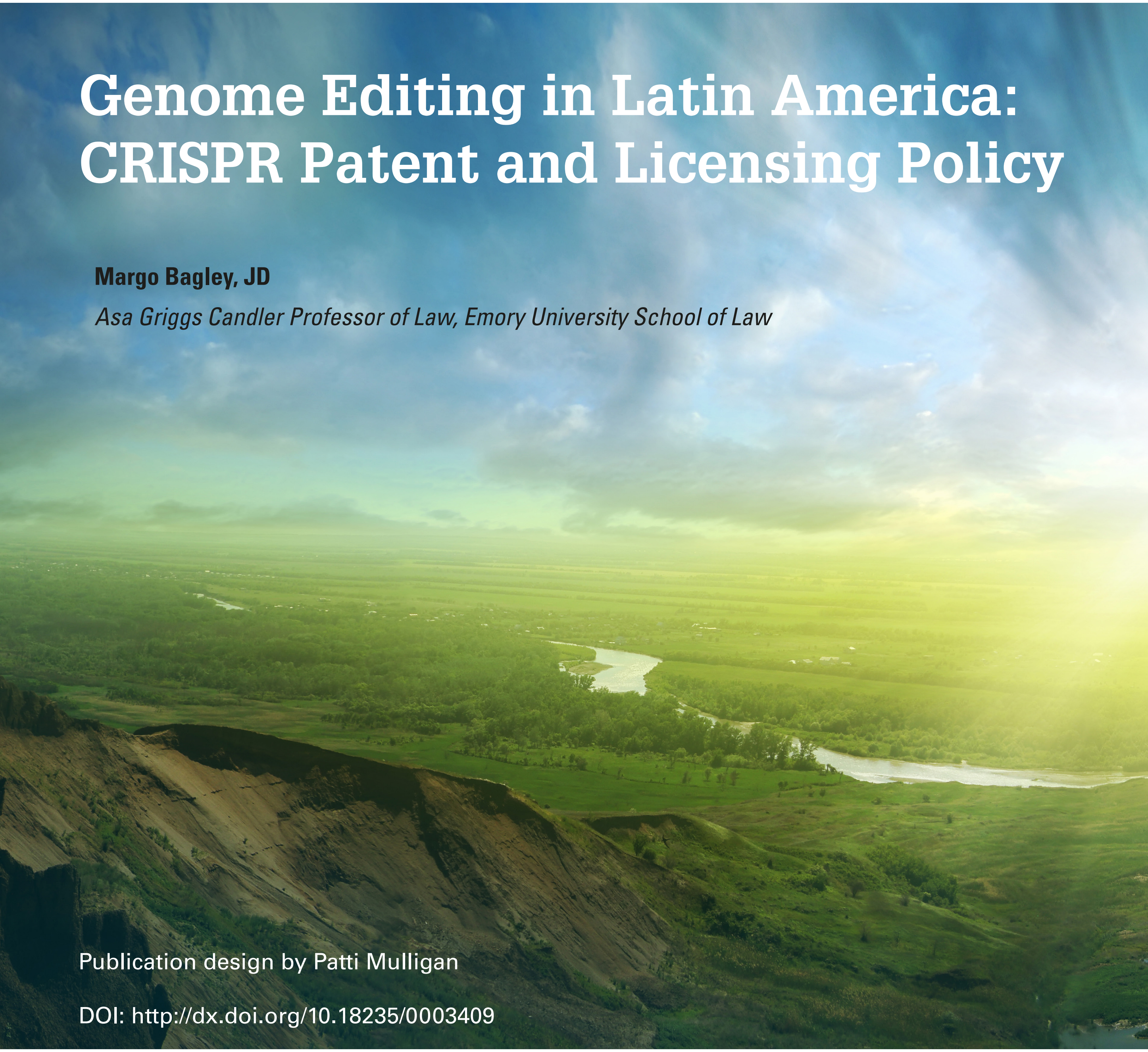

# Genome Editing in Latin America: CRISPR Patent and Licensing Policy

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Genetic Engineering and Society Center, NC State University

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# Foreward

The power and promise of genome editing, CRISPR specifically, was first realized with the discovery of CRISPR loci in the 1980s.[i] Since that time, CRISPR-Cas systems have been further developed enabling genome editing in virtually all organisms across the tree of life.[i] In the last few years, we have seen the development of a diverse set of CRISPR-based technologies that has revolutionized genome manipulation.[ii] Enabling a more diverse set of actors than has been seen with other emerging technologies to redefine research and development for biotechnology products encompassing food, agriculture, and medicine.[ii] Currently, the CRISPR community encompasses over 40,000 authors at 20,000 institutions that have documented their research in over 20,000 published and peer-reviewed studies.[iii] These CRISPR-based genome editing tools have promised tremendous opportunities in agriculture for the breeding of crops and livestock across the food supply chain. Potentially addressing issues associated with a growing global population, sustainability concerns, and possibly help address the effects of climate change.[i] These promises however, come along-side concerns of environmental and socio-economic risks associated with CRISPR-based genome editing, and concerns that governance systems are not keeping pace with the technological development and are ill-equipped, or not well suited, to evaluate these risks.

The Inter-American Development Bank (IDB) launched an initiative in 2020 to understand the complexities of these new tools, their potential impacts on the LAC region, and how IDB may best invest in its potential adoption and governance strategies. This first series of discussion documents: "Genome Editing in Latin America: Regulatory Overview," and "CRISPR Patent and Licensing Policy" are part of this larger initiative to examine the regulatory and institutional frameworks surrounding gene editing via CRISPR-based technologies in the Latin America and Caribbean (LAC) regions. Focusing on Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, and Uruguay, they set the stage for a deeper analysis of the issues they present which will be studied over the course of the next year through expert solicitations in the region, the development of a series of crop-specific case studies, and a final comprehensive regional analysis of the issues discovered.

—**Todd Kuiken,** Senior Research Scholar,
Genetic Engineering and Society Center, NC State University

i. Anzalone, A. V., Koblan, L. W. & Liu, D. R. Genome editing with CRISPR–Cas nucleases, base editors, transposases and prime editors. *Nat. Biotechnol.* **38**, 824–844 (2020).

ii. Kuiken, T., Barrangou, R. & Grieger, K. (Broken) Promises of Sustainable Food and Agriculture through New Biotechnologies: The CRISPR Case. *Cris. J.* **1–7** (2021). doi:10.1089/crispr.2020.0098

iii. Huang, Y., Porter, A., Zhang, Y. & Barrangou, R. Collaborative networks in gene editing. *Nat. Biotechnol.* **37**, 1107–1109 (2019).

# GENOME EDITING IN LATIN AMERICA: CRISPR PATENT AND LICENSING POLICY

**Margo Bagley, JD**

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## I. INTRODUCTION

Genome-editing using CRISPR-Cas technologies offers the potential to both address many of the world's disease and food security issues and be lucrative at the same time. As such, it is not surprising that increasing numbers of patent applications are being filed by a growing number of entities on CRISPR-related inventions. According to the IP Studies database, there are more than 8100 CRISPR patent families worldwide as of January 30, 2021, 1400 of which are directed to plant agricultural advances involving plant organisms and cells.[1]

Patents grant their owners the right to exclude others from making, using, selling, offering to sell, or importing the patented invention during the ~20-year term of the patent. However, patent rights are territorial, so inventors must seek patents in each country/region where they desire protection. Claimed inventions also must generally be examined for novelty, inventive step, adequate description, and subject matter eligibility before a utility patent will issue. Thus, claim scope may differ by country due to differences in examination processes and substantive laws.

In the CRISPR space, this has led to a patchwork of patents with sometimes differing claims depending on the jurisdiction. Thus, companies wishing to use foundational CRISPR tools for agricultural gene editing purposes will likely need to navigate a complex and dynamic patenting landscape which may involve obtaining licenses from multiple entities.

The goal of this discussion document is to provide an overview of the CRISPR plant agriculture patent landscape, as well as to identify and describe key licensing protocols for Latin American companies and institutes interested in engaging in CRISPR plant agricultural research. Part II describes the numbers and locations of CRISPR plant agriculture-related patents being pursued in the Latin American countries of interest for this study (Argentina, Bolivia, Brazil, Colombia, Honduras, Mexico, Paraguay, Peru, Uruguay) as well as the organizations behind the filings. Part III identifies the holders of foundational CRISPR plant agriculture-related patents and describes their general licensing protocols necessary for deploying the technology in the region. The brief concludes by noting that the CRISPR plant agriculture patent landscape is changing rapidly, and it will be incumbent on researchers to regularly assess the need for licenses from other entities.

1 CRISPR patent statistics provided in this discussion document were obtained from the IP Studies CRISPR database, a fee-based service that tracks the filing and grant of patents relating to CRISPR genome editing worldwide. See https://www.ipstudies.ch/crispr-patent-analytics/.

# II. CRISPR PATENT FILINGS

It is widely accepted that the discovery of the CRISPR-Cas9 genome editing system has revolutionized plant agricultural research.[2] As shown in Figure 1, the relative ease of use, efficiency, 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.[3] Moreover, genome editing can reduce by half the time it takes to develop an improved trait: from 8-12 years with conventional crossbreeding, mutation breeding, or transgenic breeding, down to 4-6 years with CRISPR tools.[4]

CRISPR-Cas9, has dominated work in this area, with researchers developing and using a plethora of Cas9 protein variants and applications, including base editing, in various plants.[5] However, early community-wide focus on CRISPR-Cas9 has led to many competing and overlapping patents creating licensing and freedom to operate (FTO) concerns.[6] This has contributed to researchers investigating alternatives, like CRISPR-Cas 12 a & b, 13, and 14 and CRISPR-Cms1, and MAD7 for genome editing applications.[7] Several such CRISPR nucleases have the potential to be useful in plant agriculture and are the subject of further research.[8] Nevertheless, Cas9 in its various forms is by far the most widely used and patented nuclease for CRISPR plant agriculture applications.[9]

2 See, e.g., C.C.M. van de Wiel, New traits in crops produced by genome editing techniques based on deletions, *Plant Biotechnol. Rep.* (2017) 11:1-8; Naoki Wada et al., Precision genome editing in plants: state-of-the-art in CRISPR/Cas9-based genome engineering, *BMC Plant Biology* (2020) 20:234;

3 See, e.g., Kunling Chen et al, CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture, *Annu. Rev. Plant Biol.* (2019), 70:667-97, (detailing traits); Corteva Agriscience, How CRISPR Works in Agriculture, https://crispr.corteva.com/wp-content/uploads/2020/12/FINAL_Corteva-How-CRISPR-Works-Infographic_12.01.2020.pdf (detailing traits).

4 See Kunling Chen et al, CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture, *Annu. Rev. Plant Biol.* (2019), 70:667-97 (Figure 1).

5 See, e.g., Naoki Wada et al., Precision genome editing in plants: state-of-the-art in CRISPR/Cas9-based genome engineering, *BMC Plant Biology* (2020) 20:234 ("the simplicity, ease, and high efficiency of the CRISPR/Cas9 system have facilitated its development into the most widely applied genome-editing tool"); Haocheng Zhu, Chao Li, and Caixia Gao, Applications of CRISPR-Cas in Agriculture and Plant Biotechnology (Supplementary Information), 21 *Nature Rev. Molecular Cell Biology*, (Nov. 2020) (detailing more than 60 applications (across 24+ different crops) of CRISPR-Cas9 for crop improvement since 2018).

6 See, e.g., Marc Doring & Daniel Lim, Questions about CRISPR, (Apr. 2017) www.intellectualpropertymagazine.com, ("After the first few foundational patents, the CRISPR IP landscape will only become more complex—there are now hundreds, if not thousands, of CRISPR-related patent applications filed worldwide, by a wide array of companies. If even a fraction of these applications proceed to grant, we will be faced with an incredibly complex web of patent rights: many different owners holding patents of varying levels of strength and likely validity, with varying overlap and differing global coverage.").

7 See, e.g., Kunling Chen et al, CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture, *Annu. Rev. Plant Biol.* (2019), 70:667-97, (discussing the successful use of CRISPR-Cas 9, Cas12a & b, Cas 13, and Cms1 in plant genome editing). Inscripta MAD7 at https://www.inscripta.com/technology/

8 See e.g., Haocheng Zhu, Chao Li, and Caixia Gao, Applications of CRISPR-Cas in Agriculture and Plant Biotechnology, 21 *Nature Rev. Molecular Cell Biology*, (Nov. 2020); Allen & Overy, Benson Hill Biosystems developing "CRISPR 3.0" system based around Cms1 family of Cas proteins, (Sept. 2017), https://www.allenovery.com/en-gb/global/news-and-insights/publications/benson-hill-biosystems-developing-crispr-3-0-system-based-around-cms1-family-of-cas-proteins.

9 See e.g., Julia Jansing et al., Genome Editing in Agriculture: Technical and Practical Considerations, *Int. J. Mol. Sci.* (2019), 20(12), 2888, ("The most recent addition to the toolbox of programmable nucleases (and the most widely used in plants) is Cas9 from Streptococcus pyogenes (SpCas9), which is part of the CRISPR/Cas9 system").

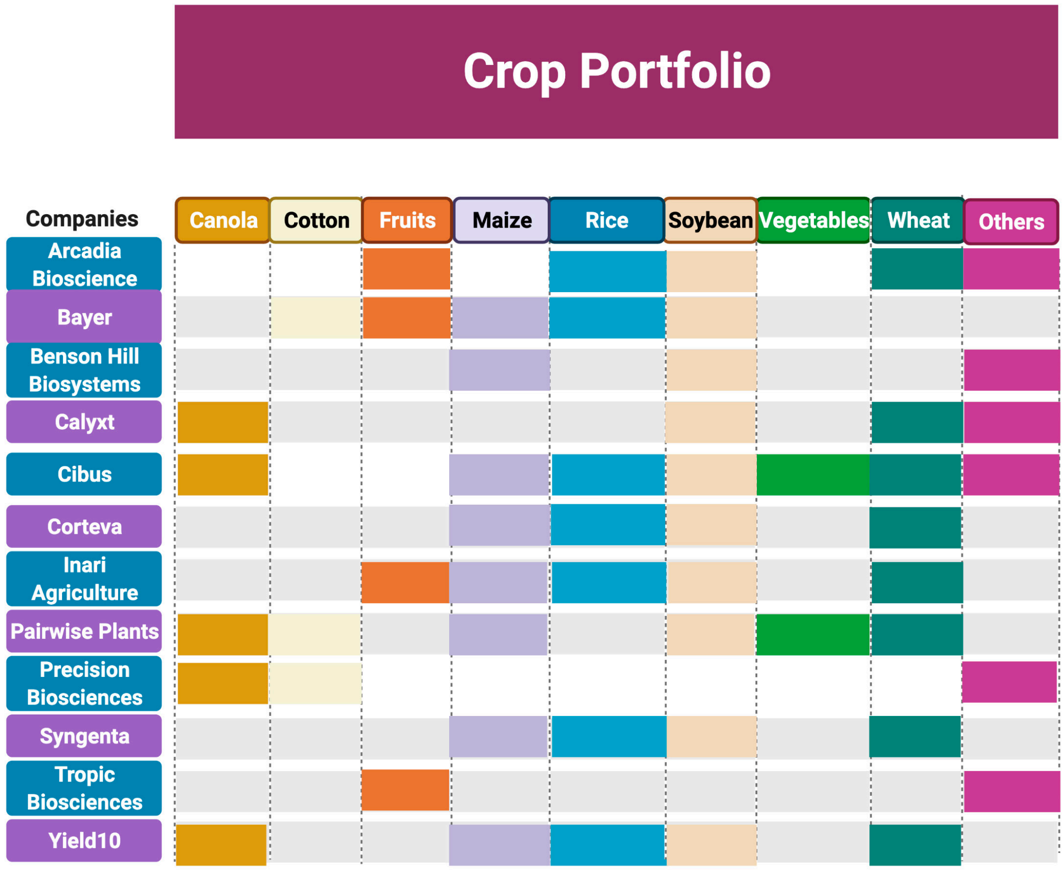


*Figure 1. Crops in which CRISPR-Cas9 Technologies are Being Deployed*[10]

According to the IP Studies CRISPR patent database and as shown in Figure 2, there are more than 1400 patent families worldwide, comprising numerous published patents and patent applications covering the use of CRISPR tools in plant agriculture (e.g. modified plants and/or modified plant cells) and the number of filings have been increasing over time.[11] More than 175 CRISPR plant agriculture patent families exist, comprising at least 300 total published patent applications and/or published patents (patent filings) in at least six of the nine Latin American countries of particular interest to this project, namely, Argentina (65), Brazil (155), Colombia (10), Mexico (51), Peru (2), and Uruguay (17), as shown in Figures 3 through 9.[12] Note that because some of these are applications, they may never actually be granted as patents.

10 See https://ihsmarkit.com/research-analysis/special-reports-gene-editing-technologies-2020.html. The "Other" category includes barley, cucumber, lettuce, potato, sorghum, sunflowers, camelina, and tobacco. See, e.g., Syngenta obtains non-exclusive IP license from Broad Institute for CRISPR-Cas9 genome-editing technology for agriculture applications, (Nov. 2017), https://www.businesswire.com/news/home/20171102005938/en/Syngenta-obtains-non-exclusive-IP-license-from-Broad-Institute-for-CRISPR-Cas9-genome-editing-technology-for-agriculture-applications; and Yield10 Bioscience Signs Research License Agreement Covering CRISPR-Cas9 Genome-Editing Technology with the Broad Institute and Pioneer, (Aug. 2018), https://www.globenewswire.com/news-release/2018/08/08/1548914/0/en/Yield10-Bioscience-Signs-Research-License-Agreement-Covering-CRISPR-Cas9-Genome-Editing-Technology-with-the-Broad-Institute-and-Pioneer.html.

11 A patent family encompasses all patent filings in different countries for one invention. For example, one patent family (1 of 175) could have one individual patent member in Argentina and another one in Brazil like the patent family of WO2019185609 which includes one patent application in Brazil (BR112020017535) and one patent application in Argentina (AR115018). Patent filings are published patents and patent applications. Note that because some of these published documents are applications, they may never actually issue as patents. There is generally an 18-month delay between filing of an application and publication so the numbers for 2019 and 2020 can be expected to rise further.

12 In addition, the database shows Chile (28), Costa Rica (4), and Ecuador (2) also have received CRISPR plant agriculture patent filings.

## Published Patent Applications and Patents

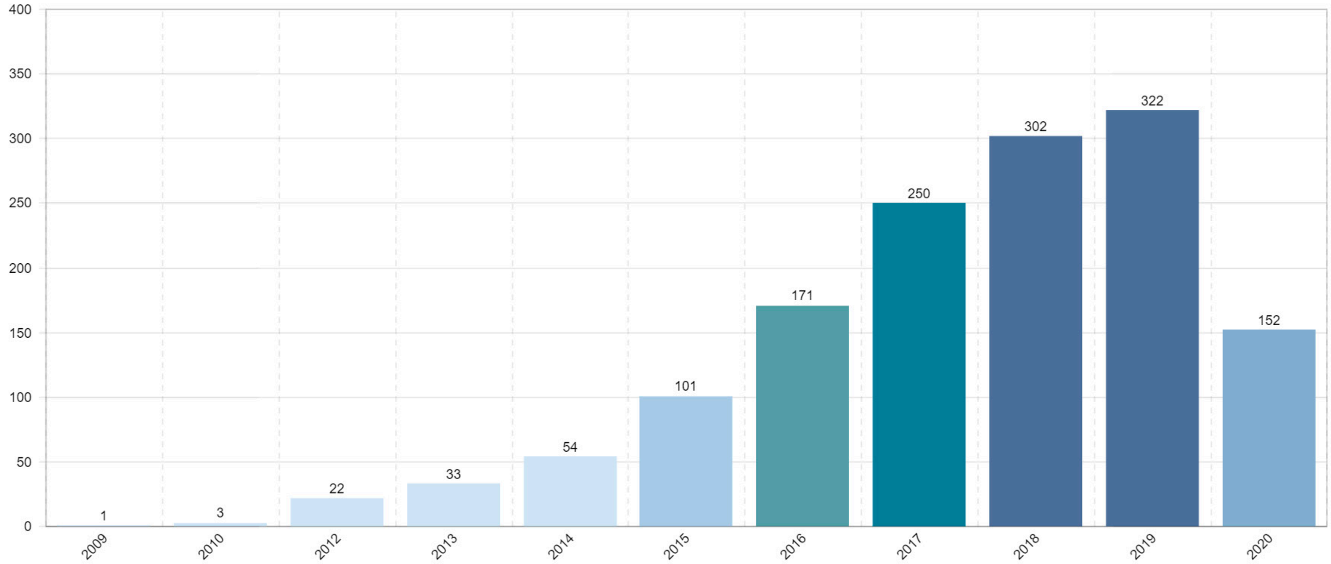


*Figure 2. CRISPR Plant Agriculture Patent Families Worldwide*

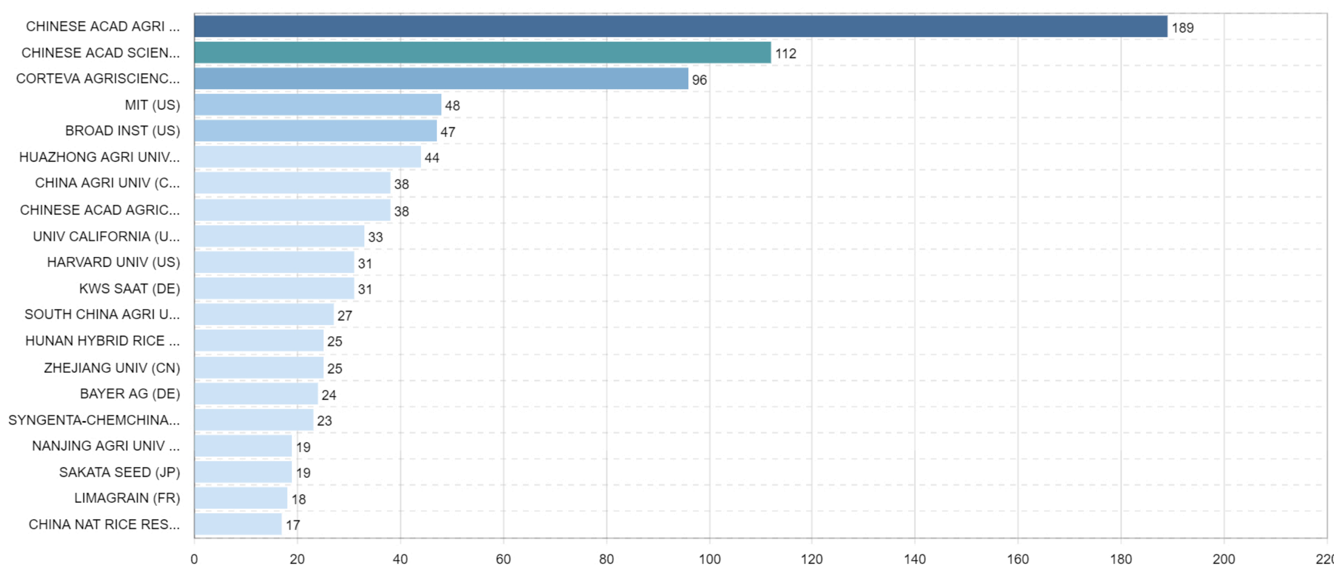


*Figure 3. Top 10 Filers of CRISPR Plant Agriculture Published Patents and/or Patent Applications Worldwide (as of January 2021)*[13]

13 Some patent applications may be affiliated with multiple entities, thus the numbers listed for each entity are not necessarily cumulative to the total number of published applications or patents. https://www.ipstudies.ch/crispr-patent-analytics/. Also, many Chinese patent applications are published without the normal 18-month delay, which may artificially increase their comparative volume at a given point in time. See Jacqueline Martin-Laffon, Marcel Kuntz, and Agnes E. Ricroch, Worldwide CRISPR Patent Landscape Shows Strong Geographical Biases, 37 *NAT. BIOTECH.* 601-621, (Jun. 2019).

# Published Patent Applications and Patents

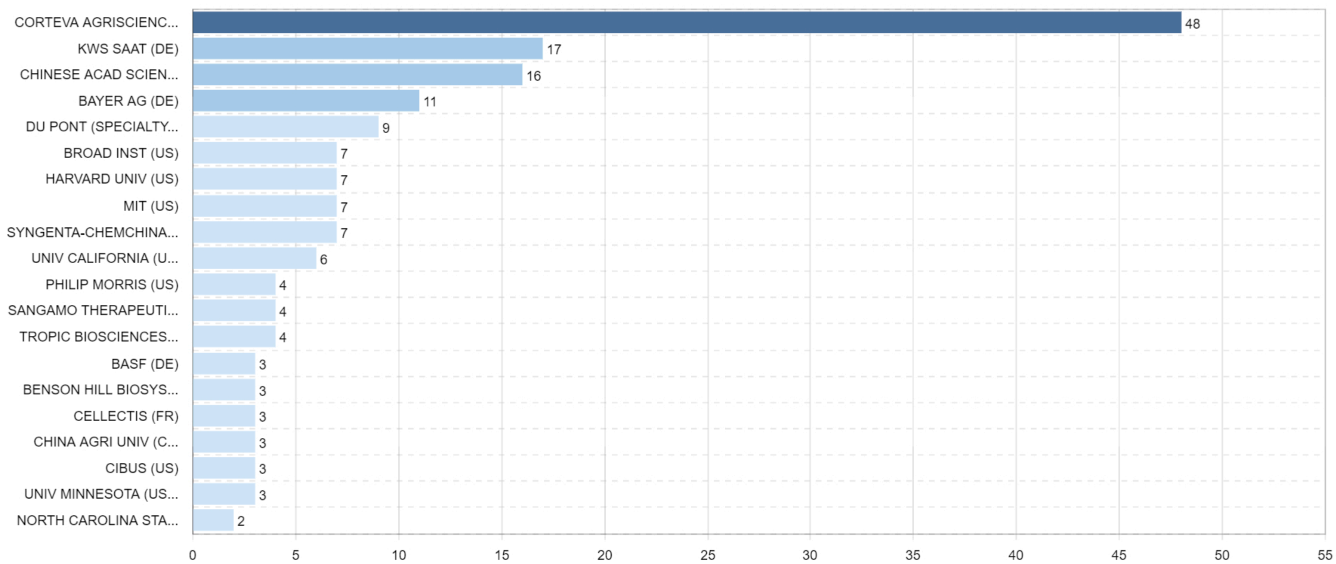


*Figure 4. Top 20 Plant Agriculture Patent Filers in Latin American Countries of Interest*[14]

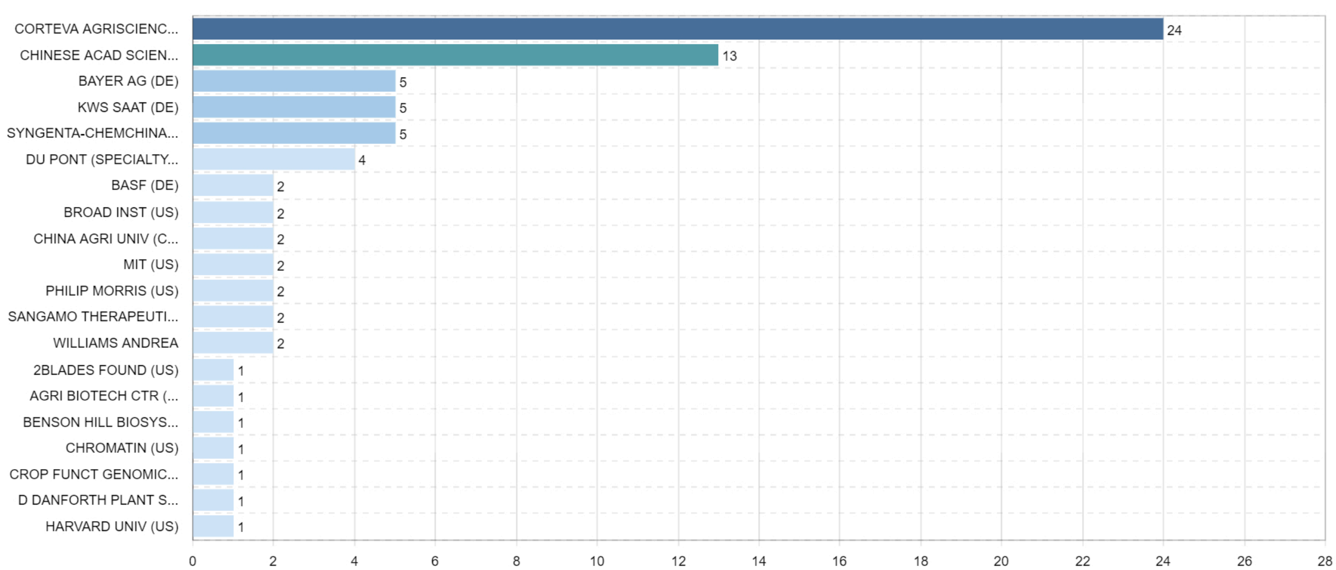


*Figure 5. Top CRISPR Plant Agriculture Patent Filers in Argentina*[15]

14 Ibid.

15 Additional filers/affiliates include Huazhong Agr. Univ. (CN), J.R. Simplot (US), Reynolds Tobacco (US), S.W. Seed Co., Soft Flow (HU), Tianjin Genovo Biotech (CN), Univ. Estadual De Campinas (BR), Univ. Gent (BE), Univ. Laval (CA), Vlaams Inst. Biotech (BE).

# Published Patent Applications and Patents

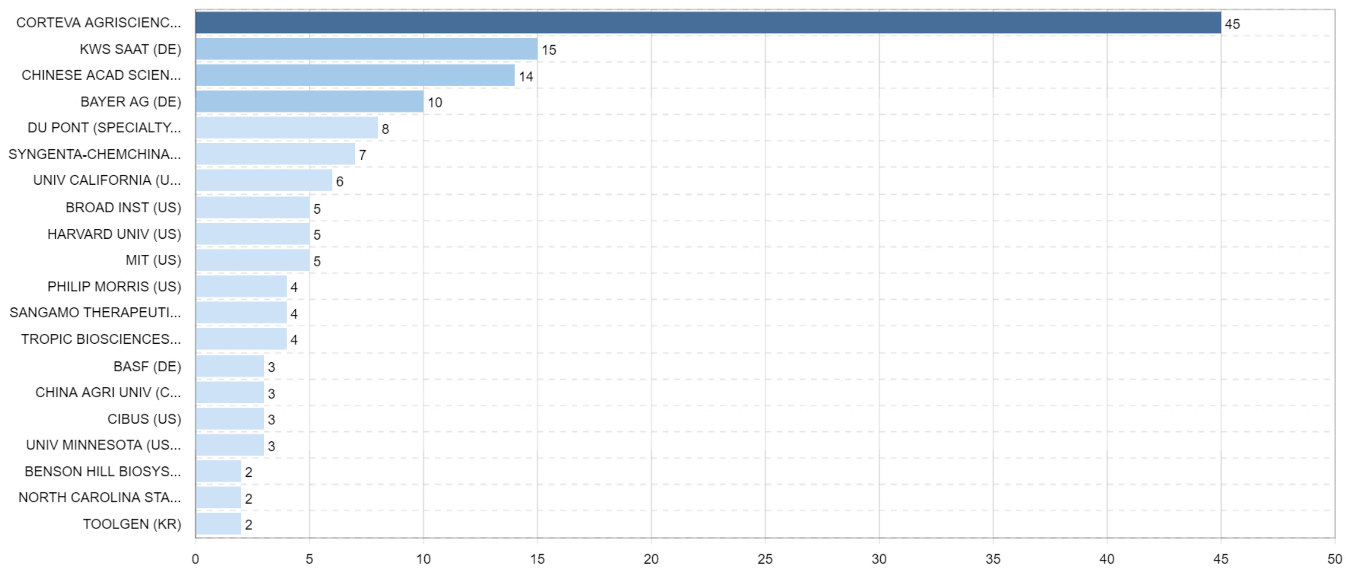


*Figure 6. Top CRISPR Plant Agriculture Patent Filers in Brazil*[16]

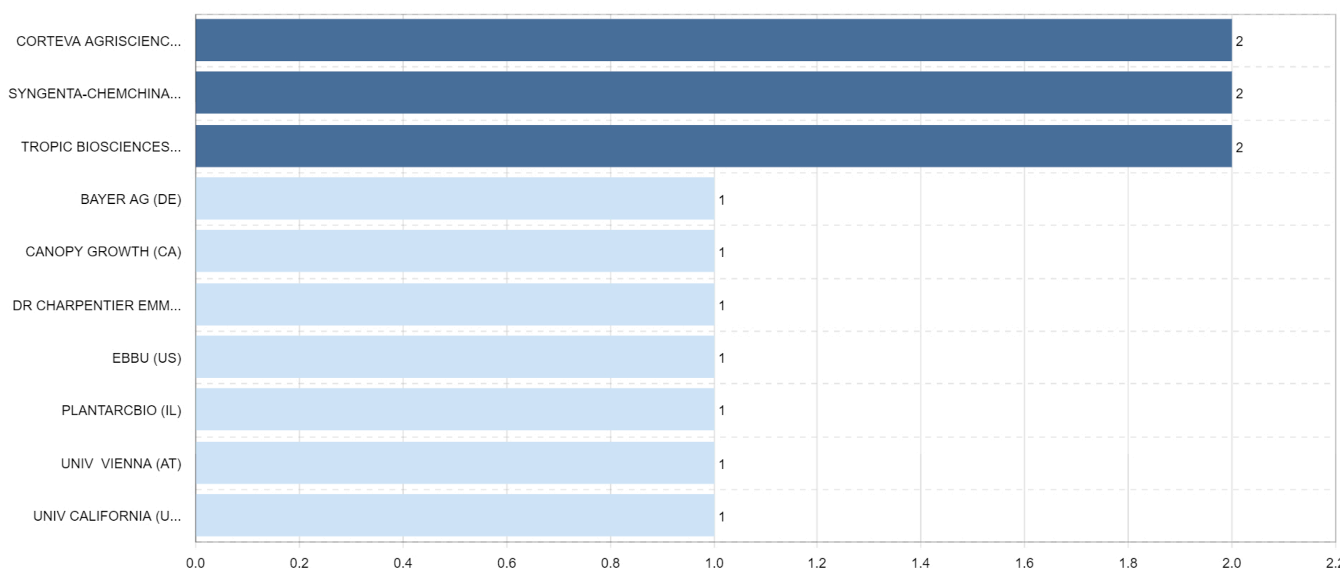


*Figure 7. CRISPR Plant Agriculture Patent Filers in Colombia*

16 Additional applicants/affiliates include Andrea Williams (GB), 2 Blades Found. (US), Agri. Biotech. Ctr. (HU), AICT (KR). Benchbio PVT (IN), Canopy Growth (CA), Cellectis (FR), Ceres (US), China Nat. Rice Res. Inst. (CN), Chinese Acad. Agri. Sciences (CN), Chromatin (US), Crop. Funct. Genomics Ctr. (KR), Dr. Emmanuelle Charpentier (FR), Ebbu (US), Encoded Therapeutics (US), Fed. Univ. Rio De Janiero (BR), Futuragene (IL), Hortigenetics Res. (TH), Huazhong Agri. Univ. (CN), Illumina (US), Inst. Basic Science (KR), Iowa State Univ. (US), Israel State (IL), Japan Tobacco (JP), Keygene (NL), Kobe Univ. (JP), Namdhari Seeds Pvt. (IN), Osaka Univ. (JP), Penn State Univ. (US), Pivot Bio (US), Plantarcbio (IL), Rockefeller Univ. (US), S.W. Seed Co., Seoul Nat. Univ. (KR), Soft Flow (HU), Swetree Tech (SE), Tianjin Genovo Biotech (CN), Tweed (CA), Univ. of Vienna (AT), Univ. of Florida (US), Univ. of Illinois (US), Univ. of Iowa (US), Univ. of Laval (CA), Univ. of Missouri (US), Univ. of Pennsylvania (US), Univ. of Sheffield (UK), U.S. Govt. (US), Weizmann Inst. (IL).

## Published Patent Applications and Patents

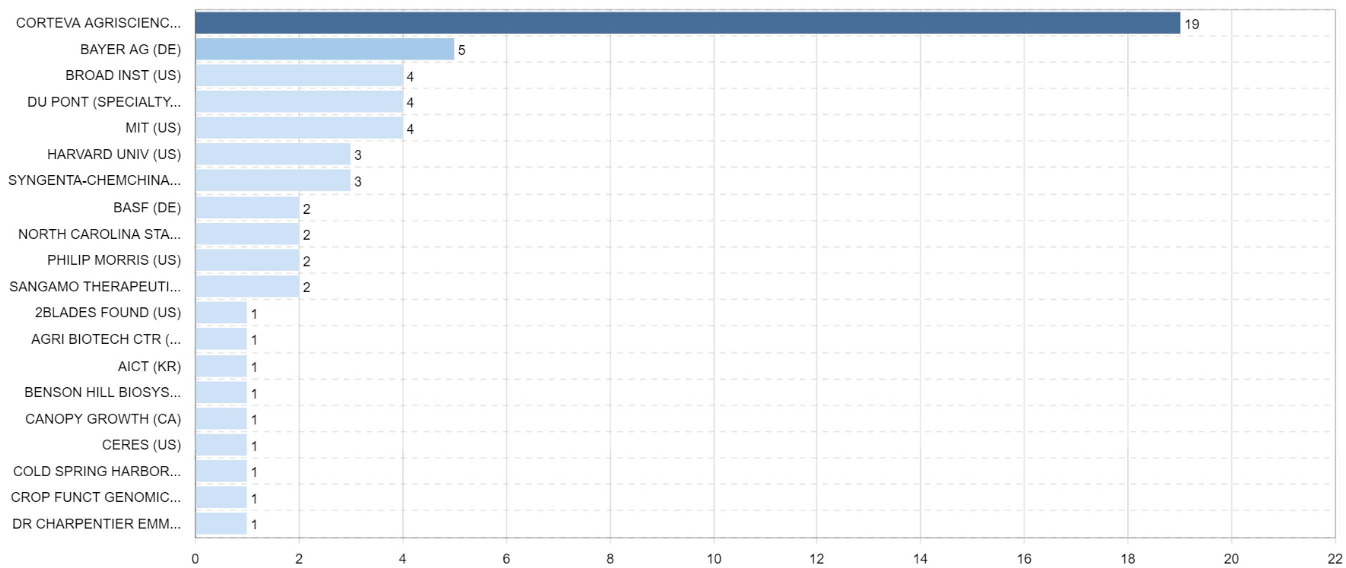


*Figure 8. Top CRISPR Plant Agriculture Patent Filers in Mexico*[17]

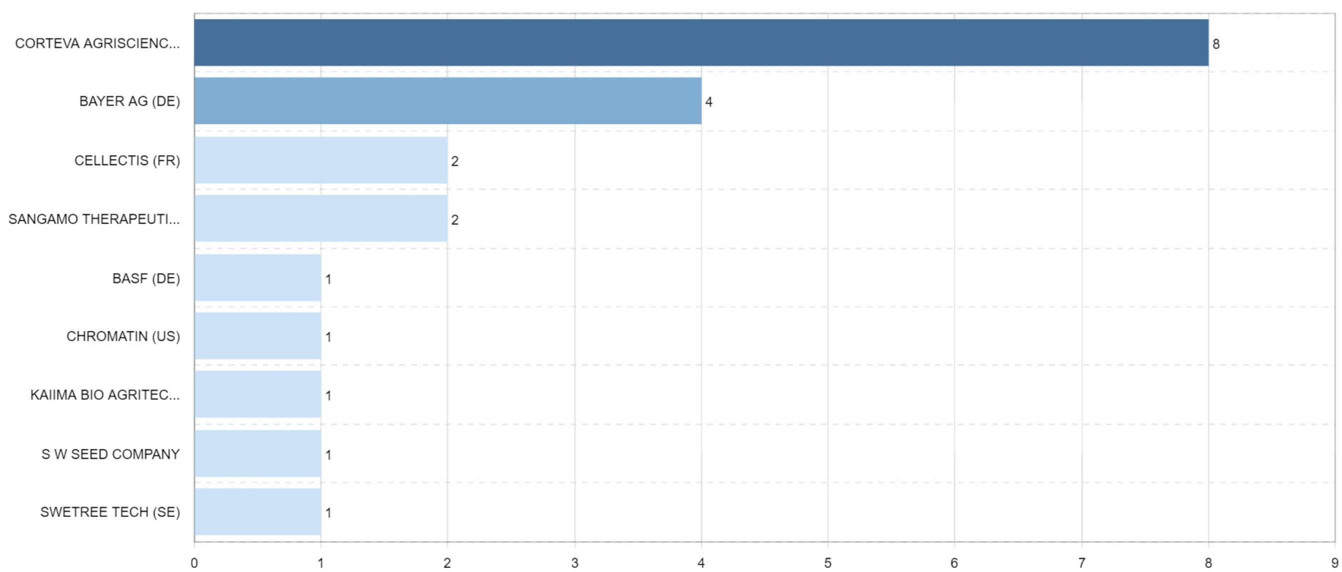


*Figure 9. CRISPR Plant Agriculture Patent Filers in Uruguay*

17 Additional filers (each showing one filing but multiple entities may be affiliated with the same filing) include Ebbu (US), Illumina (US), Inst. Basic Science (KR), Iowa State Univ. (US), Israel State (IL), J.R. Simplot (US), Pivot Bio (US), Plantarcbio (IL), Rijk Zwaan (NL), Seoul Nat. Univ. (KR), Soft Flow (HU), Tweed (CA), Univ. Vienna (AT), Univ. California (US), Univ. Iowa (US), Univ. Minnesota (US).

Obtaining patent protection in multiple countries is expensive and time-consuming. It is thus not surprising that many of the patent applications claiming CRISPR plant agriculture inventions filed in the U.S., for example, have not also been filed in each of the Latin American countries of interest for this study, due to cost or other reasons. For countries in which foundational CRISPR-Cas9 patents have not been filed, it may appear that researchers would be free to use the technology without fear of patent infringement liability. That would, however, be risky, as the inventors/patent owners may have filed other, related applications relevant to CRISPR research in the region.

Moreover, to export agricultural products made using the CRISPR technology to jurisdictions like the U.S, where more patents are in force, would likely require a license. This is because importing a product into the U.S. that was made by a process patented in the U.S. is an act of infringement.[18] It may be difficult for a CRISPR patent owner to confirm that their claimed invention was used to produce a product as opposed to another gene editing tool or natural mutation. However, pursuant to Article 34 of the World Trade Organization's Agreement on Trade Related Aspects of Intellectual Property (TRIPS Agreement), the laws of many countries employ a presumption that may put the burden on the alleged infringer to prove they did not use the claimed invention. As such, obtaining licenses to foundational CRISPR technologies, at a minimum, appears to be the most prudent course of action for entities planning product commercialization.

# III. CRISPR PATENT LICENSING PROTOCOLS

As noted earlier, the numbers of patent applications being filed on CRISPR-related inventions, including in agriculture, are increasing rapidly. Moreover, in most countries, patent applications are not published until 18 months after their earliest effective filing date. Furthermore, patent claims may be broadly written with uncertain scope.[19] All of this means that it simply is not possible to know with certainty all of the possible patent owners one might need to seek licenses from to utilize a particular CRISPR-Cas tool for a particular application.

In addition, researchers using licensed CRISPR tools are also developing and patenting new, non-obvious inventions which would themselves need to be licensed if one desired to use them. Also, there may be other tools (e.g. promoters, agrobacterium delivery vehicles) that facilitate CRIPSR-Cas use that may have patent issues to be navigated. Nevertheless, the following are protocols for some of the major licensors of CRISPR tools for plant agriculture that Latin American researchers are likely to find useful in deploying genome editing in crops. Further information on these licensors, their licensees, and license terms are provided in Figures 10 and 11 and Table 1.

## A. CRISPR-Cas9: Corteva Agriscience (formerly Dow DuPont Pioneer)

Corteva is positioning itself as a comprehensive source for licensing foundational CRISPR-Cas9 patents for plant agriculture.[20] By obtaining the right to sublicense CRISPR-Cas9 patents for agriculture owned or controlled by the Broad Institute, the University of California Berkeley (UC Berkeley), ERS Genomics, Caribou Biosciences, Vilnius University, its own Corteva/Pioneer portfolio, and more,

18 35 U.S.C. §271(g).

19 See Benjamin N. Gray and W. Murray Spruill, CRISPR-Cas9 Claim Sets and the Potential to Stifle Innovation, 35 *Nature Biotech.*, 630 (Jul. 2017).

20 With the Broad Institute's limitation that licensees cannot use the licensed technology to enable gene drives, create terminator (sterile) seeds, or produce tobacco products for human consumption. Issi Rozen, Licensing CRISPR for Agriculture: Policy considerations, https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations.

Corteva can offer interested parties a single license bundle.[21] Corteva licensees thus gain rights to use, in plant agriculture, Cas9 technologies owned by multiple entities. According to the IP Studies CRISPR database, as of January 2021, Corteva alone had filed at least 48 plant agriculture patent applications in the Latin American countries of interest to this study and 96 worldwide.[22]

The bundle license approach is interesting and important because several of the licensors, most particularly the Broad Institute, UC Berkeley and related entities, are engaged in intense patent disputes at the United States Patent & Trademark Office (USPTO) and the European Patent Office (EPO) regarding priority to key aspects of the foundational CRISPR-Cas9 technology.[23] However, because the parties involved in those particular disputes have granted licenses to Corteva for plant agriculture applications, potential licensees need not approach the different entities for separate negotiations on these foundational patents and applications, saving time and enhancing certainty.[24]

Corteva's portfolio of licensable patents and applications includes both foundational CRISPR-Cas9 patents and more recently developed products and methods that rely on Cas9. As its website states "Corteva intends to enable others wanting to develop agricultural products using CRISPR through access to intellectual property, technology capabilities, infrastructure and scientific expertise."[25]

Currently, Corteva offers five types of licenses:

(1) an internal only R&D license;
(2) a commercial seeds and crop trait products license;
(3) a commercial license for other (non-livestock) agricultural products (such as using a plant as a factory to produce therapeutic proteins);
(4) a license to provide CRISPR-Cas9 services; and
(5) a no-cost academic research license.

As of the time of this writing, Type (1) internal only licenses are the least expensive, involving an upfront license issue fee payment and an annual fee that varies based on a company's R&D budget and number of full-time equivalent employees (FTEs). However, if a company later changes direction and wants to develop commercial products with CRISPR, it would need to convert to a more costly Type (2) license.[26] Type (2) commercial licenses generally include the fees for Type (1) plus commercial milestone payments and royalties which vary by crop and market. Type (3) and (4) licenses generally involve Type (1) fees plus royalties based on a percentage of either net sales or of additional revenue generated from utilizing the technology. Not surprisingly, milestone and royalty payments are to be negotiated, and "financial terms of the licenses scale with the size of the third party seeking the license and the addressable market."[27]

21 It should be noted that the license is a three-way license agreement signed by Corteva Agriscience, the Broad Institute, and the licensee.

22 See Figures 3 and 4.

23 As the Broad Institute website describing the disputes notes "this is a complex patent and licensing landscape that threatens innovation." Broad Institute, For Journalists: Statements and Background on the CRISPR Patent Process, (Sept. 2020), https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process.

24 Issi Rozen, Removing a major CRISPR licensing roadblock in agriculture - The Broad Institute of MIT and Harvard announce an agreement that removes a major roadblock that had threatened to limit the potential of CRISPR-Cas9 genome editing to dramatically advance agriculture, *SeedQuest* (Oct. 2017), https://www.seedquest.com/news.php?type=news&id_article=92751&id_region=&id_category=&id_crop=. See also Let MPEG LA Help Solve the CRISPR Puzzle, https://www.mpegla.com/crispr/ (creating a CRISPR patent pool).

25 Corteva Agriscience, Our Promise, https://crispr.corteva.com/our-promise-crispr-cas-corteva-agriscience/.

26 See https://www.globenewswire.com/news-release/2018/08/08/1548914/0/en/Yield10-Bioscience-Signs-Research-License-Agreement-Covering-CRISPR-Cas9-Genome-Editing-Technology-with-the-Broad-Institute-and-Pioneer.html ("The joint license covers intellectual property consisting of approximately 48 patents and patent applications on CRISPR-Cas9 technology controlled by the Broad Institute and Pioneer. Under the agreement, Yield10 has the option to renew the license on an annual basis and the right to convert the research license to a commercial license in the future, subject to customary conditions as specified in the agreement."). There are indications that entities obtaining Type 1 licenses may later be able to negotiate more favorable terms.

27 Corteva Agriscience, CRISPR-Cas, https://openinnovation.corteva.com/crispr-cas/.

The foundational CRIPSR-Cas9 patents and patent applications owned by the Broad Institute and UC Berkeley and licensed by Corteva, contain broad claims that appear to cover use of any of the many CRISPR-Cas9 nucleases in eukaryotic (and prokaryotic) organisms. However, a 2017 article by two Benson Hill Biosystem researchers questions the validity of some of the claims in the foundational UC Berkeley and Broad Institute patents and applications in view of the written description and enablement requirements of U.S. patent law.[28] According to the authors, the inventors' genome editing success at the time of filing the applications was with specific SpCas9 (UC Berkeley) and SaCas9 (Broad Institute) nucleases, but it has since been shown that many Cas9 orthologs have low sequence identity to SPCas9 and SaCas9. Such orthologs also may have different biochemical properties and thus may not be similarly effective in genome editing.[29]

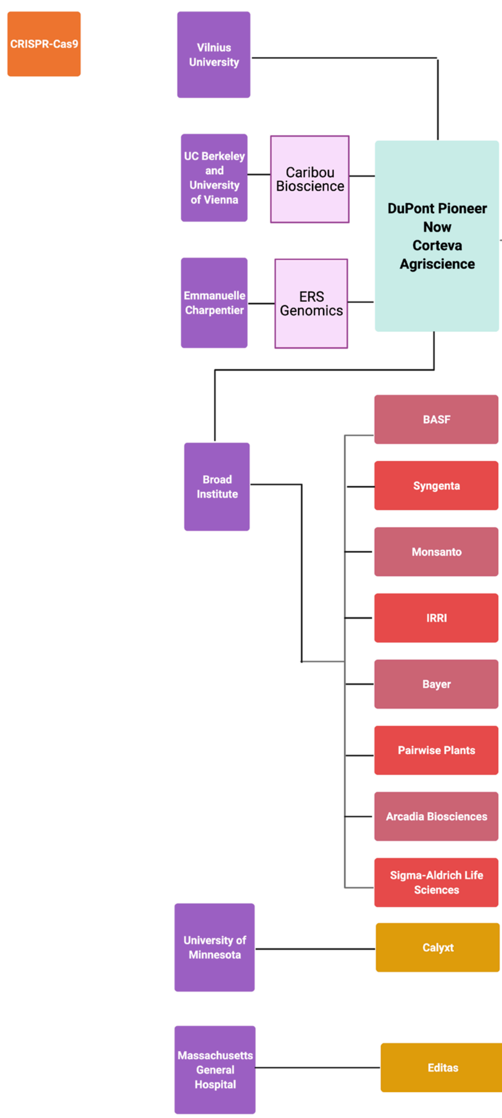


*Figure 10. Reported CRISPR-Cas9 Licenses in Plant Agriculture*[30]

28 Benjamin N. Gray and W. Murray Spruill, CRISPR-Cas9 Claim Sets and the Potential to Stifle Innovation, 35 *Nature Biotechnology* 630 (Jul. 2017) ( Noting that "the broadest claims made by the Broad Institute are drawn to 'a nucleotide sequence encoding a Type-II Cas9 protein' while the broadest claims made by UC Berkeley recite 'a Cas9 protein.'").

29 See F. A. Ran et al., In vivo genome editing using Staphylococcus aureus Cas9, *Nature*, 2015 Apr 9;520(7546):186-91. doi: 10.1038/nature14299.

30 See https://ihsmarkit.com/research-analysis/special-reports-gene-editing-technologies-2020.html; see also https://www.ipstudies.ch/crispr-patent-analytics/. The IP Studies database also shows CRISPR-Cas9 plant agriculture patent licenses From Toolgen to Thermo Fisher Scientific and Monsanto

Nevertheless, issued patents are presumed valid, and unless and until any of the patents are actually challenged and invalidated, entities seeking to use any CRISPR-Cas9 nucleases in plant agriculture genome editing applications would appear, at a minimum, to need a license from Corteva Agriscience or risk a lawsuit for patent infringement.[31] Moreover, while necessary, such a license may not be sufficient: a number of entities outside of Corteva have also filed for patents on CRISPR-Cas9 inventions, as have some licensees of CRISPR-Cas9 foundational patents. As such, assessing freedom to operate before commercializing inventions developed using CRISPR tools is advised.

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

While interested parties can license the Broad Institutes' Cas9 nucleases through Corteva for plant agricultural uses, they also can approach Broad directly for CRIPSPR/Cas9, Cas12a, and Cas12b licenses.[32] Cas12a, originally named CRISPR/cpf1, is generating increasing interest for plant agricultural uses. The Broad Institute licenses each of its nucleases separately, largely because each family of patents has a different set of co-owners based on varying inventor collaborations.

The Broad Institute structures its plant agriculture licenses similarly to Corteva and provides the same five non-exclusive license types.[33] The Broad's license terms also generally involve an upfront fee, annual fee based on total FTEs, and, for commercial trait and seed development, milestone and royalty payments. Trait milestones are assessed trait by trait and by crop species. So, for example, if a particular trait is developed for corn and also for tomatoes, milestone payments would be due for each crop and would differ based on the difference in the size and value of the crop market. Trait royalty payments are normally based on either net trait revenue or net sales.

Whether licensing directly from the Broad Institute or through Corteva, licensees must agree to abide by the Broad Institute's limitation that the licensed technology cannot be used to enable gene drives, create terminator (sterile) seeds, or produce tobacco products for human consumption.[34] As with Corteva, researchers at the Broad are continuing to develop innovative new genome editing nucleases and approaches so it is likely that additional technologies may be available for licensing in the future.

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(Bayer), Kobe Univ. to Bio Palette, Cellectis to Calyxt, and Penn State Univ. to an undisclosed ag company.

31 Ibid. (Quoting one of the UC Berkeley inventors, Nobel prize winner Dr. Jennifer Doudna as analogizing the scope of her invention as compared to that of the foundational Broad Institute patent thusly: "They have a patent on green tennis balls; we will have a patent on all tennis balls." The authors further note that "if the broadest UC Berkeley claims currently under examination issue as written, a researcher wishing to use Cas9 would need a license not only to the Broad Institute patent rights but also to the UC Berkeley rights. This situation would apply equally if a researcher wished to use SpCas9 or a distantly related Cas9 ortholog with very little sequence identity with SpCas9.")

32 As well as any other nucleases for which the Broad has obtained patent protection and is granting licenses including base editors and prime editors such as those from Dr. David Liu's lab. See Ryan Cross, David Liu unveils a search and replace CRISPR tool and a start-up to commercialize it, *Chem. & Engr. News*, Vol. 97, Is. 42 (2019).

33 Other non-standard licenses may be negotiated as well. The Broad Institute licenses non-exclusively for agricultural uses, but exclusively to Editas Medicine for human therapeutics.

34 Issi Rozen, Licensing CRISPR for Agriculture: Policy considerations, https://www.broadinstitute.org/news/licensing-crispr-agriculture-policy-considerations.

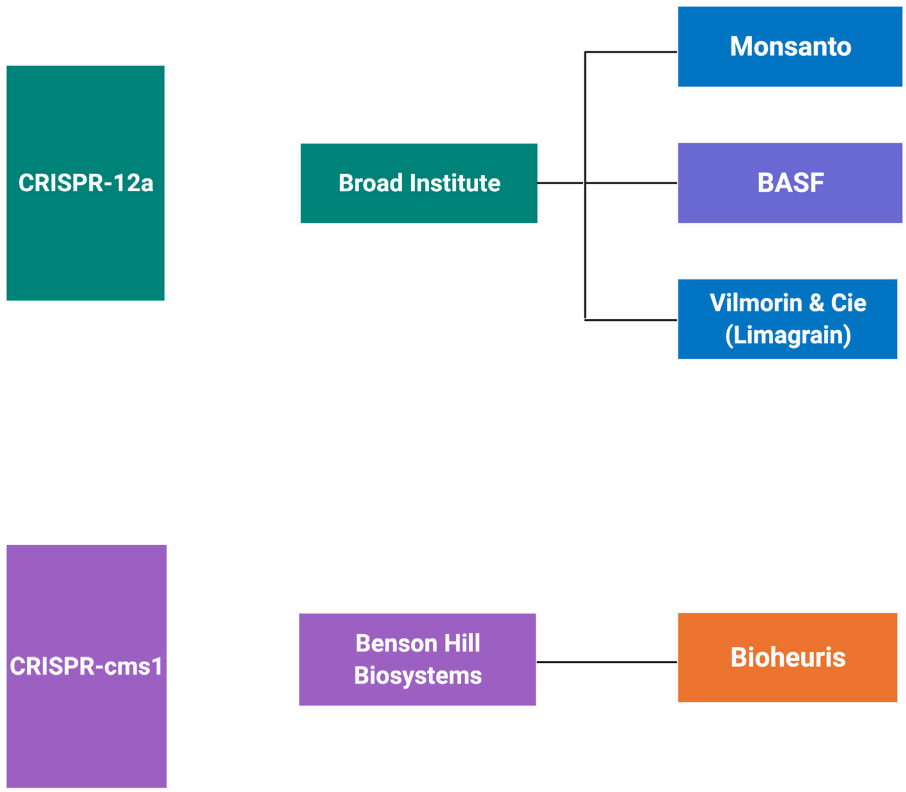


*Figure 11. Reported CRISPR-12a and CRISPR-Cms1 Licenses in Plant Agriculture*[35]

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

Benson Hill Biosystems (Benson Hill) has positioned itself as a provider of a viable, cost-effective alternative to CRISPR-Cas9 and CRISPR-Cas12a & b with its suite of Cms1 effector proteins it calls "CRISPR 3.0".[36] These Cms1 proteins are only 10-15% identical to Cas9 at the amino acid level. One key benefit of Cms1 nucleases is their smaller size, which provides a more compact system for precision genome editing. According to the company:

> Benson Hill's patented portfolio of the CRISPR Cms1 family represents a major expansion of the genome editing toolbox that is currently available to researchers. Specifically, CRISPR Cms1 nucleases are smaller than most CRISPR Cas9 and Cpf1 nucleases and have a simple RNA structure, significantly streamlining delivery of core genome editing reagents.[37]

By steering clear of the patent battles and dense patent landscape surrounding CRISPR-Cas9 and its many applications, Benson Hill licensees can, it is presumed, develop effective genome edited products at a lower cost and with greater clarity regarding patent rights. This makes CRISPR-Cms1 nucleases a competing technology to CRISPR-Cas9 and 12a & b that LAC researchers are exploring.[38]

35 See https://www.ipstudies.ch/crispr-patent-analytics/.

36 See Benson Hill Biosystems receives patent for novel CRISPR technology, EurekAlert (Feb. 2018), https://www.eurekalert.org/pub_releases/2018-02/bhb-bhb022018.php.

37 See Benson Hill Biosystems CRISPR Cms1 portfolio, https://bensonhill.com/wp-content/uploads/2019/05/CRISPR-Nuclease-Portfolio-General.pdf.

38 See Gregory D. Graff & Jacob S. Sherkow, Models of Technology Transfer for Genome-Editing, *Ann. Rev. Genom. Hum. Genet.* 2020. 21:509–34, 525 (Mar. 2020) ("the more that genome editing diversifies, the more its constituent technologies are likely to diverge rather than interfere and compete with one another. For example, discoveries of new nucleases beyond Cas9 fall outside of the principal patent dispute. More types of genome-editing technologies, espe-

| 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 |

*Figure 12.Benson Hill Biosystems CRISPR Cms1 portfolio[39]*

Benson Hill has developed and tested at least five different Cms1 nucleases, four of which are shown in Fig. 12, and all of which have the potential to generate target mutations across multiple plant crop species, with primary testing having been performed initially in rice.[40] As a smaller company, Benson Hill takes a very flexible approach to licensing based on the size, type, and needs of the potential licensee. Licenses may involve one large upfront fee, milestone payments, and/or royalty payments. The agreements are individually negotiated to arrive at a reasonable license option tailored to the economic realities of the different crop markets involved.

Interestingly, Benson Hill's first publicly announced license in 2018 was to a start-up in Argentina, Bioheuris. According to the CEO and co-founder of Bioheuris, Carlos Perez:

> "For decades, advanced genomics R&D was limited to just a handful of large multi-national companies working on just a few crops… Benson Hill's CRISPR 3.0 technology equips our scientists to develop the herbicide-tolerance targets farmers need using faster, less costly non-GMO methods. The ability to access such cutting-edge science through a truly fair and equitable partnership is the model our industry needs to bring real choice and profitability to farmers.[41]"

Based in Argentina's Rosario Agbiotechnology Institute, Bioheuris is focused on using genome editing to develop herbicide tolerant soybean, sorghum and wheat crops for its strategic partnership with Rotam CropSciences Ltd., a Hong Kong-based crop protection company.[42]

## D. Chinese Research Entities

As shown in Figure 3, Chinese entities currently file the largest number of CRISPR plant agricultural patents worldwide, with the leading filer being the Chinese Academy of Agricultural Sciences, a state-owned entity. As of this writing, no reports of CRISPR-Cas plant agriculture patent licenses from any of the listed Chinese patent owners have been documented in the IP Studies database or through independent search in the Chinese language.

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cially where they are interchangeable for certain applications, may serve to operate as competing tools").

39 "Benson Hill's patented portfolio of the CRISPR Cms1 family represents a major expansion of the genome editing toolbox that is currently available to researchers. Specifically, CRISPR Cms1 nucleases are smaller than most CRISPR Cas9 and Cpf1 nucleases and have a simple RNA structure, significantly streamlining delivery of core genome editing reagents." (https://bensonhill.com/wp-content/uploads/2019/05/CRISPR-Nuclease-Portfolio-General.pdf).

40 See Allen & Overy, Benson Hill Biosystems developing "CRISPR 3.0" system based around Cms1 family of Cas proteins, (Sept. 2017), https://www.allenovery.com/en-gb/global/news-and-insights/publications/benson-hill-biosystems-developing-crispr-3-0-system-based-around-cms1-family-of-cas-proteins.

41 eFarm News Argentina, Bioheuris accesses to CRISPR 3.0 technology from Benson Hill Biosystems, (May 2018), https://efarmnewsar.com/2018-05-17/bioheuris-accesses-to-crispr-3-0-technology-from-benson-hill-biosystems.html

42 See https://www.rotam.com.

This may indicate a government approach of making access available to domestic entities only or simply keeping the fact of any such licensing confidential.[43] However, some CRISPR patents are the result of collaborations between Chinese researchers and non-Chinese entities and thus may be licensable by the non-Chinese entity.[44] Latin American researchers should thus assess whether approaching relevant Chinese patent holders for license agreements is necessary in light of their particular plant agricultural endeavors.

# IV. CONCLUSIONS

At the rate patent applications are being filed worldwide on CRISPR genome editing technologies for plant agricultural uses, it is not possible to know with certainty all of the possible patent owners one might need to seek licenses from to utilize a particular CRISPR-Cas tool for a particular plant agriculture application. Nevertheless, holders of foundational CRISPR technology patents appear eager to facilitate use of the technology in plant agriculture by making non-exclusive licenses broadly available. In addition, the various CRISPR patent holders are continuing to develop innovative new genome editing nucleases and approaches so it is likely that additional technologies may be available for licensing from multiple entities in the future.

Researchers using licensed CRISPR tools are also developing and patenting novel CRISPR-derived inventions with those tools. Such patented inventions may also need to be assessed for freedom to operate purposes and possible licensing. Moreover, there may be other tools (e.g. promoters, agrobacterium delivery vehicles) that facilitate CRIPSR-Cas use that may have patent issues to be navigated.

It is important to note that none of the CRISPR licensors provides 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 continually assess the patent landscape and determine whether licenses from other entities may be required.

43 Also, Syngenta, a major player in the agricultural space, is now owned by Chem China and has licensed the Broad Institute's CRISPR-Cas9 technology for use in multiple crops, including wheat, rice, tomato, corn, and sunflower. See Syngenta obtains non-exclusive IP license from Broad Institute for CRISPR-Cas9 genome-editing technology for agriculture applications, (Nov. 2017), https://www.businesswire.com/news/home/20171102005938/en/Syngenta-obtains-non-exclusive-IP-license-from-Broad-Institute-for-CRISPR-Cas9-genome-editing-technology-for-agriculture-applications.

44 For example, PCT publication number WO2018CN90067 for Methods of identifying, selecting, and producing southern corn rust resistant crops, lists as applicants both Dupont Pioneer (now Corteva) and Huazhong Agricultural University. It is not known whether the application is included in Corteva's license agreement.

**Table 1: CRISPR Plant Agriculture Licensing Information for Corteva Agriscience, The Broad Institute, and Benson Hill Biosystems**

| Licensor | Types of Licenses offered | Technology | Financial Terms | Contact Information |
|---|---|---|---|---|
| Corteva Agriscience and The Broad Institute | (1) an internal only R&D license<br>(2) a commercial seeds and crop trait products license<br>(3) a commercial license for other (non-livestock) agricultural products<br>(4) a license to provide CRISPR-Cas9 services<br>(5) no-cost academic research license. | CRISPR-Cas9 licenses for agricultural uses, as outlined here. | License Issue Fee and Annual Maintenance Fee<br>› Scales based on the size of a company's R&D budget or FTEs<br>Commercial Milestone Payments<br>› Variable, depending on crop and market<br>Royalties<br>› Percentage of net sales or percentage of additional revenue gained from utilizing the technology<br>› There are no fees for academic and non-profit institutions that use the technology for internal, academic, and non-commercial R&D only purposes | Corteva Agriscience:<br>Gwendolyn Humphreys<br>gwendolyn.humphreys@corteva.com |
| The Broad Institute | Same categories as above, with possible modifications | CRISPR-Cas9, Cas 12a & b, and more | Similar to above | The Broad Institute:<br>partnering@broadinstitute.org |
| Benson Hill Biosystems | No set categories. The agreements are individually negotiated to arrive at a license option tailored to the economic realities of the licensee and crop markets involved. | CRISPR-Cms1 | Flexible approach to licensing based on the size, type, and needs of the potential licensee. Licenses may involve one large upfront fee, milestone payments, and/or royalty payments. | Benson Hill Biosystems<br>https://bensonhill.com/get-in-touch/ |

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