioma que desea escuchar.
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# Mensajes introductorios

**Pedro Martel**
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# Mensaje introductorio

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Universidad de Alaska-Anchorage
EE.UU.

# Agenda

I. Introductions & Agenda Overview
II. Regional Policy and Intellectual Property
III. Stakeholder Interviews
IV. Case Studies – Banana and Sugar Cane
V. Investment Needs Identification

# Estructuras regulatorias para la edición génica

Presentado por: Jennifer Kuzma

Co-Investigador Principal

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# Current LAC & International regulatory structures for gene editing

- "Living Modified Organism means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology" [Cartagena Protocol]

- Point of regulatory investigation: whether certain gene-edited or genome-edited (GED) crops possess a **novel combination** of genetic material and/or contain **transgenes** in the final product to fall within the LMO definition

- Gene editing is not a singular technology or technique; it refers most often to a set of techniques that enable the manipulation of a genome with greater precision than previous iterations of genetic engineering.

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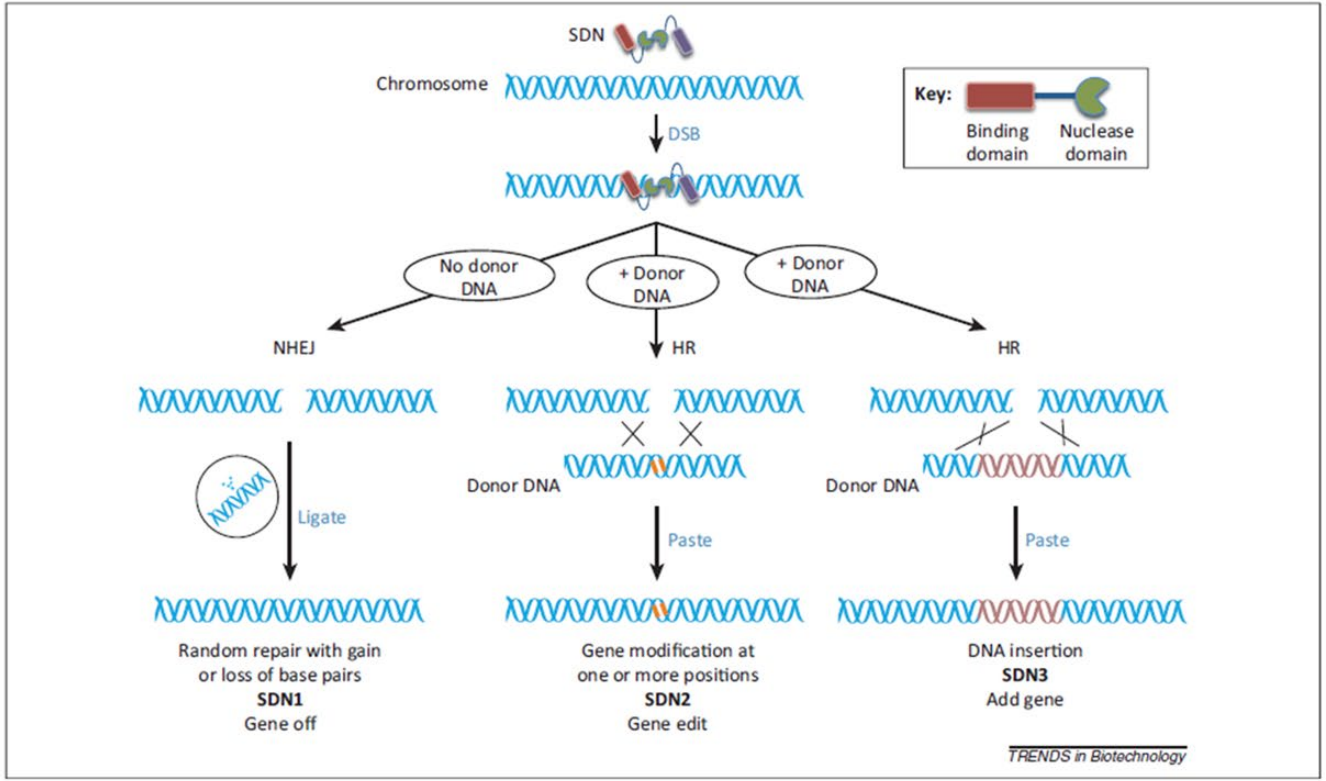
**Gene Editing**
**Genome Editing**
**(GED)**




**SDN 1** **SDN 2** **SDN 3**

Podevin et al. 2013

**Important for Regulation**

IDB Inter-American Development Bank

# Findings: Current LAC regulatory structures for gene editing

- Several nations in the LAC region appear to be coalescing around a particular viewpoint on gene editing as it relates to LMOs or GMOs, with some leading the world with a clearly defined framework for evaluating gene edited crops.

- Many GED products will not be regulated as LMOS or first-generation GMOs, although they are evaluated on a case-by-case basis.
  - Argentina was the first in the region with Brazil, Chile, Colombia, Paraguay, Honduras and Guatemala following.

  - Certain gene edited products are not considered LMOs or like first-generation GMOs (do not possess a novel combination of genetic material or do not contain transgenes) if SDN coding genes and DNA repair templates are backcrossed out of the plant after incorporation of the edit.
    - Mostly SDN1 (site-directed nuclease), SDN2 and ODM are not generally considered GMO, although there is evaluation on a case-by-case basis.

  - Other gene edited techniques and their products are likely to be considered GMOs
    - SDN3 – involves a template guided repair of a DSB using a sequence donor typically containing an entire gene **which allows the introduction of the gene (transgene)** or genetic element at the target site. Could also be entire cisgene, coming from same species, in some cases.

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# Genome Editing in Latin America: Regional Regulatory Overview

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go.ncsu.edu/ges-idb-crispr

JULY 2021

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# Overview of Gene edited crop oversight in select LAC countries.

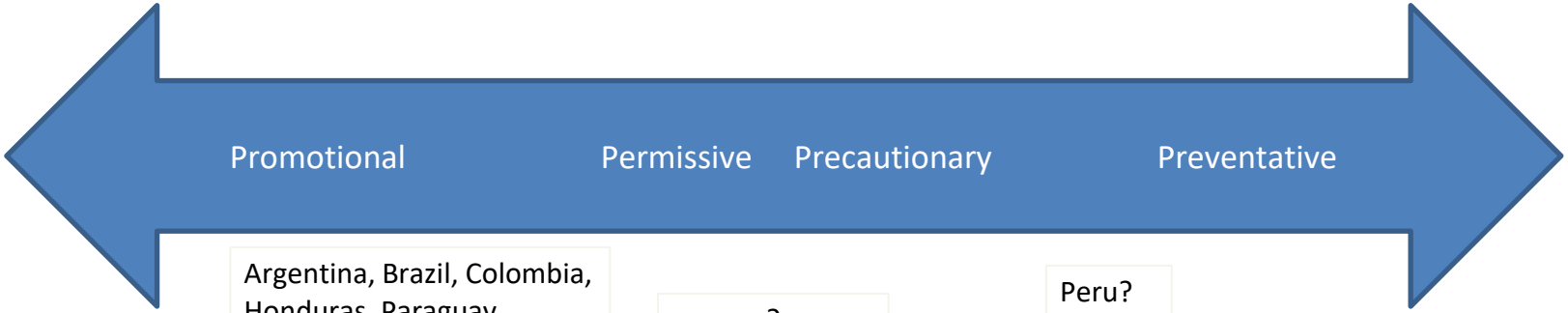
| Country | Party to Cartagena Protocol on Biosafety | GMO regulation | Genome editing specific regulations | Signature to WTO precision biotech statement (See Box 1.) |
|---|---|---|---|---|
| Argentina | No | Yes | Yes—2015 | Yes |
| Bolivia | Yes | Yes | No | No |
| Brazil | Yes | Yes | Yes—2018 | Yes |
| Colombia | Yes | Yes | Yes—2018 | No |
| Honduras | Yes | Yes | Yes—2019 | Yes |
| Mexico | Yes | Yes | No | No |
| Paraguay | Yes | Yes | Yes—2019 | Yes |
| Peru | Yes | Yes (current ban on all GMOs) | No | No |
| Uruguay | Yes | Yes | No | Yes |

*Table 2. Overview of Gene edited crop oversight in select LAC countries.*

# Draft Cross-comparison of GED Formal Regulatory Approach

Below, nations are placed on the spectrum primarily according to the regulatory capture of GED as 1st generation transgenic GMOs or not. Or if no information on GED policies yet, on their approach to 1st generation GMOs.

Note: Countries in same category below may differ in their institutional structure, whether a specific law or regulation for GMOs exists (or older product-based laws & regulations are used), whether they are parties to CBD, and whether they require GM food labeling




US, Australia, Canada, Japan

EU, New Zealand

(potentially China, UK)

# Analysis of GM vs NBT/GED crops in Argentina

from Whelan et al. 2020

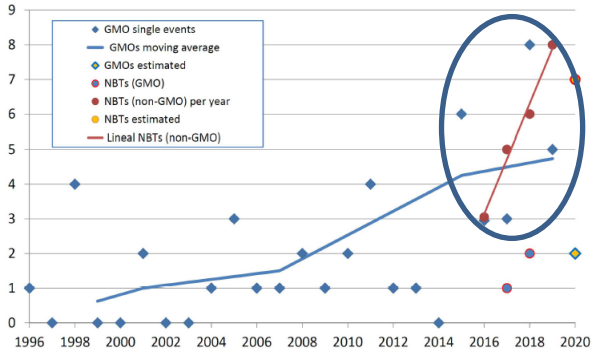



**FIGURE 1 |** The timeline of GMO approvals in Argentina and the determination of conventional or GMO status for products obtained using different NBTs. The horizontal axis represents the year of the regulatory decision, and the vertical axis represents the number of products. See text for details.

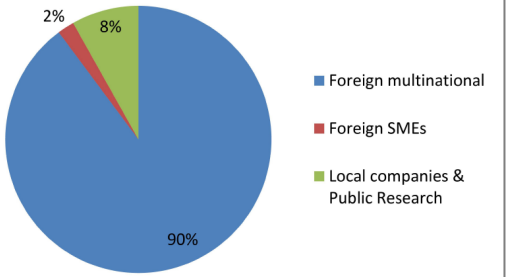



**FIGURE 2 |** GMO products by developer profiles. See text for details.

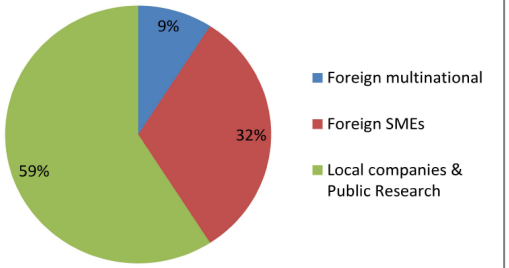



**FIGURE 3 |** NBT (non-GMO) products by developer profiles. See text for details.

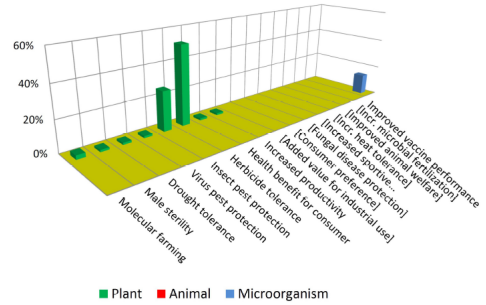



**FIGURE 6 |** Introduced traits in GMO products. See text for details.

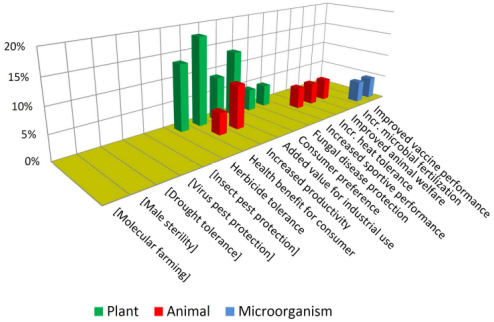



**FIGURE 7 |** Introduced traits in NBT (non-GMO) products. See text for details.

Trend of greater diversity in developers and traits for NBTs/GED crops

# U.S. data on Gene edited crops

- No comparable “diversity” analysis for U.S. NBT/GED crops
  - However about 100 gene edited crops went through “Am I regulated” inquiry process from 2010 to 2020 and may now be grown in the field and used in the agricultural supply chain
  - Some of these would now have to undergo a regulatory status review under 2020 USDA SECURE rule
- George et al 2022 report on gene edited crops in AIR process

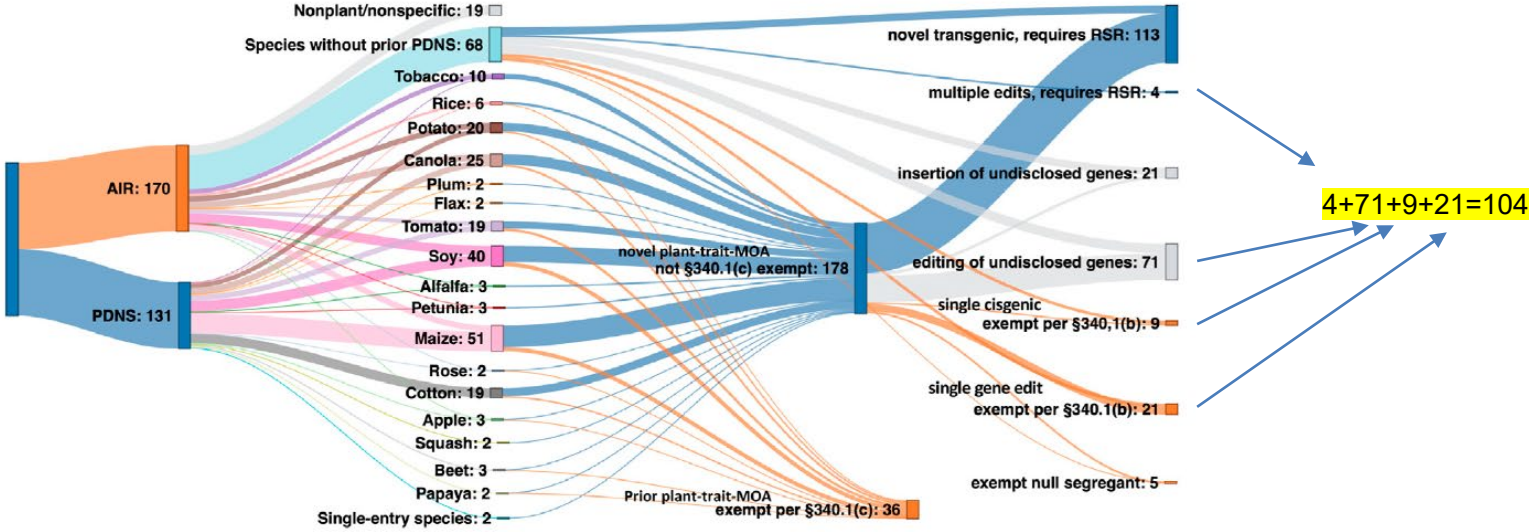



**FIGURE 8 |** The theoretical regulatory pathway of 30 years of US agricultural biotechnology submissions had they been considered under SECURE at the time of development. Starting from left: submissions under AIR and PDNS, the individual species they contain, and their projected exempt or regulated status under SECURE.

# Summary

- Rapid growth of submissions to regulatory agencies around the world for gene edited crops
- Some appearing in food markets (e.g. Calyxt high oleic acid soybean in U.S., Sanatech GABA tomato in Japan)
- Some evidence of greater diversity of producers (including local organizations vs multi-nationals) and traits with GED crops
- Greater attention in international negotiations and studies on gene edited crops (CBD-CPB, etc)

# Panorama actual de licencias de edición génica y protocolos en la agricultura

Presentado por: Margo Bagley

Co-Investigador Principal

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# CRISPR Patent and Licensing Policy

Margo A. Bagley, JD
Asa Griggs Candler Professor of Law,
Emory University School of Law
Visiting Professor of Law
Harvard Law School

# CRISPR PATENT AND LICENSING POLICY

- Purpose of IP Policy Brief:
  - Provide overview of CRISPR plant agriculture patent landscape in relevant countries
  - Identify and describe key licensing protocols for LAC companies and institutes interested in engaging in CRISPR plant agricultural research

https://publications.iadb.org/en/genome-editing-latin-america-crispr-patent-and-licensing-policy

IDB Inter-American Development Bank

# CRISPR being used in many crops

The relative ease of use, efficiency, speed (reducing time to develop an improved trait by half), and flexibility of the system has resulted in its use in a wide variety of crops to develop several traits of interest, including higher yields, herbicide resistance, drought tolerance, disease resistance, faster growth, and more.

One patent application claim mentions: grains, corn, wheat, rice, barley, rye, oats, sorghum, millet, sunflower, safflower, cannabis, cotton, soy, canola, alfalfa, Arabidopsis, cannabis, potato, Brassica, peanut, tobacco, tropical fruits and flowers, **banana**, duckweed, gladiolus, **sugar cane**, pineapples, dates, onions, pineapple, cashews, pistachios, flowers, ornamentals, conifers, deciduous, grapes, citrus, roses, apples, peaches, strawberries, almonds, coffee, oaks, beans, legumes, watermelon, squashes, cabbage, turnip, mustard, cacti, pecans, flax, sweet potato, soybean, coconut, avocado, maize beets, cantaloupe and vegetables.

# CRISPR PATENT FILINGS

- Increasing number of competing techniques and patents
  - This creates licensing and freedom to operate concerns
  - Has led to several different alternatives like CRISPR-Cas 12 a & b, 13, 14, CRISPR-Cms1, MAD7, base editing, etc. for genome editing
- Cas9 remains the most widely used

# CRISPR PATENT AND LICENSING POLICY

- Patents grant a ~20-year right to exclude others from doing certain things with a claimed invention, namely:
  - Making
  - Using
  - Selling
  - Offering to sell
  - Importing
- These rights are territorial, and must be sought in every country/region protection is desired
- Inventions are assessed for novelty, inventive step, adequate description, and subject matter eligibility.

UPOV Plant Variety protection also available in all countries of interest except Honduras. Less stringent protection than utility patents (breeders and farmers exceptions possible)

| Criterion | UPOV 1978 | UPOV 1991 | Utility patents (USA) |
|---|---|---|---|
| Protection | Varieties of species or genera as listed | Varieties of all genera and species | Sexually reproduced plants (and genes, tools, methods to produce varieties) |
| Exclusion | Nonlisted species | None | First-generation hybrids, uncultivated varieties |
| Requirements | Novelty (in trade)<br>Distinctness<br>Uniformity<br>Stability | Novelty (in trade)<br>Distinctness<br>Uniformity<br>Stability | Novelty (in public knowledge)<br>Utility<br>Nonobviousness<br>Industrial application |
| Disclosure | Description (DUS) | Description (DUS) | Enabling disclosure<br>Best mode disclosure<br>Deposit of novel material |
| Rights | Prevent others from commercializing propagating materials | Prevent others from commercializing propagating materials and, under certain conditions, using harvested material | Prevent others from making, using, OR selling the claimed invention or selling a component of the invention |
| Seed saving | Allowed for private and noncommercial use | For use on own holding only (for listed crops only) | Not allowed without consent of patent holder |
| Seed exchange | Allowed when noncommercial | Not allowed without consent of rights holder | Not allowed without consent of patent holder |
| Breeder's exemption | Use in breeding allowed | Use in breeding allowed (but sharing rights in case of EDV) | Not allowed without consent of patent holder |
| Duration | 15-20 years (depending on crop) | 20-25 years (depending on crop) | 20 years from filing or 17 years from granting (prior to June 1995) |
| Double protection (PVP and patent) | Not allowed | Allowed | Allowed |

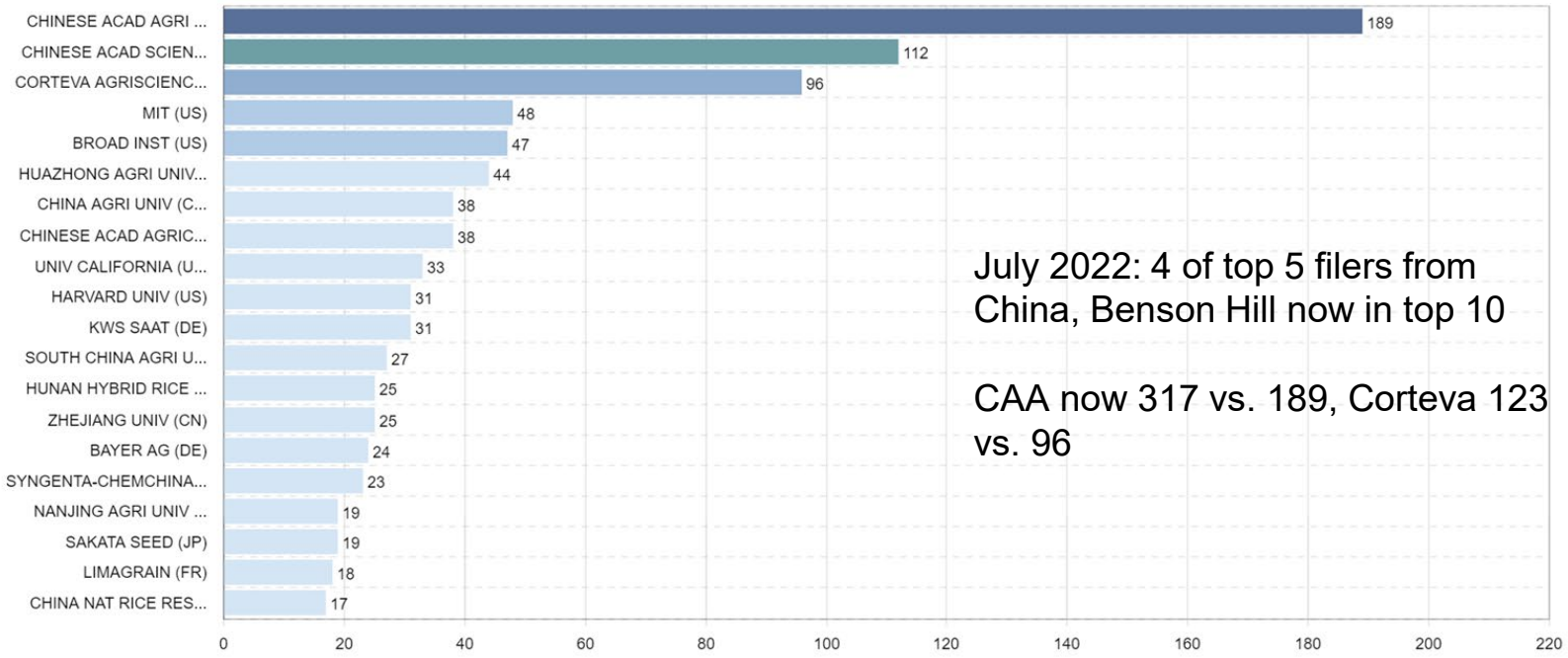
*Source:* Adapted from Helfer (2002), Krattiger (2004), and van Wijk et al. (2003).

Derek Eaton

# CRISPR PATENT AND LICENSING POLICY

- There were **8100** CRISPR patent families worldwide as of J**anuary 30, 2021**, of which **1400** related to plant agriculture
- By **July 30, 2022**, there were **12863** CRISPR patent families worldwide, of which **2377** relate to plant agriculture
  - A “patent family” encompasses all patent filings in different countries for one invention. For example,  one patent family could have one individual patent filing in Argentina, another one in Brazil, another in Mexico, etc.
  - “Patent filings” are published patents and patent applications.
- Because some of these published documents are still applications, they may never actually issue as patents.

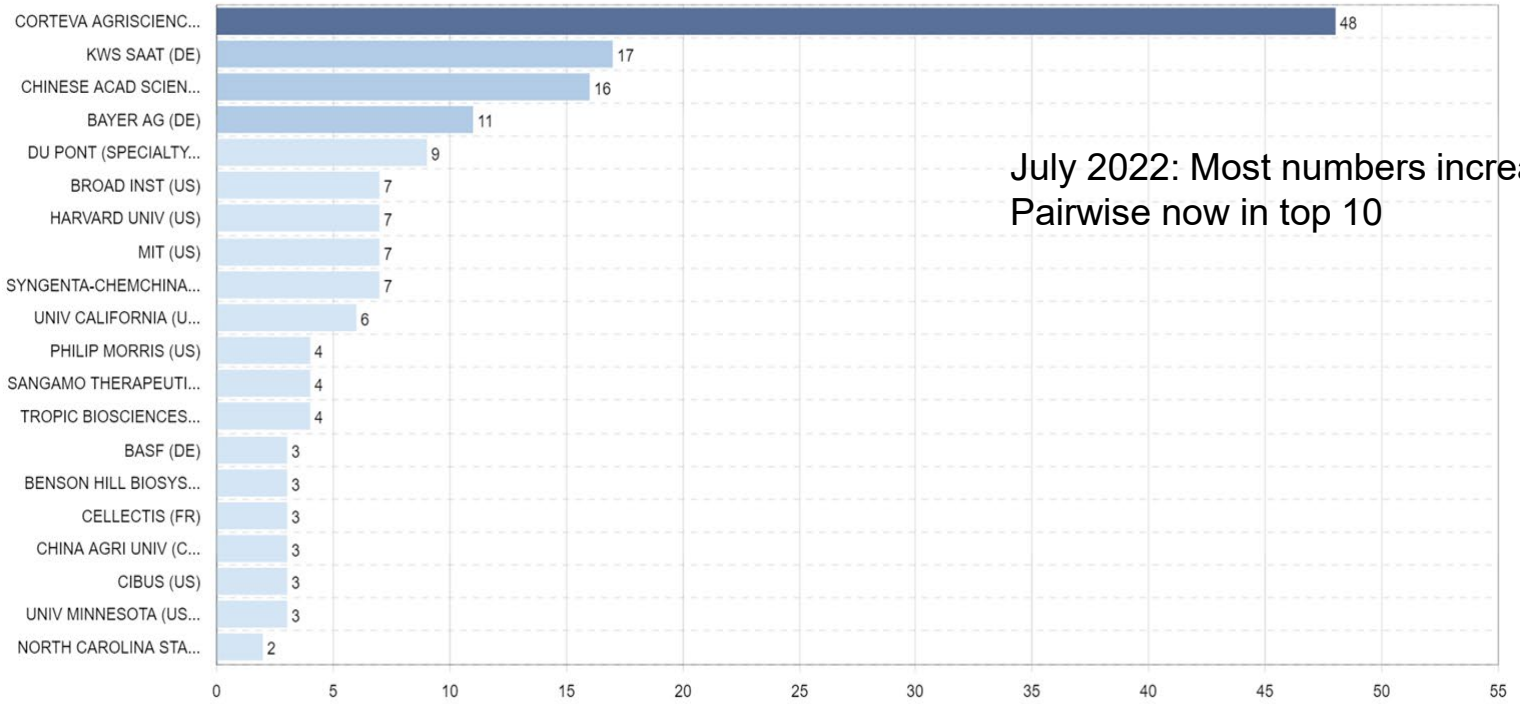
# Top 20 Filers of CRISPR Plant Agriculture Published Patents and Patent Applications Worldwide




July 2022: 4 of top 5 filers from China, Benson Hill now in top 10

CAA now 317 vs. 189, Corteva 123 vs. 96

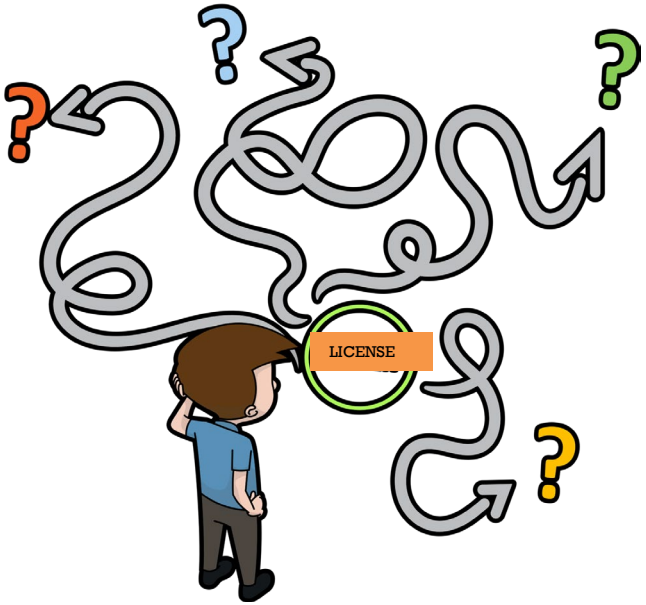
# Top 20 Plant Agriculture Filers in Latin American Countries of Interest
## (175 patent families)




July 2022: Most numbers increased;
Pairwise now in top 10

# CRISPR Patent Licensing Protocols

- The landscape is extremely complex, likely impossible to know all the possible patent owners one might need to seek a license from.

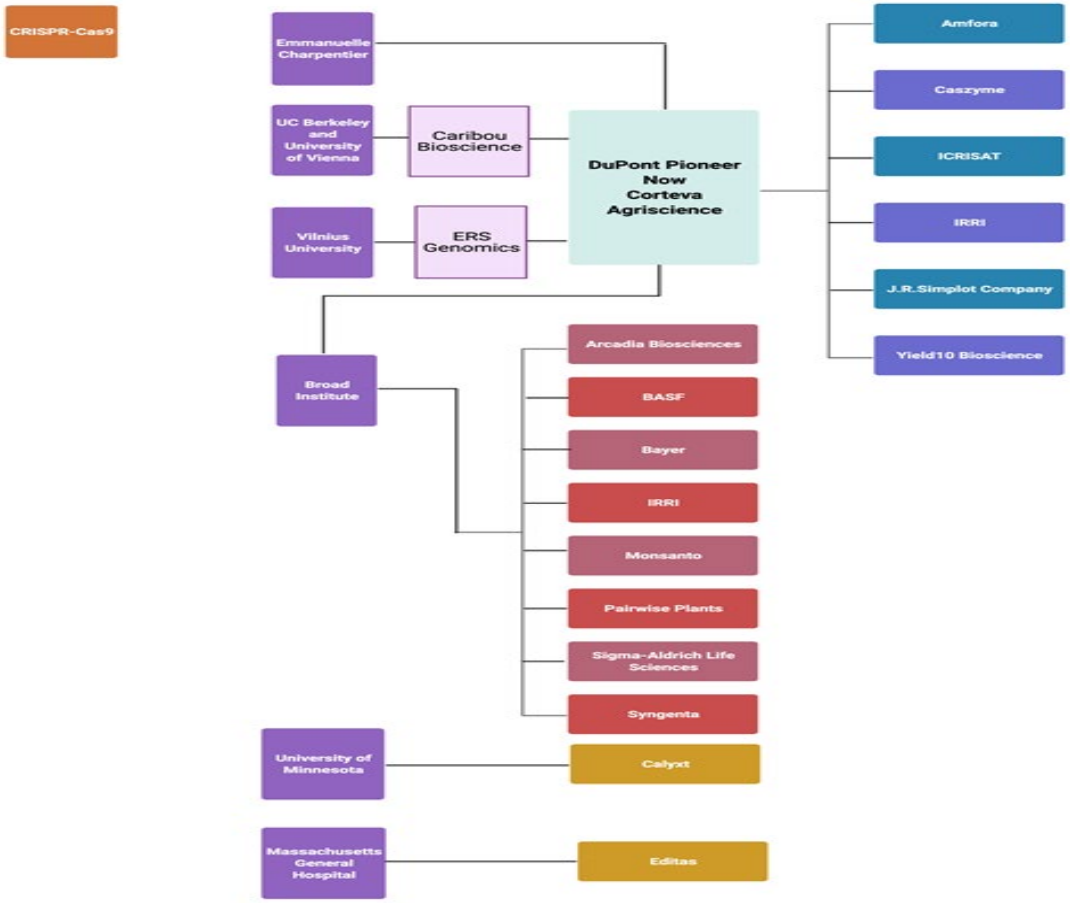


# Corteva can offer a single license bundle (to a suite of CRISPR-Cas9 patents)

## Five types of licenses:

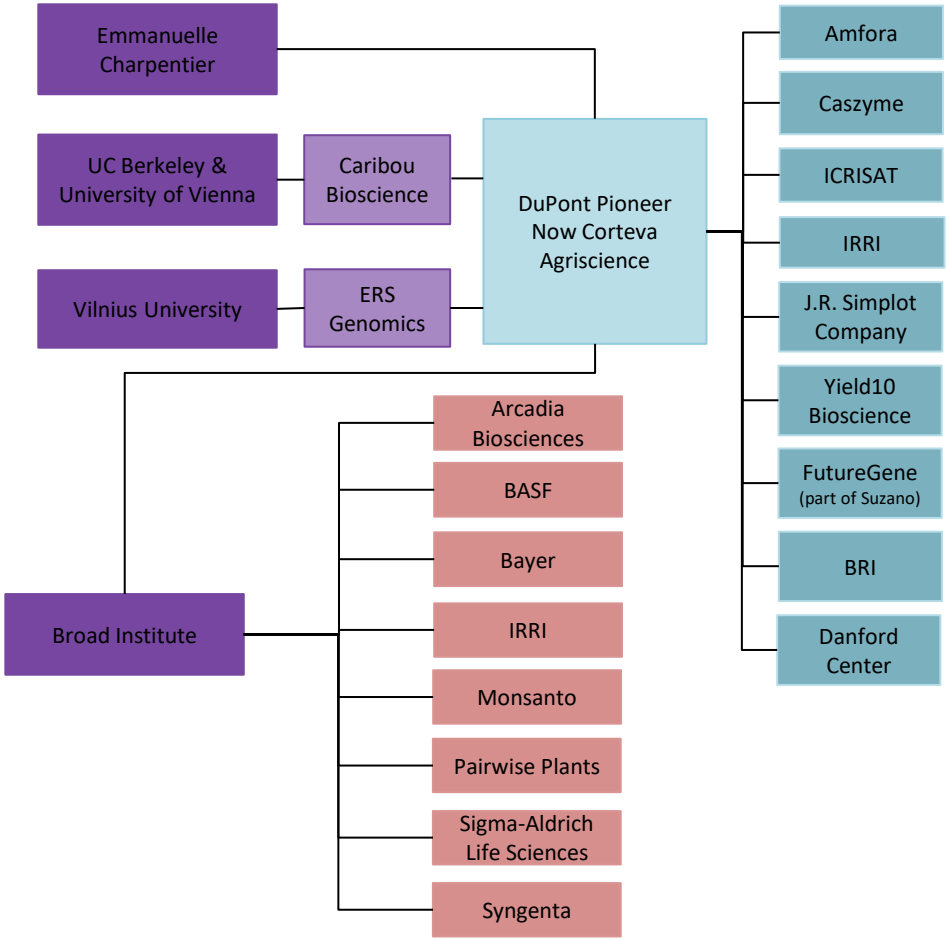
| | | | | |
|---|---|---|---|---|
| Internal only R&D; (may be advantages to seeking this early) | Commercial seeds and crop trait products; | Commercial license for other (non-livestock) agricultural products; | License to provide CRISPR-Cas9 services; and | No-cost academic research license. |

# Reported (not comprehensive) CRISPR-Cas9 Licenses in Plant Agriculture (Jan. 2021)



# CRISPER-Cas9






| | |
|---|---|
| University of Minnesota | Calytx |
| Massachusetts General Hospital | Editas |
| Toolgen | Monsanto |
| Penn State University | Undisclosed AG Biotech Company |
| Cold Spring Harbor Laboratory (CSHL) | Inari |
| Uni Missouri | Yield10 Bioscience |
| ERS Genomic | G+FLAS Life Sciences |
| MIT & Harvard | FutureGene (part of Suzano) |
| MilliporeSigma (Merck) | BetterSeeds |
| UC Davis | Any researcher |

| | |
|---|---|
| Corteva, MIT, & Harvard | CanBreed |
| | Bejo |

## Reported CRISPR-Cas9 Licenses in Plant Agriculture (July 2022)

| | |
|---|---|
| Caribou Biosciences | Regional Fish Institute (RFI) |
| | TreeCo |

# CRISPR-Cas9 and Cas12a & b: The Broad Institute

- Whether through the Broad Institute or Corteva, there are limitations on potential licensee uses:
  - Cannot use to:
    - enable gene drives (confirmed Aug. 15, 2022);
    - Create terminator seeds; or
    - Produce tobacco products for human consumption.

*https://www.broadinstitute.org/principles-disseminating-scientific-innovations*

# CRISPR-Cms1 (CRISPR 3.0): Benson Hill Biosystems

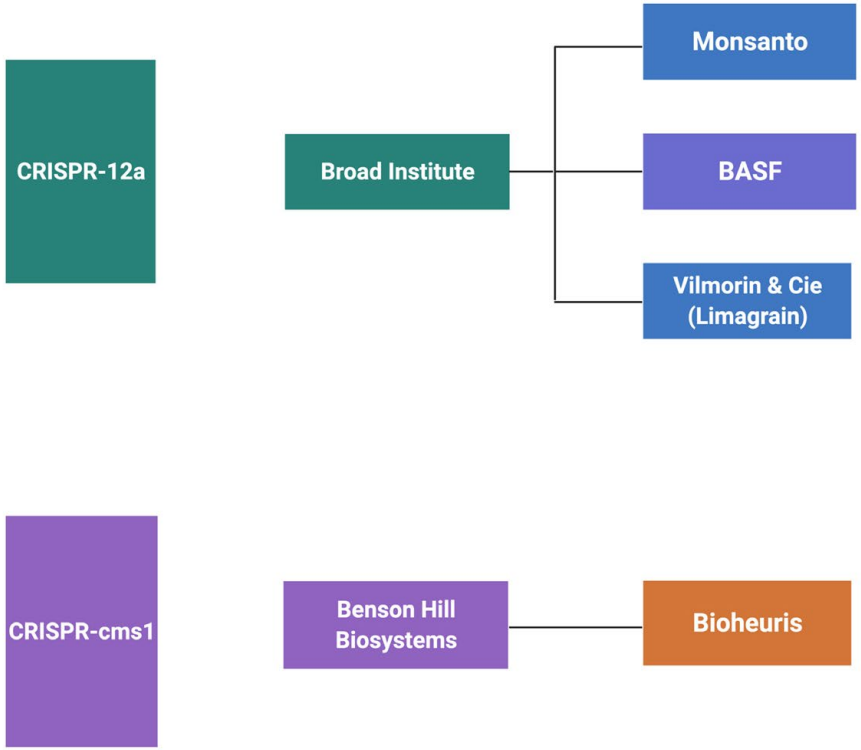
- May be able to offer lower cost licenses and greater clarity regarding patent rights.
- Agreements are individually negotiated.

| Nuclease | Type | in planta activity | Microbial activity | Mammalian Cells | in vitro activity | IP Status |
|---|---|---|---|---|---|---|
| Sm | Cms1 | Yes | Yes | In Progress | In Progress | Issued Patent |
| Su | Cms1 | Yes | In Progress | In Progress | In Progress | Issued Patent |
| Ob | Cms1 | Yes | In Progress | In Progress | In Progress | Issued Patent |
| Mi | Cms1 | Yes | In Progress | In Progress | In Progress | Issued Patent |

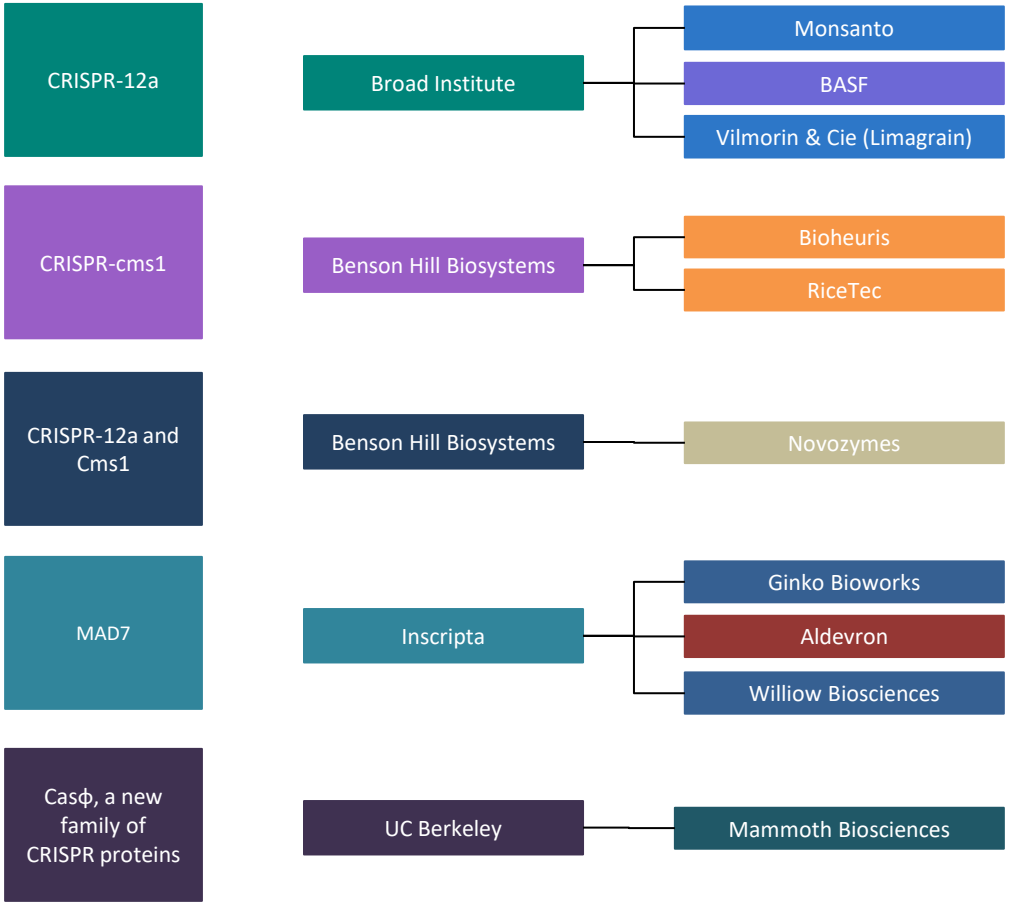
# CRISPR-Cms1 (CRISPR 3.0): Benson Hill Biosystems

- Positioned as the most cost-effective alternative.
- These Cms1 proteins are 10-15% identical to Cas9 at the amino acid level.
  - This smaller size allows for more compact system for precision genome editing.

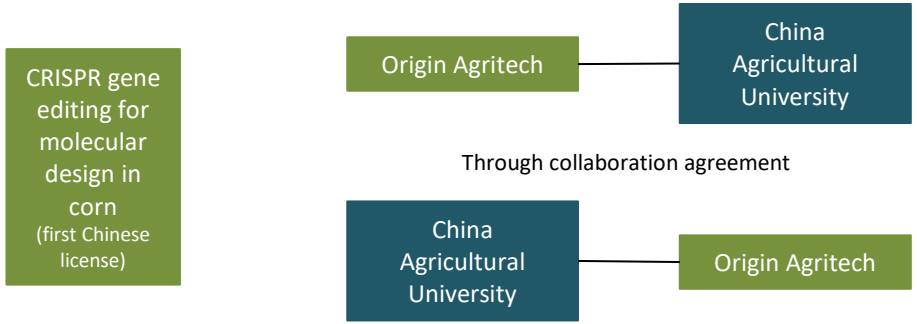
# Reported CRISPR-12a and CRISPR-Cms1 Licenses in Plant Agriculture (Jan. 2021)



# Reported CRISPR-12a (Cpf1), MAD7, and CRISPR-Cms1 Licenses in Plant Agriculture (July 2022)



# First identified Chinese CRISPR License in Plant Agriculture (July 2022)



# SDN1 Genome Editing

For genome editing that could occur in nature or through cross-breeding, it may be impossible to detect patent infringement. However, many countries put the burden of showing non-infringement of a process patent on the defendant. For example, in the U.S, 35 U.S.C 295 states:

"In actions alleging infringement of a process patent based on the importation, sale, offer for sale, or use of a product which is made from a process patented in the United States, if the court finds—

**(1)** that a **substantial likelihood exists that the product was made by the patented process**, and

**(2)** that the **plaintiff has made a reasonable effort to determine the process actually used in the production of the product and was unable to so determine**,

the **product shall be presumed to have been so made**, and the **burden of establishing that the product was not made by the process shall be on the party asserting that it was not so made**."

# Conclusions/Recommendations

For genome editing that could occur in nature or through cross-breeding, it may be impossible to detect patent infringement. However, many countries put the burden of showing non-infringement of a process patent on the defendant. M**ay be important for product commercialization in foreign markets**.

Entities seeking to commercialize products using CRISPR/Cas9 should consider obtaining research licenses in early stages to possibly obtain more favorable commercial licensing terms (**share experiences to determine if that really helps**). **Tech transfer personnel and developers should be communicating regarding which technology to use and licensing/cost/efficiency considerations**. Should consider ways to routinely share licensing experiences with others in the region

CRISPR licensors are unlikely to provide licensees with freedom to operate opinions or any guarantee that a license from them will be enough to avoid infringement. **It thus is up to the individual licensee to continue to assess the patent landscape and determine whether licenses from other entities may be required.**

# Marco regulatorio, Tecnología, y Propiedad Intelectual

## Preguntas y Respuestas

- Preguntas enviadas a través del portal y seleccionadas para responder

# La experiencia en Argentina

Presentado por: Dra. Dalia Lewi

Directora Nacional de Bioeconomía-SSAByDR
Ministerio de Agricultura, Ganadería y Pesca
República de Argentina

Presentación Final BID-NCSU

"Evaluación del marco regulatorio e institucional para edición génica en agricultura mediante tecnologías CRISPR en América Latina y el Caribe"

# Marco regulatorio para la Edición Génica y su aplicación: La experiencia en Argentina


**Dalia Lewi**

Directora Nacional de Bioeconomía-SSAByDR

Secretaría de Agricultura, Ganadería y Pesca

Ministerio de Economía Argentina

- ✓ Desarrollo de la Biotecnología agropecuaria como Política de Estado
- ✓ Sistema de Ciencia y Tecnología de alto desarrollo (CONICET, INTA, Institutos de Investigación y Desarrollo, Universidades Nacionales, Emprendimiento y Empresas Innovadoras)
- ✓ Marco regulatorio maduro y basado en la ciencia que se anticipa a cada desafío que se presente
- ✓ Entidades públicas y privadas que desarrollan productos en plantas, animales y microorganismos (OGM y NBT)

2022

## Pares de otros países

Unión Europea, Estados Unidos y Canadá

## A nivel nacional

Instituciones públicas, PyMES y empresas

¿Cómo acompañamos el surgimiento y evolución de estas técnicas con un marco normativo adecuado?

Argentina es pionera en la creación de una normativa específica para el uso de productos de edición genética

## A nivel Internacional

Empresas y PyMES

# Evolución del Marco Regulatorio

Argentina es pionera en la creación de una normativa específica para el uso de productos de edición genética.

- 2013 Relevamiento sobre el estado de arte de las NBT en el mundo
- **2015** Publicación oficial de la primera normativa sobre NBT (solo para vegetales)
- **2019** Publicación oficial de las normativas de NBT para animales y microorganismos y actualización de la normativa de vegetales.
- **2020** Unificación y actualización de la normativa de NBT.
- **2021** Publicación oficial de la actualización de la normativa de NBT Res. N°21/2021. Hasta el momento se realizaron 45 ICP para distintos organismos

# Características a destacar de la Resolución N°21/21

- Procedimiento para determinar si un producto obtenido por NBT podría estar alcanzado por la regulación de OGM o no. (Definición de OGM del Protocolo de Cartagena)
- El análisis se realiza caso a caso.
- No es restringida a una lista determinada de técnicas.
- Permite realizar la consulta cuando el producto se encuentra en etapa de diseño
- La Comisión deberá dar una respuesta al interesado en 80 hábiles.
- Anexos específicos para animales, microoganismos y plantas.

# Criterios aplicados

## Definición de OGM del Protocolo de Cartagena

Cualquier organismo vivo que posea una nueva combinación de material genético que se haya obtenido mediante la aplicación de la biotecnología moderna.

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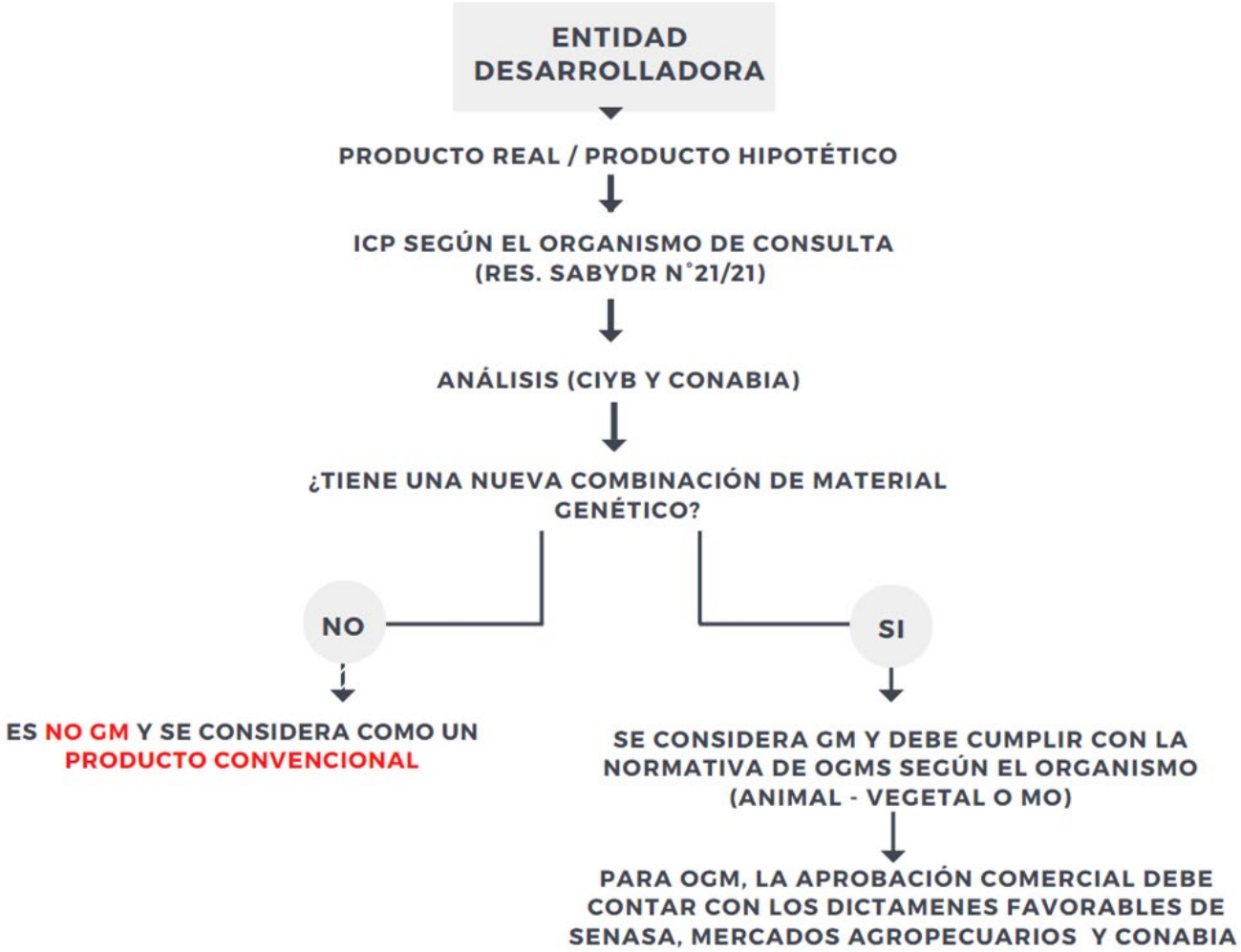
## Definición de "Nueva combinación de material genético"

Cambio producido en el genoma del organismo por la incorporación, en forma estable y conjunta, de UNO (1) o más genes o secuencias de ácido nucleico que forman parte de una construcción genética definida.

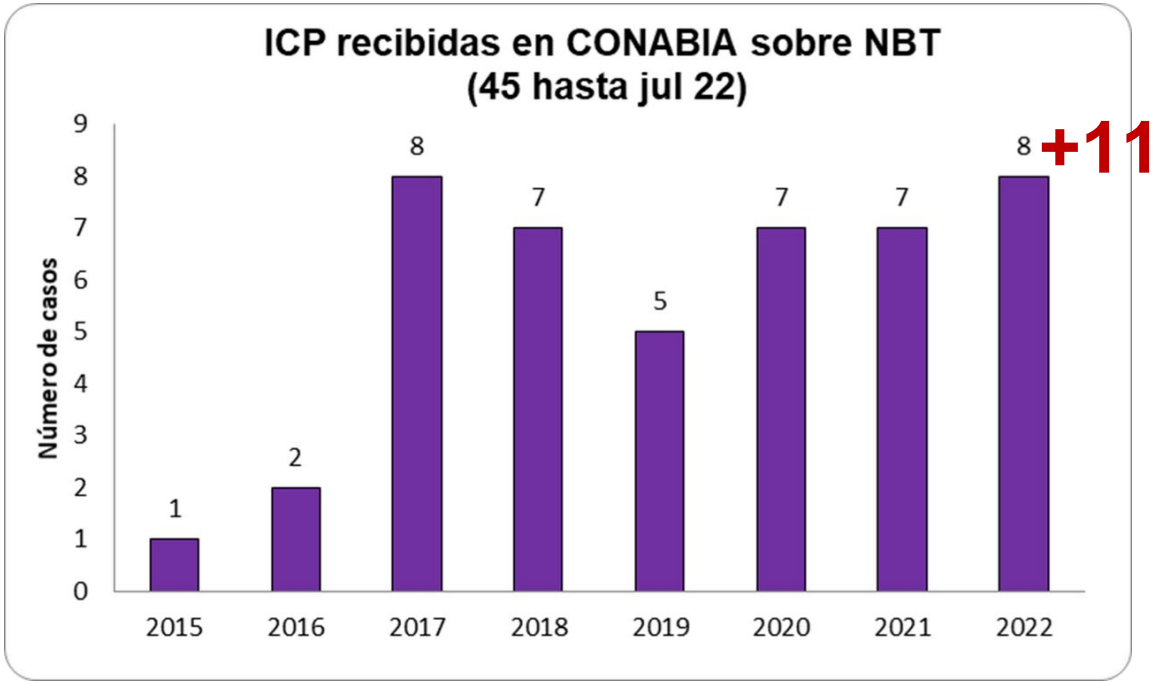
(Res. 21/21 de NBT del Ministerio de Agricultura Ganadería y Pesca)

# ICP – INSTANCIA DE CONSULTA PREVIA

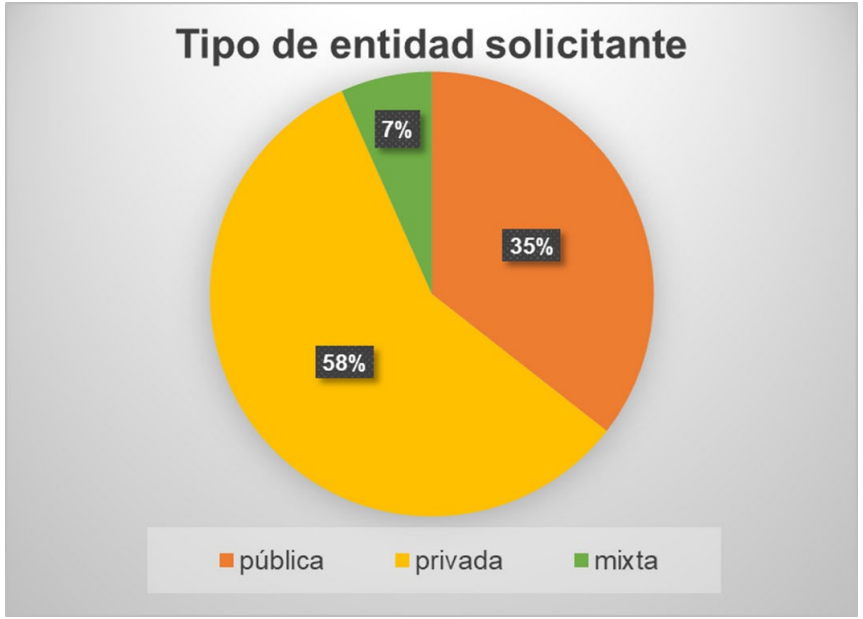
*El solicitante debe proporcionar información sobre:*


ENTIDAD DESARROLLADORA
PRODUCTO REAL / PRODUCTO HIPOTÉTICO
ICP SEGÚN EL ORGANISMO DE CONSULTA (RES. SABYDR N°21/21)
ANÁLISIS (CIYB Y CONABIA)
¿TIENE UNA NUEVA COMBINACIÓN DE MATERIAL GENÉTICO?
NO
SI
ES NO GM Y SE CONSIDERA COMO UN PRODUCTO CONVENCIONAL
SE CONSIDERA GM Y DEBE CUMPLIR CON LA NORMATIVA DE OGMS SEGÚN EL ORGANISMO (ANIMAL - VEGETAL O MO)
PARA OGM, LA APROBACIÓN COMERCIAL DEBE CONTAR CON LOS DICTAMENES FAVORABLES DE SENASA, MERCADOS AGROPECUARIOS Y CONABIA

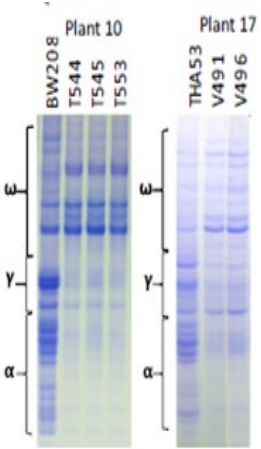
# NBT- Edición génica: ICP recibidas




# NBT- Edición génica: ICP recibidas

# Desarrollos con Edición Génica (Agro)




Sanchez Leon et al.

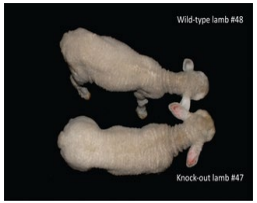




Foto: INTA

*Plant Biotechnology Journal* (2018) **16**, pp. 902–910

by Brian Wallheimer, Purdue University


Foto: INTA


# Oportunidades del Marco Regulatorio

Existe mayor variedad de fenotipos en diferentes cultivos y mayor diversidad de organismos

Es posible predecir los costos y tiempos del producto en etapa de diseño

La velocidad de los desarrollos es mayor en relación a los OGM

Permite que las entidades desarrolladoras alcancen más rápido con su producto al mercado

# ¿Mi producto debe ser regulado?

## Formulário online abierto para consultas orientativas


Tipo de organismo:

☐ Vegetal ☐ Animal ☐ Microorganismo

¿El producto es real o hipotético?

○ Real ○ Hipotético

¿El producto es un desarrollo local o es importado?

○ Local ○ Importado

¿Qué técnica de biotecnología está aplicando?

☐ Transgénesis ☐ Nuevas Técnicas de Mejoramiento ☐ Otra

Mi consulta consiste en:

☐ Saber si mi desarrollo es o no es OGM.

☐ Solicitar orientación sobre la normativa que debo atender para solicitar un permiso de experimentación.

☐ Solicitar orientación sobre la normativa que debo atender para solicitar un permiso para futura liberación comercial.

☐ Solicitar información sobre el estado de avance de la solicitud de permiso presentada (indicar número de expediente)

# Conclusiones

El espíritu de la normativa es contemplar a todos los organismos bajo una misma resolución de manera independiente sin que se vincule con las normativas comerciales para OGM.

Esta normativa da certidumbre a los grupos de trabajo local y se observa en la cantidad de desarrollos y consultas realizadas.

Secretaría de Agricultura,
Ganadería y Pesca

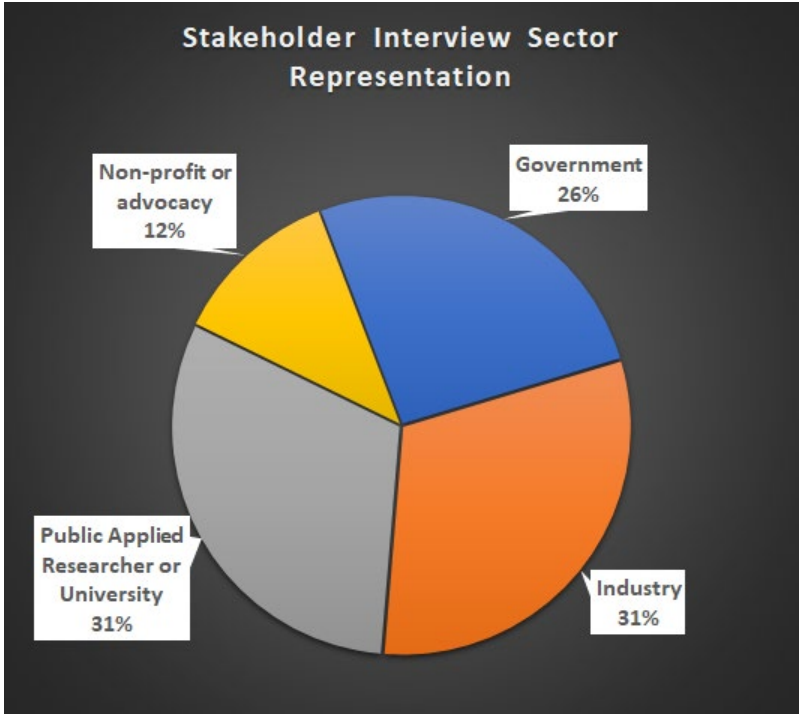
Ministerio de Economía
Argentina

# Analysis of Stakeholder Interviews

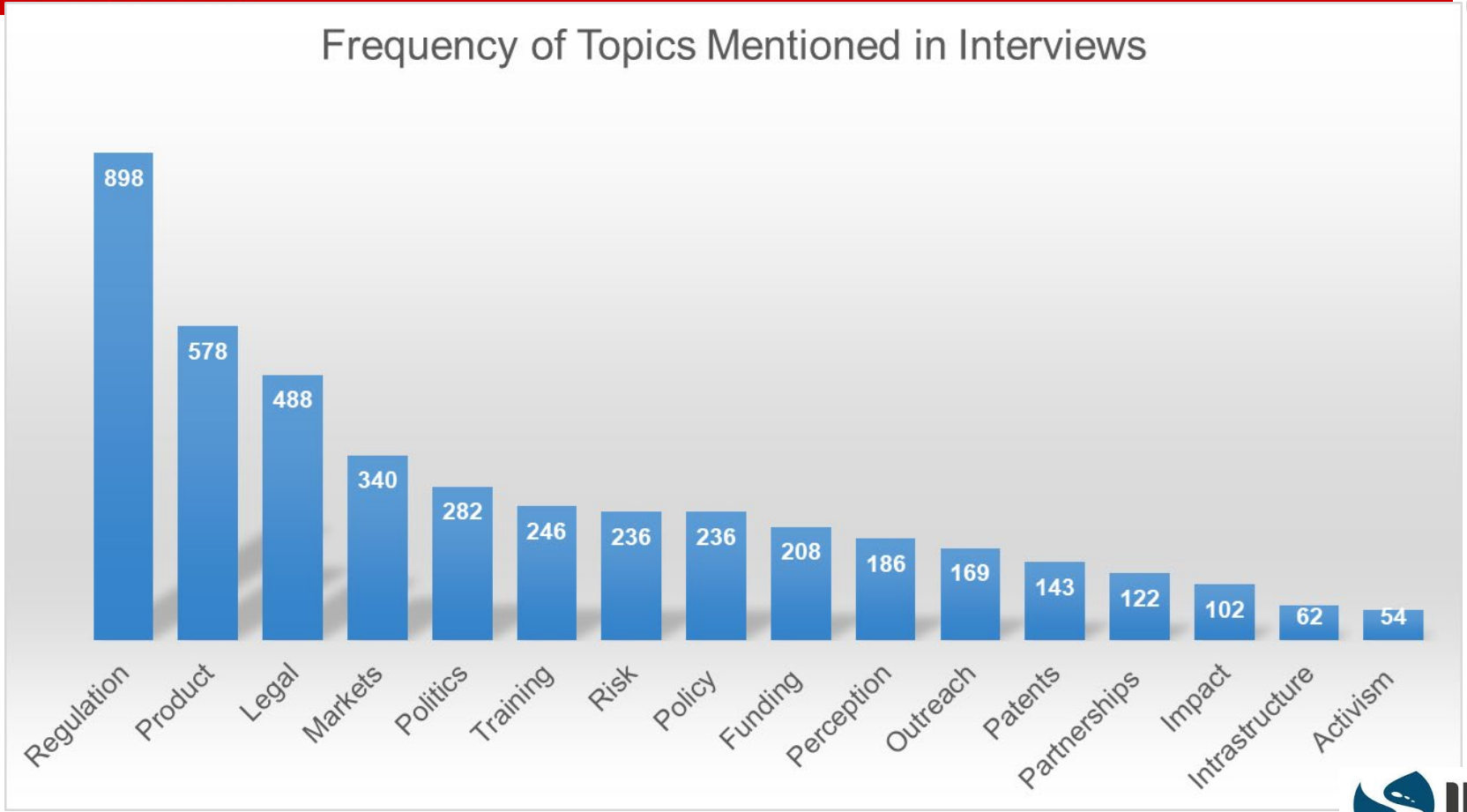
**Katie Barnhill-Dilling**
Senior Research Scholar
Genetic Engineering and Society Center
North Carolina State University

**Sebastian Zarate**, PhD Student, NC State University
**Ilaria Cimadori**, PhD Student, Yale University

# Stakeholder Interviews




- 40+ interviews conducted
- Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, Guatemala, Uruguay


Frequency of Topics Mentioned in Interviews
898
578
488
340
282
246
236
236
208
186
169
143
122
102
62
54
Regulation
Product
Legal
Markets
Politics
Training
Risk
Policy
Funding
Perception
Outreach
Patents
Partnerships
Impact
Intrastructure
Activism

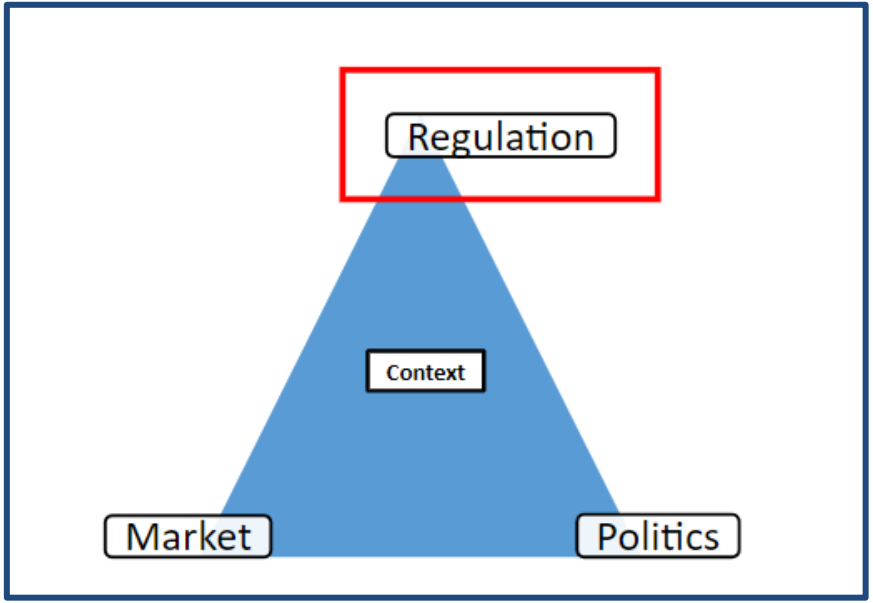
# Challenges

- **Regulation and legislation challenges**. Need to clarify an actionable regulatory framework and harmonize with domestic and international legislation. Regulation harmony in the continent
- **Bureaucratic limitations**. Researchers struggle to obtain the necessary items for their experiments and their labs. Importing them is often time consuming and not a well understood by customs officials. This is critical for product developers. (Peru, Bolivia).
- **Limited partnerships opportunities and career development for students.** Either there are few opportunities or there is a lack of opportunities to collaborate with different institutions. This is something that is been addressed but needs more support.
- **Partisanship of public officials and limited public engagement**. Close connection between policymakers and government officials with interests (either pro or against gmos). Taking a political position influence the regulation enforced. Strong influence from European NGOS steering public opinion, and lack of involvement of the public (few outreach activities and access to information about emerging technologies).
- **Close connection between market needs and product development.** In countries that have the capacity to develop products and patents related to biotech, there is a clear influence of the market (trade) and the products down the pipeline. This represent an issue for crops that are not as attractive for the market (local).

# Priorities

- Develop and enforce **flexible regulations** that facilitate researchers work, that respond to their needs. Avoid legal conundrums by rethinking usable and working definitions, that allow multiple stakeholders to engage with the regulation.
- Provide **training opportunities** for scientists and risk analysis experts.
- Foster **partnerships between private and public entities**, including universities, and research centers from other countries.
- Develop **education and outreach strategies** around different types of crops, valued not only by industry but also by farmers or other communities (include NGOs and local communities points of view).
- Develop platforms to facilitate **access to information about gene editing tools** as well as risk analysis/communication process to the public.

# Regulatory & Political Context



# Regulation: Interview Quotes

*Regulation & Harmonization*

"**It is a great challenge to understand the regulatory framework**, [...]. One is already thinking about it, that it has to do with the viability of the project itself if the amount of economic resources is insufficient" (Paraguay).

"We can see the regulation experience countries, we can learn from them. Long track, done by others, learn from them, **many things can be harmonized [for] more coherent regulation**. Argentinian regulation or Colombian regulation, Brazil regulation is a bit complicated….Open the door to access for different technologies, more than 25 years, they don't have it yet" (Colombia)

# Regulation: Interview Quotes

## *Regulation & Partnerships*

"In 2017, we went there, we trained them. […]. I went to Guatemala to advise their officials and their academics. And with our advice and our training, they finally made of their legislation and put it in the same level, in same the agreement, in same terms as ours. **Since then, we are an example of international cooperation in these regulation issues.** And now we have heard that El Salvador wants to join." (Honduras).

"We also understand that outside the country there are places where the regulations are more advanced, so everything we can take advantage of that is happening outside of the country through **collaborations that ANAPO is doing with different entities like Biotrigo of Brazil"** (Bolivia)

# Regulation: Interview Quotes

***Regulation and politics***

"We right now have a central left political party in place, and they don't want to approve anything that has to do with new technologies. It is **more a political stuff than a technical stuff.** Because the Biosafety Commission already endorsed the procedures, and the procedures are waiting to be approved by the Minister of Agriculture which is waiting for ever" (Costa Rica)

"There are contradictions, inexplicable moratoriums, irreconcilable discourses, from the agencies that protect the environment and those that promote the agricultural sector. **There is little understanding between what the law says and what officials do**. The law had many heated debates, which reconciled biosafety and are based on gradual, experimental, pilot tests and later commercial releases, which obey international principles". (México)

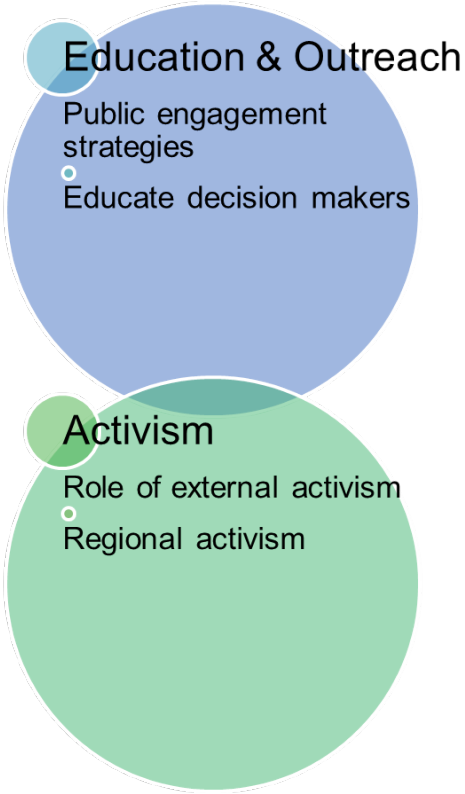
# Regulation: Interview Quotes

*Regulation and product development*

"**Industrial biotechnology companies must send their samples to the analyzers in other countries because we don't have certified labs here in Brazil**. It is absolutely unbelievable. And why there are no labs with this kind of certification? Because it adds additional costs that do not compensate for the labs to follow the rules" (Brazil).

"When you go to customs, they ask you for all the paperwork, they ask you for basically a permit from the university, so they don't have to charge you extra import taxes. That took us like close to four months because the university is also very slow. There all these legal documents that you get asked in the process that just make the whole team very slow. **In the end it was like a year to get all the documentation**." (Peru)

# Social Dimensions



# Outreach and training: Interview Quotes

***Expertise and outreach involving CRISPR technologies and gene editing***

“Because gene editing has implications that cannot be restrict to one community, **this must involve debate. Discuss several dimensions of gene editing**... organize a global assembly, there were some problems because of the pandemic and funding” (Brazil)

“We wanted to shown that… **we were talking about a different technology**. We don't care if you are against or if you are supporting GMOs. We don't care… Because we are going to show you how the new technology is producing novel organisms. In the case of Peru, we were inviting people from the Ministry of Agriculture, National Research Institute and three offices from the Ministry of the Environment… **We wanted to show them that this is a new technology. That it is important to explain how the technology works**. And the different sectors are going to be able to see how they can use the technology and how safe or unsafe the technology is. ” (Costa Rica)

# Activism: Interview Quotes

## *External influence*

"There is influence **"from European environmental organizations with strong investments and with talks to the population that introduce a lot of fear over not only the production of transgenic crops but also on the consumption of these products**. There is a heavily financed environmentalism in Bolivia, with a presence in the civil society but also in the different governments" (Bolivia).

"There are always activists from different groups. **Most of these groups were international groups like Via Campesina, Greenpeace and others.** Some of them were **supported by international institutes from Europe** in general… Very rarely we saw small farmers or students… So it was not kind of spontaneous presence of people against GMOs. **It was internationally organized…**" (Brazil)

# Activism: Interview Quotes

***From within the region***

"In the country there was a discussion over the introduction of the first event, soyRR, which was requested by ANAPO. There was a big discussion in the government. **The discussion also took place in civil society, with environmental activists against the introduction of this event in Bolivia on one hand** but on another the producers wanted to introduce it to increase crop yield" (Bolivia)

# Concluding Thoughts

- Regulation is the dimension that shapes all others.
  - Product development
  - Training
  - Capacity Building
  - Partnerships
- Attending to social dimensions opens up decision making about new agricultural technologies which may shape acceptance and adoption.

# Stakeholder Interviews:

# Question and Answer

# Actualización: Casos de Estudio

## Edición génica en banano

**Maria Mercedes Roca**

Director Ejecutivo

Bioscience ThinkTank

# Estudio de caso I:

# Edición génica en banano

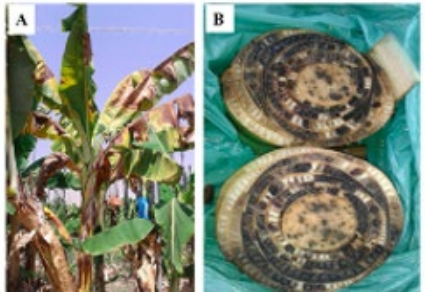
# (Honduras y Guatemala)

**Principales enfermedades de banano y plátano (musaseas}:**

- Sigatoka del banano por *Mycosphaerella fijiensis*
- Marchitéz o Mal de Panamá por *Fusarium sp Raza Tropical 4*

Sigatoka Negra

Fusarium Raza Tropical 4




# Importancia del banano y plátano en la seguridad alimentaria y reducción de la pobreza

- Los bananos y plátanos, producidos en más de 135 países, son un cultivo básico para la seguridad alimentaria de más de 400 millones de personas

- Son una fuente esencial de ingresos en muchos países en desarrollo

- Las enfermedades como Sigatoka y Fusarium representan un grave riesgo

Objetivos de Desarrollo Sostenible (ODS)

# La Sigatoka negra en banano (*Mycosphaerella fijiensis*)

## Sigatoka negra

**Nombre común**
Sigatoka negra o raya negra

**Nombre científico**
*Mycosphaerella fijiensis Morelet*

**Tipo de plaga**
Hongo Ascomycete

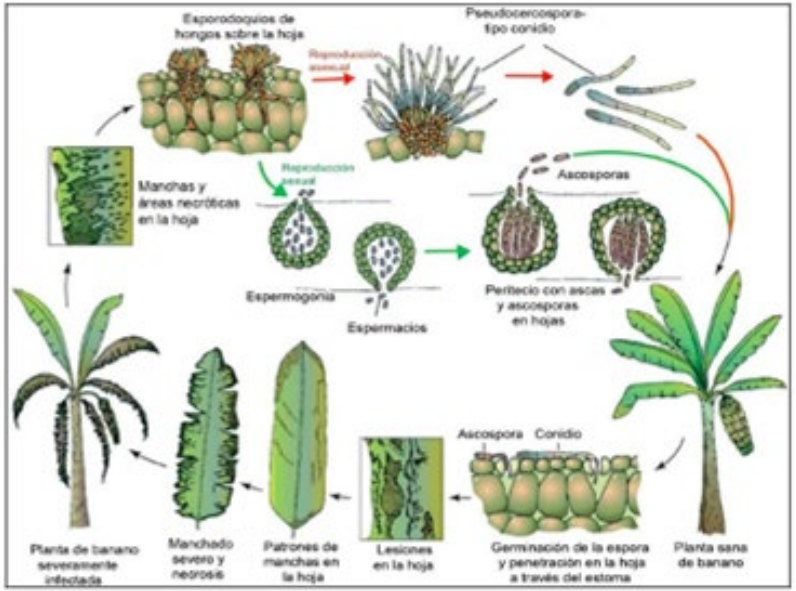
**Cultivo que ataca**
Bananos y plátanos

**Dispersión**
Global a nivel del trópico

**Órganos que ataca**
Ataca principalmente el tejido foliar, evitando el proceso de fotosíntesis

**Condiciones predisponentes**
Alta temperatura, alta humedad, mal drenaje, mala nutrición

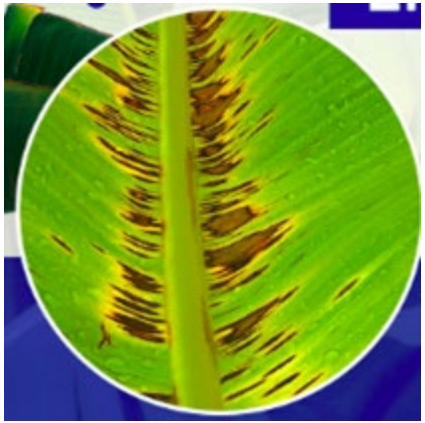
Fuente: CropLife




Fuente: Intagri, adaptando Agrios (2005)

El plátano y el banano (Musa spp.) son alimentos básicos para más de 400 millones de personas y una fuente de empleo e ingresos para muchos países de LATAM

# La Sigatoka negra en banano (*Mycosphaerella fijiensis*)



- Enfermedad **foliar** más destructiva y de mayor valor económico - puede causar pérdidas de hasta un **50% en el rendimiento y** 100 % de la producción debido al deterioro en la calidad.

- La Sigatoka apareció en Centroamérica (Honduras) en 1934. **Está presente en todos los países de producción bananera**

- **Causa gran impacto económico, por reducción en producción y por los altos costos de manejo.**

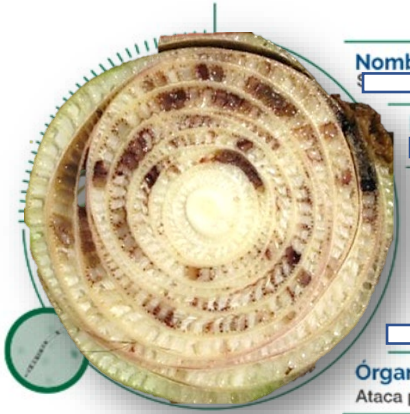
- La alta virulencia de *M. fijiensis* enfoca las medidas preventivas hacia el manejo adecuado de labores culturales en la plantación y al monitoreo continuo de la evolución de la enfermedad,

- **Se estima que el costo de aplicación de fungicidas por Ha/ por aplicación es de US$ 1500-2000/Ha/año, con alrededor de 50 aplicaciones**

# La marchitéz o Mal de Panamá por *Fusarium sp. Raza Tropical 4 (RT4)*

Hongo de suelo y principal riesgo de la industria bananera

***Fusarium oxysporum f.sp cubensis***
***Raza Tropical 4***



**Nombre común**
*Marchitez o mal de Panamá*

**Nombre científico**
*Fusarium oxysporum sp cubense* RT4

**Tipo de plaga**
Hongo Ascomycete

**Cultivo que ataca**
Bananos y plátanos

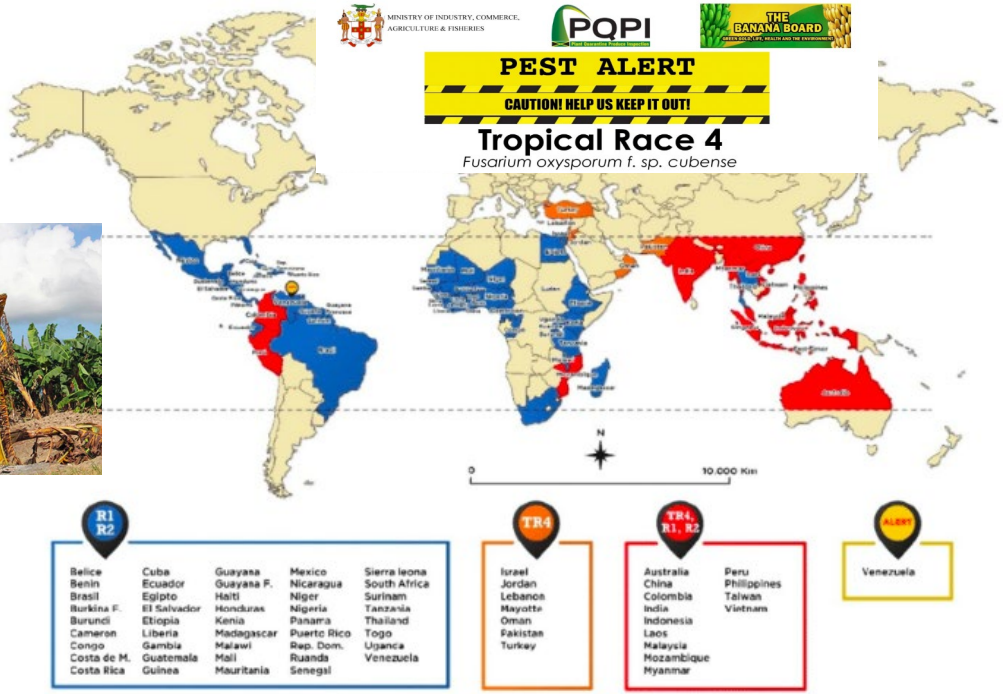
**Dispersión**
*Marchitez o mal de Panamá*

**Órganos que ataca**
Ataca principalmente el tejido foliar, evitando el proceso de fotosíntesis

**Condiciones predisponentes**
Alta temperatura, alta humedad, mal drenaje, mala nutrición

**El hongo no es erradicable, no responde a fungicidas y permanece en el suelo por décadas, aún en ausencia del hospedero**

# Distribución geográfica de *Fusarium oxysporum f.sp cubense* RT4




Geographical distribution of Fusarium oxysporum f. sp. cubense (Foc) races. Source: Adapted from CABI/EPPO [25], EPPO [26] and PROMUSA [27].

IDB
Inter-American Development Bank

# Marchitéz o Mal de Panamá - Raza Tropical 4
## *Fusarium oxysporum f. sp. cubense tropical race 4 (TR4)*

- Enfermedad más destructiva de plátano, banano y heliconias. No se ha identificado ningún tratamiento químico, ni ningún sustituto resistente aceptable.

- La variedad Cavendish es altamente susceptible. Más del 40% de la producción mundial de banano y casi todo el comercio de exportación es Cavendish.

- En Australia (Dr. James Dale y su grupo) desarrollaron un Cavendish transgénico con resistencia a la RT4. Una línea transformada con **RGA2, un gen aislado de un plátano diploide resistente a RT4, y la otra con un gen derivado de un nematodo, Ced9.**

- La expresión del transgén en las líneas RGA2 está fuertemente correlacionada con la resistencia. Los homólogos endógenos de RGA2 también están presentes en Cavendish, pero se expresan diez veces menos que en nuestra línea transgénica más resistente.


La expresión de estos homólogos puede elevarse también mediante la **edición génica, para proporcionar una resistencia no transgénica**

Fuente: Nature https://www.nature.com/articles/s41467-017-01670-6

# Búsqueda de resistencia por transgénesis, cisgénesis y edición génica a *Fusarium oxysporum f. sp. cubense raza tropical 4 (RT4)*

**Estrategia combinada :**

1. Introducción de genes de resistencia a Cavendish (cisgénesis y transgénesis)

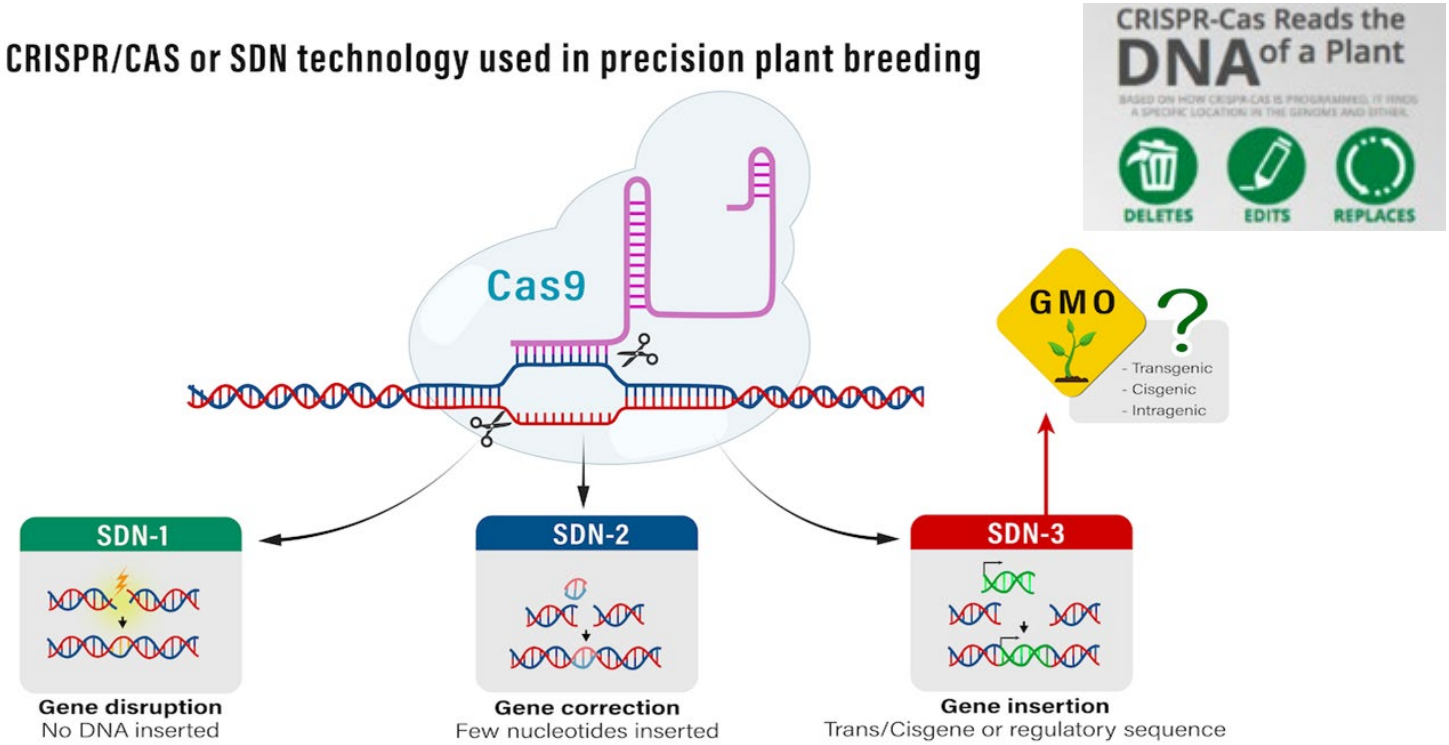
2. Introducción de promotores para mayor expresión de genes endògenos de resistencia

3. Identificación y posterior silenciamiento de genes de susceptibilidad

**Fuente** : Nature https://www.nature.com/articles/s41467-017-01670-6

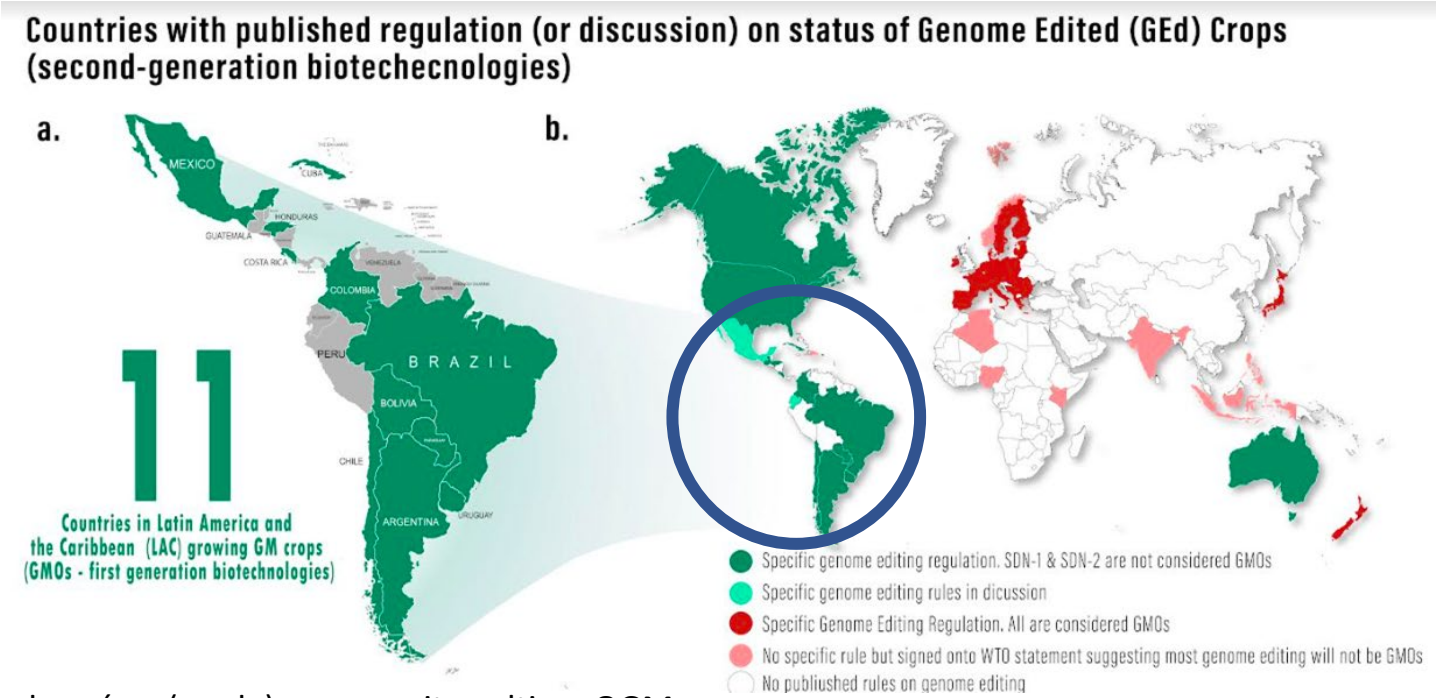
Dr. James Dale, Queensland University of Technology (QUT), Australia, comunicación personal. Colaboración con Del Monte y Filipinas

# CRISPR o Edición Génica




**Fuente**: MM Roca et al. Cisgenics Crops in Latin América, Springer 2022, en imprenta

# 2022: Países (en verde) ya con regulación para cultivos editados




a. Regulación de países (verde)que permite cultivar OGMs
b. Países con regulación ya establecida para cultivos editados

**Fuente**: MM Roca et al. Cisgenics crops in Latin América, Springer 2022, en imprenta

## Banano GM y editado con resistencia a Sigatoka y Fusarium y RT4 *puede posiblemente ser* evaluado en Honduras y Guatemala



- Avances por empresas privadas como Tropic Bioscience (UK/Israel) en coordinación con Dole y FHIA en Honduras

- Solicitud entregada a Comité Nacional de Biotecnología
- y Bioseguridad Agrícola (CNBB) en Honduras

  - Sigatoka : variedades transgénicas y editadas
  - Fusarium RT4 : variedades editada





**Comité Nacional de Biotecnología y Bioseguridad (CNBB), Liderado por la Secretaría de Agricultura y Ganadería #SAG a través del Servicio Nacional de Semillas**

https://www.facebook.com/watch/?v=438199710194971

Pairwise & Tropic Bioscience firman acuerdo para utilizar tecnología de edición de cultivos

# Honduras: marco regulatorio de biotecnología agrícola


https://es.slideshare.net/lacbiosafety/marco-regulatorio-de-bioseguridad-honduras-un-estudio-de-caso-para-centroamrica

# Caso de Estudio: Edición Génica en Banano

## Preguntas al equipo

# Actualización: Casos de Estudio
## Edición génica en Caña de Azúcar:

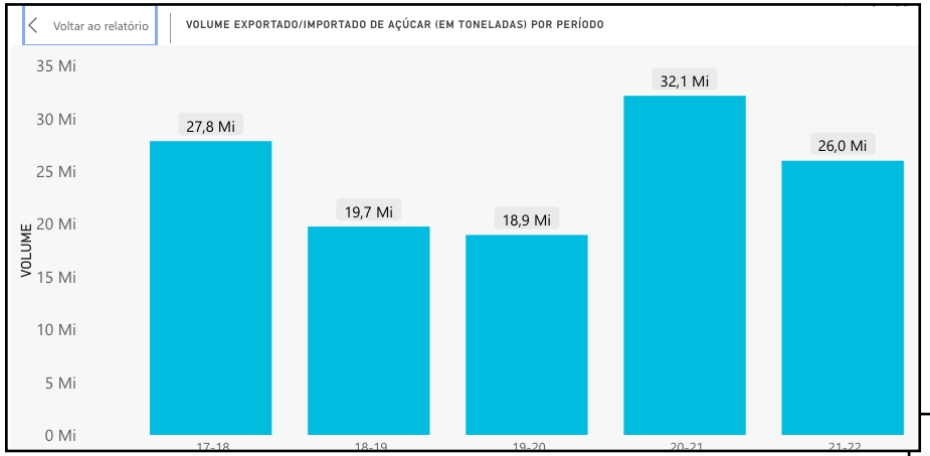
**Luciana Ambrozevicius**
Consultante Independiente

# Estudio de Caso

## Edición génica en Caña de Azúcar: Brasil y Bolivia

IDB
Inter-American Development Bank

# Caña de Azúcar: Importancia en Agricultura Tropical En Brasil

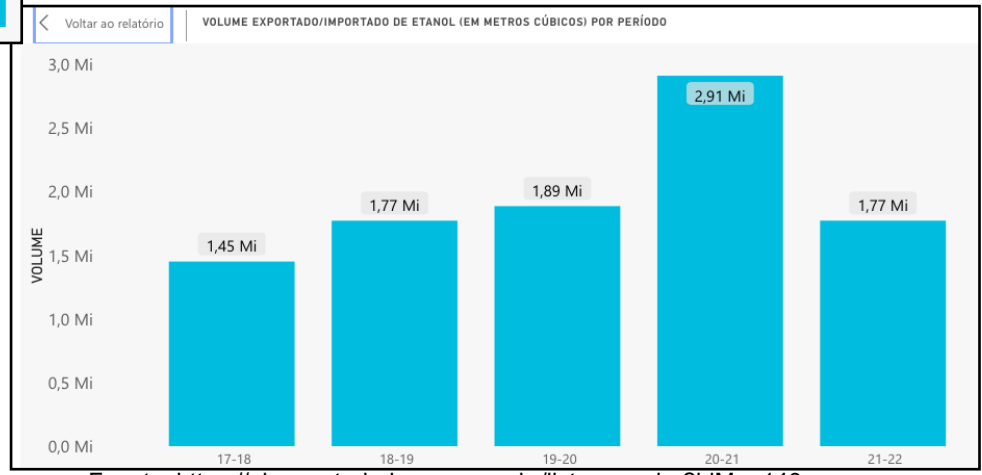



- Area total: 10Mi ha
- Producción total: 642Mi ton
- Productores: 70.000

(São Martinho, Terreaus, COFCO)

- Ingenios: 404
- Rendimiento medio: 74t/ha

Fuente: Sugar Tech (Jan-Feb 2022) 24(1):112–133




Fuente: https://observatoriodacana.com.br/listagem.php?idMn=143

# Caña de Azúcar: Potencial de Mejora Genética

- Embrapa: entidad pública-privada

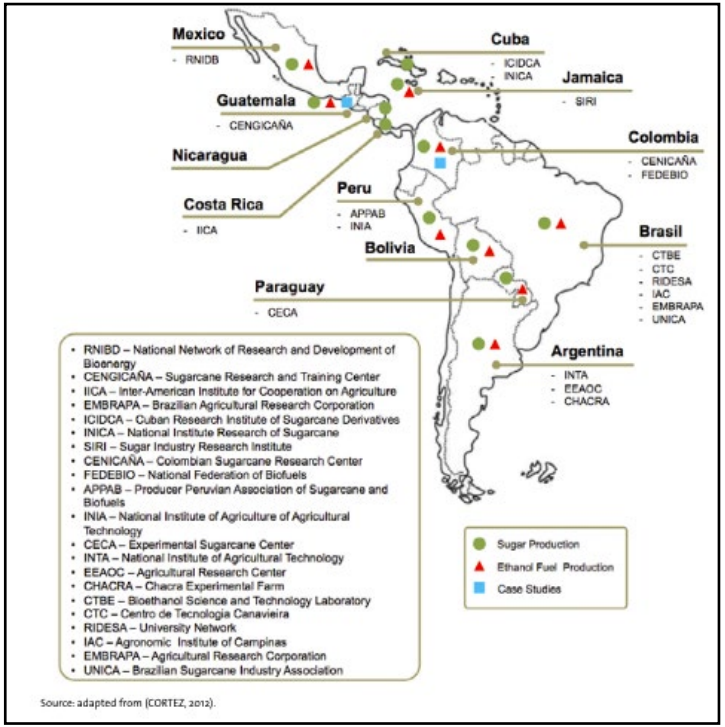
- *Knockdown* de genes SP80-3280 - BAHD01 (Flex I) y BAHD05 (Flex II)

- Disminución de ácido ferúlico (FA) y ácido paracumárico (pCA) en la pared celular

  - Mejor digestibilidad de biomasa vegetal y acumulación de azúcares

**FLEXCANE - Sucrose accumulation**


Fuente: Hugo Molinari

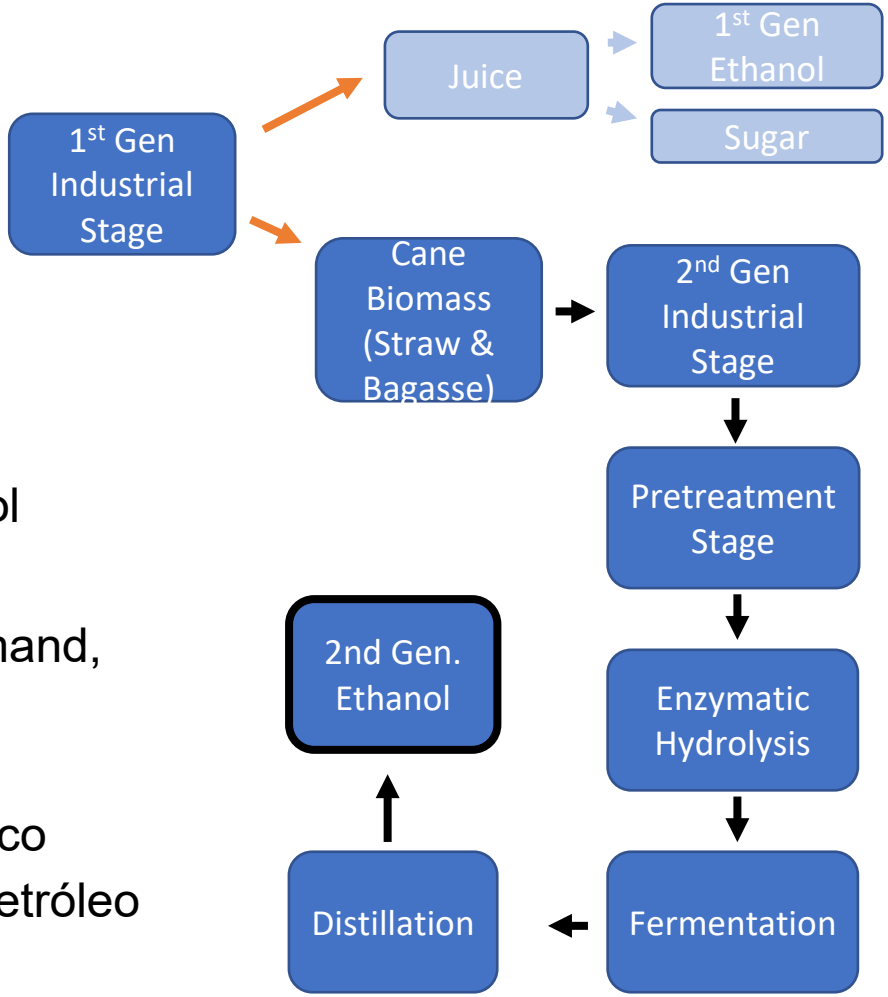



Fuente: Current status and perspectives for bioenergy in Latin America & Caribbean: addressing sugarcane ethanol. 2016

# Caña de Azúcar: Flexibilidad de Usos

- Costos R$0.26/L E2G vs. R$0.22/L E1G
- Uso de levadura GM: 5-10% más de etanol
- Uso de levadura GeD: Globalyeast, Lallemand, YesSinergy
- Importante en discursos de cambio climático

E2G - 73% remoción carbono en relación petróleo




Fuente: Costa (2014)

# Caña de azúcar: Contexto Regulatório

**RN CTNBio 16/2018**

"*As **TIMP** abrangem um conjunto de novas metodologias e abordagens que diferem da estratégia de engenharia genética por transgenia, por resultar na ausência de ADN/ARN recombinante no produto final*"

I - producto con ausencia comprobada de ADN/ARN recombinante, obtenido por técnica que utiliza OGM como progenitor;

II - producto obtenido por técnica que utiliza ADN/ARN que no se multiplicará en una célula viva;

III - producto obtenido por técnica que introduce mutaciones sitio dirigida, generando ganancia o pérdida de función génica, con ausencia comprobada de ADN/ARN recombinante en el producto;

IV - producto obtenido por técnica donde hay expresión, temporal o permanente, de moléculas de ADN/ARN recombinante, sin presencia o introgresión de esas moléculas en el producto; y

V - producto donde se utilicen técnicas que emplean moléculas de ADN/ARN que, absorbidas o no de forma sistémica, no provoquen modificación permanente del genoma

**No se consideran OGMs por ley nacional**

# Información Económica

| Caña de Açúcar | Tiempo | Costo (US$) |
|---|---|---|
| Convencional | 6 a 15 años | 10 millones |
| Modificado Genéticamente (OGM) | 10 a 12 años | mais de 100 millones* |
| Editado Genéticamente (Convencional) | 2 a 5 años | 500 mil a 5 millones |

*costos para desregulación

Fuente: Entrevistas

## Convencional X CanaFlex

- 10 años
- 10% área
- 12% más sacarificación
- 15% más sacarosa tallos
- 200% más sacarosa hojas

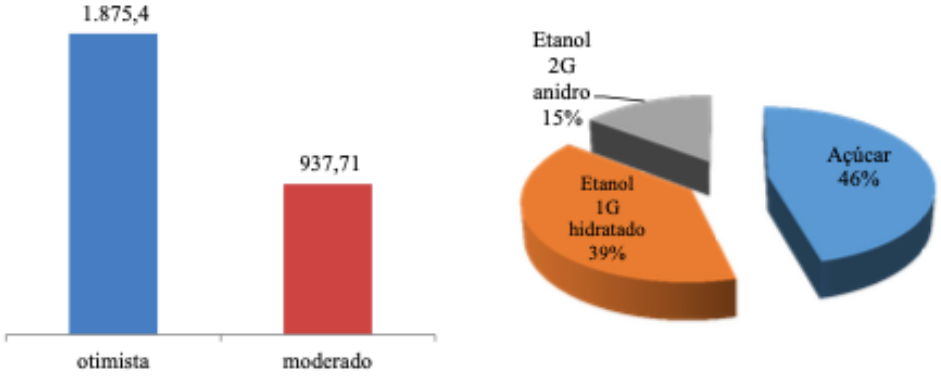



Figura 4 – Renda adicional total no décimo ano, em R$ milhões e distribuição % por produto.

Fuente: Molinari et. al. 2021.

# Oportunidad de Caña GeD en el Sector Boliviano

- Sector de caña de azúcar es mucho más joven y menos desarrollado
  - Bolivia (10Mi ton)
- 5 plantas (potencial de 250 Mi L etanol)
- Producción concentrada en Santa Cruz
- Centro de Investigación de Ingenio Guabira: cruzamientos de variedades Bolivia y Brasil
- Exportación de azúcar e importación de etanol


Elaborado de AEMP (2018)

# Oportunidad Caña GeD en el Sector Boliviano

- Apoyo reciente de incrementar uso doméstico de etanol; por el gobierno y  el sector privado
- Mandato para mezclar con gasolina:
  - 2018: 10%  |  2025: 25%
- Ventas y objetivos
  - 80Mi L en 2018
  - 160Mi L en 2022
  - 380Mi L en 2025 (anuncio original)
- Se requiere:
  - Aumento de superficie,  y en productividad

**Bolivian government agrees with sugar mills and sugarcane producers to purchase 160 million liters of ethanol for 2022**

Bnamericas
Published: Friday, November 26, 2021


Imagen: Ingenio Azucarero Guabira

**Mecanização da colheita revoluciona cana boliviana**

Tendo o Brasil como referência na produção da cultura, o país vizinho importa variedades, profissionais e conhecimento para se desenvolver

PUBLICADO EM 29/03/2018 ÀS 10H31 POR ROBERTA SILVEIRA, DE FERNÁNDEZ ALONSO (BOL)

# Preguntas a Explorar - Brasil

- Evolución de costos/L de producción E2G
- Factores que influyen la velocidad de adopción
- Royalties para variedades GeD adoptadas
- Barreras de propiedad intelectual
- Mejoramiento genético (productividad estancada)
- Aspectos de sustentabilidad (cambio climático)
- Aspectos de trazabilidad y comercio exterior

# Preguntas a Explorar - Bolívia

- Posibilidad de aumentar producción a corto, mediano, y largo plazo
- País con mucho potencial agrícola, con bajo nivel de población (11 millones)
- Oportunidad del sector cañero en un sistema de regulación resistente en otros cultivos (ej. maíz).
- Posiblemente más aceptación de un producto desarrollado dentro de la región, que por compañia transnacional
- Creciente avance en incentivos para adoptar la biotecnología
- Sistema regulatorio avanzando positivamente para GeD
- Superación de las barreras existentes y intercambio
  - Muchos productores y empresas brasileras en Bolivia

# Innovación: Part de La Solución

"This situation **opens a tremendous opportunity to both Brazil and the rest of the Latin American region to re-visit their own internal energy programs**, **and put in place the necessary investments** that will lead to more efficient and highly productive food and energy systems. This packaging' of policy to address both the food and energy sector is a strategy that was followed by Brazil, since the early 1970s, which has resulted in its position as a net exporter of both major energy and food commodities. There is an example in that, to be followed by other Latin American countries – as well as **important lessons to be learned, in terms of how environmental concerns can be better protected, and land use policies more effectively implemented**"

Fuente: Biofuels and Rural Economic Development in Latin America and the Caribbean, FAO y IBD. 2010.

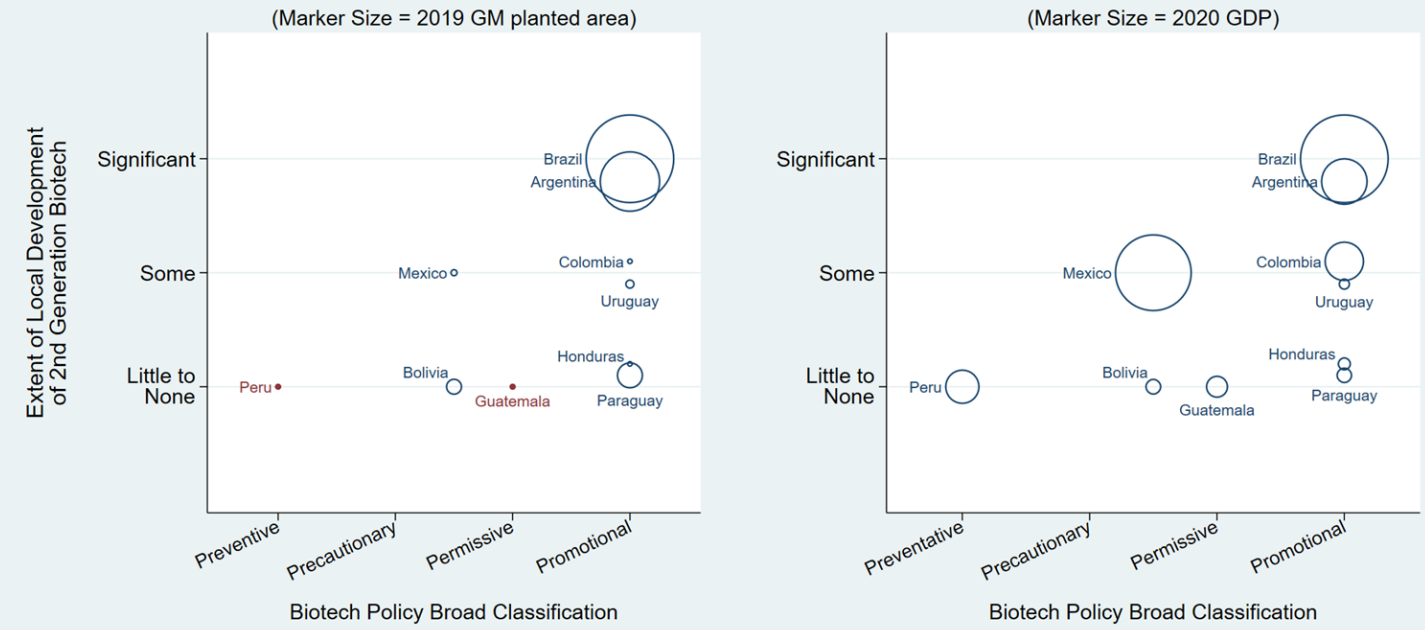
# Caso de Estudio:
# Edición Génica en Caña de Azúcar

## Preguntas al equipo

# Discusión sobre la evaluación de necesidades e identificación de áreas de inversión

**Michael Jones**
Profesor Asistente de Economía
Universidad de Alaska-Anchorage
EE.UU.

# Rich diversity in the region with respect to economic development, regulatory environments and local biotech development efforts




Sources: Planted Area via ISAAA; GDP via World Bank; Policy Category names via Paarlberg (2000)

# Investing in Knowledge and Technology Production Processes

- **Formal workforce training**
  - National, regional and international (non-regional) universities
  - Upskilling
  - Capacity building

- Many smaller and less-developed countries rely on LATAM regional training programs, particularly Brazil, Argentina, Mexico, Colombia (CIAT)
  - Stated needs for financially supporting students to travel within the region or abroad for training.
  - Note: past leadership of Zamorano University in Honduras in agricultural training, but notable absence in the biotechnology space

# Investing in Knowledge and Technology Production Processes

- **Regulators** in countries with established gene editing procedures (notably Brazil, Argentina, Honduras, Uruguay) generally felt they possessed the human capacity to conduct risk assessments and evaluations
- Support requested for expanded regional collaboration between countries
  - Existing coordination/collaboration between high-level regulators and developers from MERCOSUR
    - Expansion or replication potential across other regions?
  - IICA clearly an important player, carries high regard among many interview participants, with ongoing courses
    - Directly resulting in key position docs (2018 WTO statement)
  - Inclusion of regulator bodies and senior ministry, political figures

[CIAT / Zamorano, iGEM]

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Inter-American Development Bank

# Investing in Knowledge and Technology Production Processes

- **Regulators**, even within countries with developed regulatory structures for gene-edited products, still differ in procedures for prior consultation or post-review for GMO vs. conventional designation
  - Publicly available web databases for firms and application details - omitting CBI - exist in some cases (e.g. Brazil) but remain private in others (e.g. Honduras, Argentina).

  [ IICA courses requested - 2018 WTO statement on gene editing harmonization]
- Given successful collaboration on initial policy formation, investments could expand cross-country collaboration and further harmonization on prior- and post-consultation processes, and disclosure protocols

[Mercosur]

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# Investing in Knowledge and Technology Production Processes

- **Regulators**, even within countries with developed regulatory structures for gene-edited products, still differ in procedures for prior consultation or post-review for GMO vs. conventional designation

- Honduras is recognized by many developers to have an expedited and low-friction review processes
  - Described as a regional site to test regulatory status and agronomic potential of new products

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# Business Landscape Development for New Biotechnologies

- **Profound differences in the size and scope of local labor markets to absorb trainees. Classic concerns of brain drain, weaker labor markets for specialized training. Compounding difficulty with underlying economic uncertainty in many countries.**
- Brazil:
  - 237 biotech enterprises (including ~35 animal health, ~24 agriculture, ~19 in bioenergy) [*Source: Br-Biotec (2019)]*
  - Less confidence in academic market: “public universities aren't opening new positions” and lack translational funding for commercialization, technology transfer [interviews]
- Honduras:
  - “Somebody goes abroad [to train in biotechnology] and they're afraid to come back because they think they won’t have anything to do… we don’t have the critical mass of scientific trained people to put them to work”

# Business Landscape Development for New Biotechnologies

- **Profound differences in the size and scope of local labor markets to absorb trainees. Classic concerns of brain drain, weaker labor markets for specialized training. Compounding difficulty with underlying economic uncertainty in many countries.**

- Argentina:
  - Growing local developer landscape with start-up presence
    - 66% [of 25] of GeD prior consultations submitted 2015-2021 were local (Goberna *et al.*, 2022)
  - "Argentine Biodevelopment Initiative", reducing information cost burdens for local developers, virtual outreaches & quick info form
  - Valuable experience to communicate on evolving needs

# Business Landscape Development for New Biotechnologies

- **Profound differences in the size and scope of local labor markets to absorb trainees. Classic concerns of brain drain, weaker labor markets for specialized training. Compounding difficulty with underlying economic uncertainty in many countries.**

- Uruguay:
  - Less collaboration described between the public and private sector, no GMO products have been locally developed
  - Development of Biotech Center for start-ups, with Korea
  - Lack of infrastructure for firms to 'scale up' – need for improved investment/debt structure to provide opportunities
  - Industry has previously led public sector researchers to prioritize away from biotechnology due to concerns for market acceptance (outside of major row crops; e.g. rice)

# Business Landscape Development for New Biotechnologies

- Licensing considerations are clearly complex and presenting an obstacle to move forward
- Public sector researchers, in particular, use CRISPR-Cas (etc.) nucleases without initially understanding commercialization paths and licensing requirements

- Some large public-private entities have advanced experience navigating licensing and could provide regional leadership (e.g. Embrapa, CGIAR centers)
  - Sponsoring cross-country collaboration focused on academic/public product translation could be impactful

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# (Some) major themes where needs arise:

- Expansion of **student training** opportunities

- Enhanced **cross-country collaboration** in:
  - Prior and post-consultation review procedures and disclosure protocols, tools for reducing information cost burdens
  - Expanding and coordinating **data sharing/recognition agreements** on biosafety and agronomic performance, where feasible and applicable
  - Anticipation of **licensing requirements**, optimal timelines for engagement, particularly for public entities

- Consider expansion of bio-developer centers, with **support for investment recruitment**, showcasing, and facilitation of scaling up of SMEs

# Needs Assessment and Investment:

# Question and Answer

# Next Steps and Concluding Thoughts

# ¡Gracias por su participación!

- Equipo
- IDB

Sitio de web del proyecto:
https://research.ncsu.edu/ges/research/idb-crispr/#top

Preguntas o comentarios enviar email para:
gescenter+idb@ncsu.edu