https://research.ncsu.edu/ges/research/idb-crispr/

CRISPR Patent and Licensing Policy

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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

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 CRISPR 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

With such a promising field there are a lot of competing and overlapping patents

- This creates licensing and **freedom to operate** concerns
- Has led to several different alternatives including CRISPR-Cas 12 a & b, 12a2, 13, 14, CRISPR-Cms1, and MAD7 for genome editing

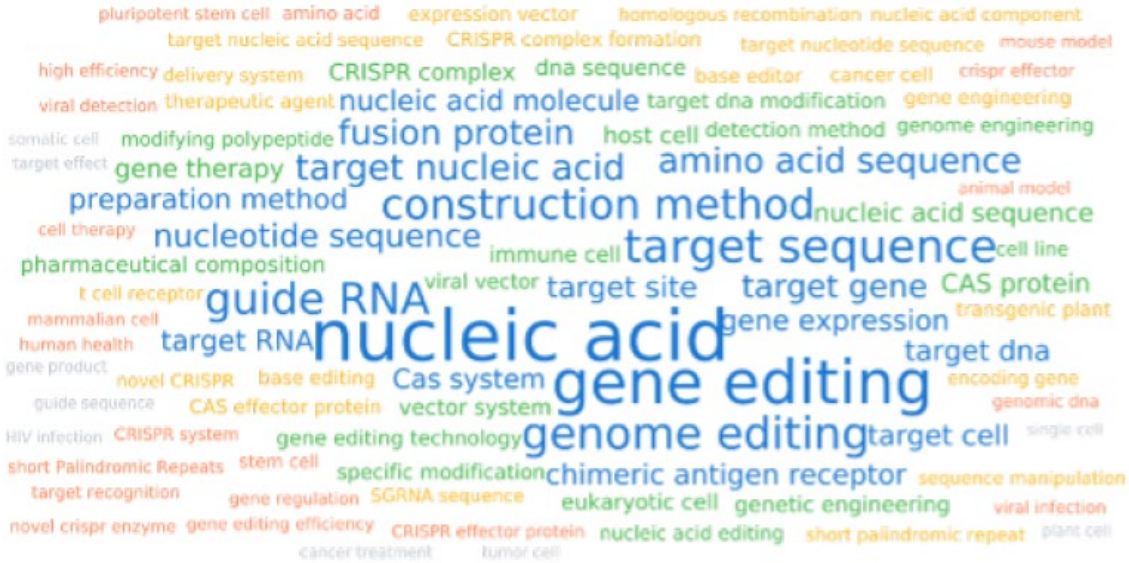
Cas9 remains the most widely used

CRISPR PATENT AND LICENSING POLICY

- There were **8100** CRISPR patent families worldwide as of January 30, 2021, of which **1400** related to plant agriculture
- By July of 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.

Innovation Word Cloud for the CRISPR Technology, Academic Assignees Only

The "Innovation Word Cloud" provides a snapshot view of the concepts found within the patent records of the academic institutions involved in CRISPR. This can be used to influence future patent searches by determining common terms in the technology space. This particular word cloud displays the most frequently occurring keywords in the most recent 5,000 patent publications in this field.



Innovation Word Cloud, PatSnap Insights

Some common terms found in CRISPR patent documents

Most commonly cited CRISPR Patent

Broad Institute US8697359 patent

1. A **method of altering expression of at least one gene product** comprising introducing into a eukaryotic cell containing and expressing a DNA molecule having a target sequence and encoding the gene product an engineered, non-naturally occurring Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)—**CRISPR** associated (Cas) (CRISPR-Cas) system comprising one or more vectors comprising: a) a first regulatory element operable in a eukaryotic cell operably linked to at least one nucleotide sequence encoding a CRISPR-Cas system guide RNA that hybridizes with the target sequence, and

b) a second regulatory element operable in a eukaryotic cell operably linked to a nucleotide sequence encoding a Type-II **Cas9** protein,

wherein components (a) and (b) are located on same or different vectors of the system, whereby the guide RNA targets the target sequence and the Cas9 protein cleaves the DNA molecule, whereby expression of the at least one gene product is altered; and, wherein the Cas9 protein and the guide RNA do not naturally occur together.

Foundational CRISPR Patent (Nobel Prize Winners)

UC Berkeley/ Univ. Wein US10266850B2 patent

1. **A method of cleaving a nucleic acid** comprising:

contacting a target DNA molecule having a target sequence with an engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-**CRISPR associated** (Cas) (CRISPR-Cas) **system** comprising

a) **a Cas9 protein**; and

b) **a single molecule DNA-targeting RNA** comprising

i) a targeter-RNA that hybridizes with the target sequence, and

ii) an activator-RNA that hybridizes with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment, wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides, wherein the single molecule DNA-targeting RNA forms a complex with the Cas9 protein, whereby the single molecule DNA-targeting RNA targets the target sequence, and the Cas9 protein cleaves the target DNA molecule.

Foundational CRISPR Patent (Nobel Prize Winners)

UC Berkeley/ Univ. Wein US10266850B2 patent

1. **An engineered and/or non-naturally-occurring Type II Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) system** comprising

a Cas9 protein or a nucleic acid comprising a nucleotide sequence encoding the Cas9 protein, and

a single molecule DNA-targeting RNA or a nucleic acid comprising a nucleotide sequence encoding the single molecule DNA-targeting RNA; wherein the single molecule DNA-targeting RNA comprises

i) a targeter-RNA that is capable of hybridizing with a target sequence in a target DNA molecule, and

ii) an activator-RNA that is capable of hybridizing with the targeter-RNA to form a double-stranded RNA duplex of a protein-binding segment,

wherein the activator-RNA and the targeter-RNA are covalently linked to one another with intervening nucleotides, and

wherein the single molecule DNA-targeting RNA is capable of forming a complex with the Cas9 protein,

whereby hybridization of the targeter-RNA to the target sequence is capable of targeting the Cas9 protein to the target DNA molecule.

PATENT BASICS

- 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** (*composition of matter, process/method, apparatus/article, machine*).

- Some countries do not allow patenting of plants or animals, or products of nature (*e.g., naturally occurring isolated DNA sequences, or sequences/products not markedly different to what exists in nature*)

- Claims are KEY for validity and infringement

PATENT BASICS

The right to exclude granted by a patent is **not** a right to practice the invention

E.g., if Corteva develops an improved CRISPR-Cas 9 editing method that is novel and non-obvious over the original Broad patented method, Corteva can get a patent on that method.

However, if practicing the new Corteva method would infringe the Broad patent, Corteva cannot practice that patented method without infringement liability. BUT, Corteva CAN prevent others from using its patented method, INCLUDING the Broad Institute!

and if Corteva's new method is substantially better than the Broad's, the Broad might want to take a license from Corteva or cross-license with Corteva.

Types of claims commonly seen in CRISPR Patents (methods, composition of matter, system)

(Pairwise US20220243217A1 (application)

1. A **plant or plant part** thereof comprising at least one non-natural mutation in an endogenous gene encoding an AGAMOUS clade MAD S-box transcription factor. . . .

10. **The plant** of any one of the preceding claims, wherein the plant is raspberry, black raspberry, blackberry, cherry, peach, avocado, strawberry, wild strawberry, apple, tomato, grape, peach, plum, apricot, pear, quince, loquat, date or almond.

Types of claims commonly seen in CRISPR Patents (methods, composition of matter, system)

Pioneer (Corteva) US9868962B2 patent

1. **A set of two Class 2 CRISPR polynucleotides** comprising:(i) a first Class 2 CRISPR polynucleotide wherein the first Class 2 CRISPR polynucleotide comprises a targeting region comprising deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) and an activating region adjacent to said targeting region; and,

(ii) a second Class 2 CRISPR polynucleotide wherein the second Class 2 CRISPR polynucleotide comprises an activating region wherein the activating region comprises DNA and a sequence that is complementary to a sequence in said activating region of the first Class 2 CRISPR polynucleotide, wherein said activating region of the first Class 2 CRISPR polynucleotide and said activating region of the second Class 2 CRISPR polynucleotide are capable of hybridizing to each other to form an activating duplex region, wherein said activating duplex region comprises a stem and a bulge, and wherein said activating duplex region is capable of binding with a Cas9.

11. **A method [process] of modifying a target nucleic acid molecule** in a non-human organism, an isolated **cell,** or in vitro, wherein said method comprises: introducing into a cell(i) a set of two Class 2 CRISPR polynucleotides comprising

18. **The method of claim** 11, wherein the cell is selected from the group consisting of a bacterial cell, an archaeal cell, a **plant cell**, an algal cell, a fungal cell, an invertebrate cell, a vertebrate cell, a mammalian cell, and a human cell.

Claim scope may vary widely by country

US Patent Application

US20210292777A1

1. A method for site-specific mutagenesis of *Medicago sativa [alfalfa]* genes by using a CRISPR/Cas9 system, wherein, the method comprises the following steps: Step (1) Constructing a universal binary expression vector MsCRISPR/Cas9 that can be used for transforming *Medicago sativa* by *Agrobacterium tumefaciens;*

Step (2) Designing a CRISPR/Cas9-based target site for a target gene in the *Medicago sativa*, and ligating the DNA fragment containing the guide sequence of the target site into the universal vector MsCRISPR/Cas9 to construct a vector MsCRISPR/Cas9::target;

Step (3) Transforming the *Medicago sativa* by the *Agrobacterium tumefaciens*, and introducing site-specific mutations into the target gene.

Guangdong Sanjie Forage Biotechnology Co

Chinese Patent CN108866093B

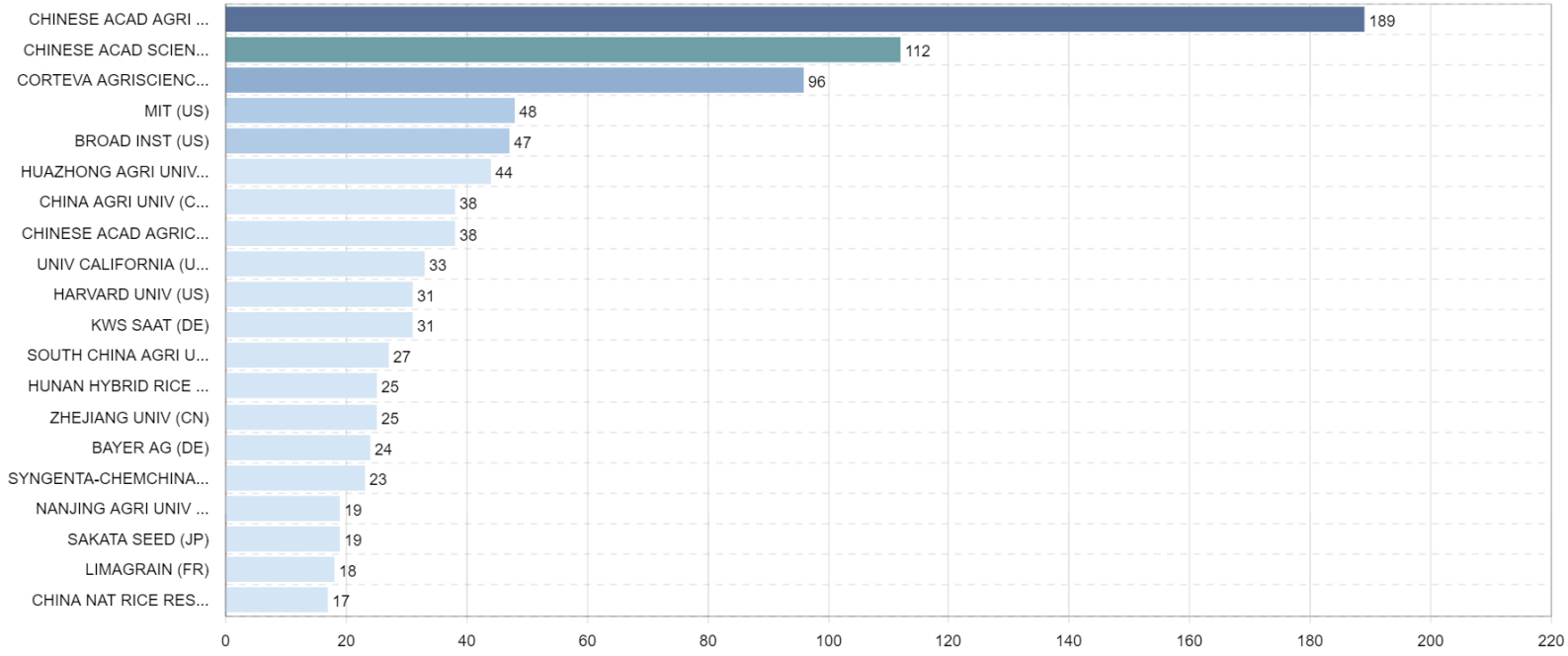
A method for site-directed mutagenesis of alfalfa gene using CRISPR/Cas9 system, comprising the steps of: constructing a universal binary expression vector MsCRISPR/Cas9 mediated and transformed by agrobacterium tumefaciens in alfalfa; the full sequence of the binary expression vector MsCRISPR/Cas9 is shown in SEQ ID NO. 1;

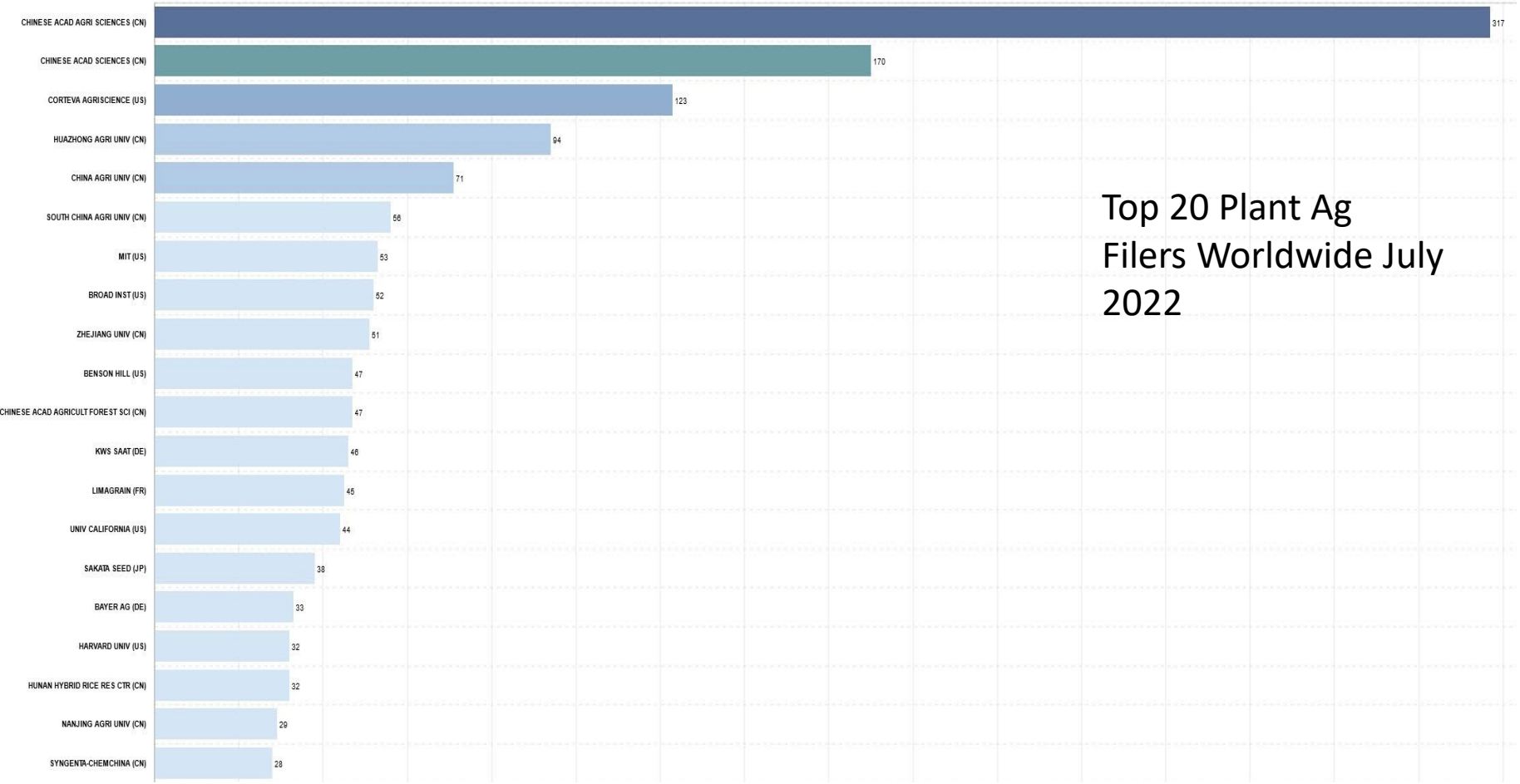
designing a target sequence based on CRISPR/Cas9 aiming at a target gene in alfalfa, and connecting a DNA fragment containing the target sequence to a universal vector MsCRISPR/Cas9 in alfalfa to construct a vector MsCRISPR/Cas9: target;

step (3) agrobacterium tumefaciens is used for mediating and transforming the alfalfa, so that the site-directed mutation of a specific gene in the alfalfa is realized;

the framework vector of the binary expression vector MsCRISPR/Cas9 for expressing the CRISPR/Cas9 system in alfalfa is a pCambia1300 vector, a T-DNA region for transforming plants is arranged on the pCambia1300 framework vector, the T-DNA region comprises a left boundary repetitive sequence LB repeat, a right boundary repetitive sequence RB repeat and sequences for transformation in the left and right boundary sequences, the sequences for transformation in the left and right boundaries of the T-DNA region comprise an Hpt gene expression element for expressing a protein resisting plant screening agent hygromycin, an expression element for expressing a Cas9 protein, an expression element for expressing sgRNA and a target sequence between two Aar I enzyme cutting sites in the sgRNA expression element, the Hpt gene expression element comprises a CaMV35S promoter sequence for starting Hpt gene transcription, a CDS sequence for expressing Hpt gene and a Camv poly A termination sequence for terminating Hpt gene transcription, the expression element for expressing the Cas9 protein internally comprises a 2xCaMV35S promoter sequence for starting the transcription of a Cas9 sequence, a DNA sequence for expressing Cas9 and a Nos terminator sequence for stopping the transcription of Cas9, and the expression element for expressing the sgRNA internally comprises a Medicago truncatula MtU6promoter sequence for starting the transcription of a sgRNA sequence and a DNA sequence for expressing the sgRNA; the MtU6promoter has a sequence shown in SEQ ID NO. 2.

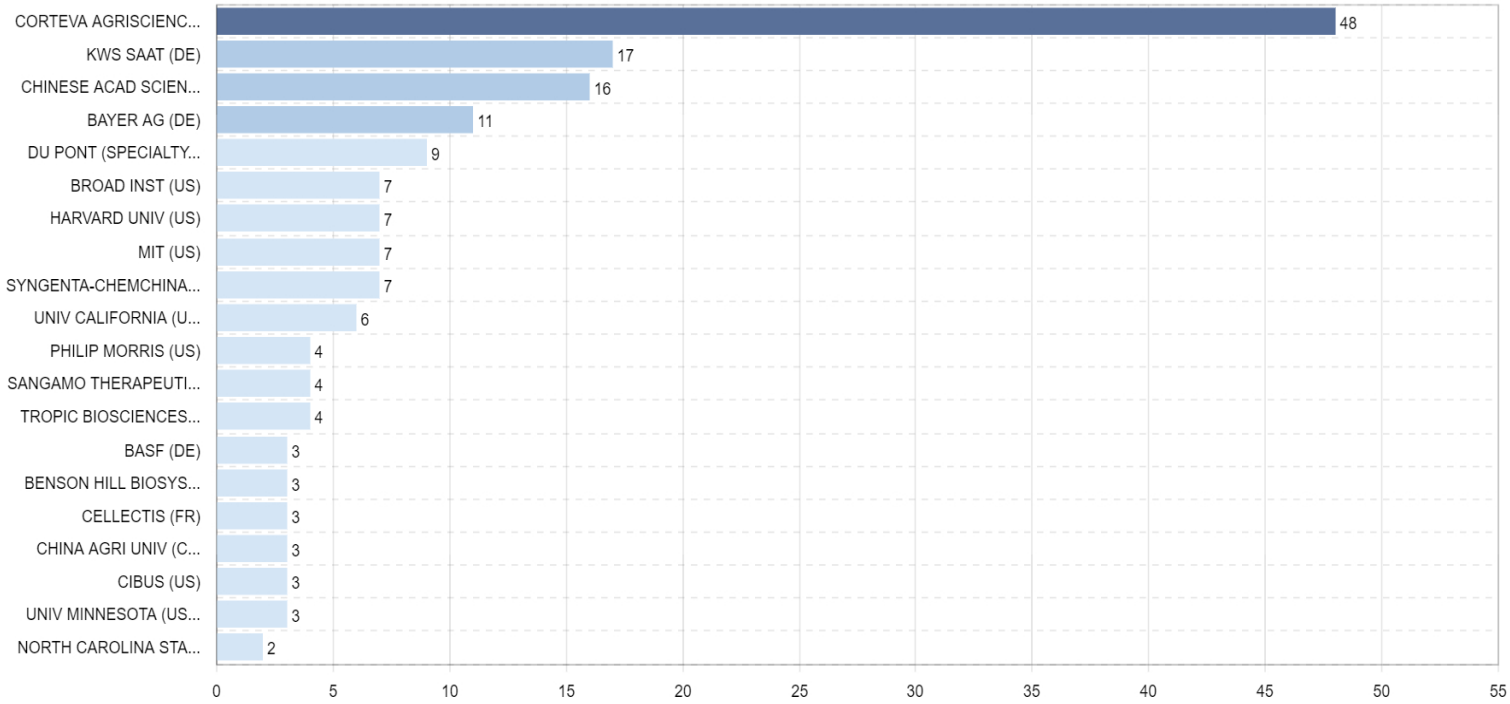
Top 20 Filers of CRISPR Plant Agriculture Published Patents and Patent Applications Worldwide

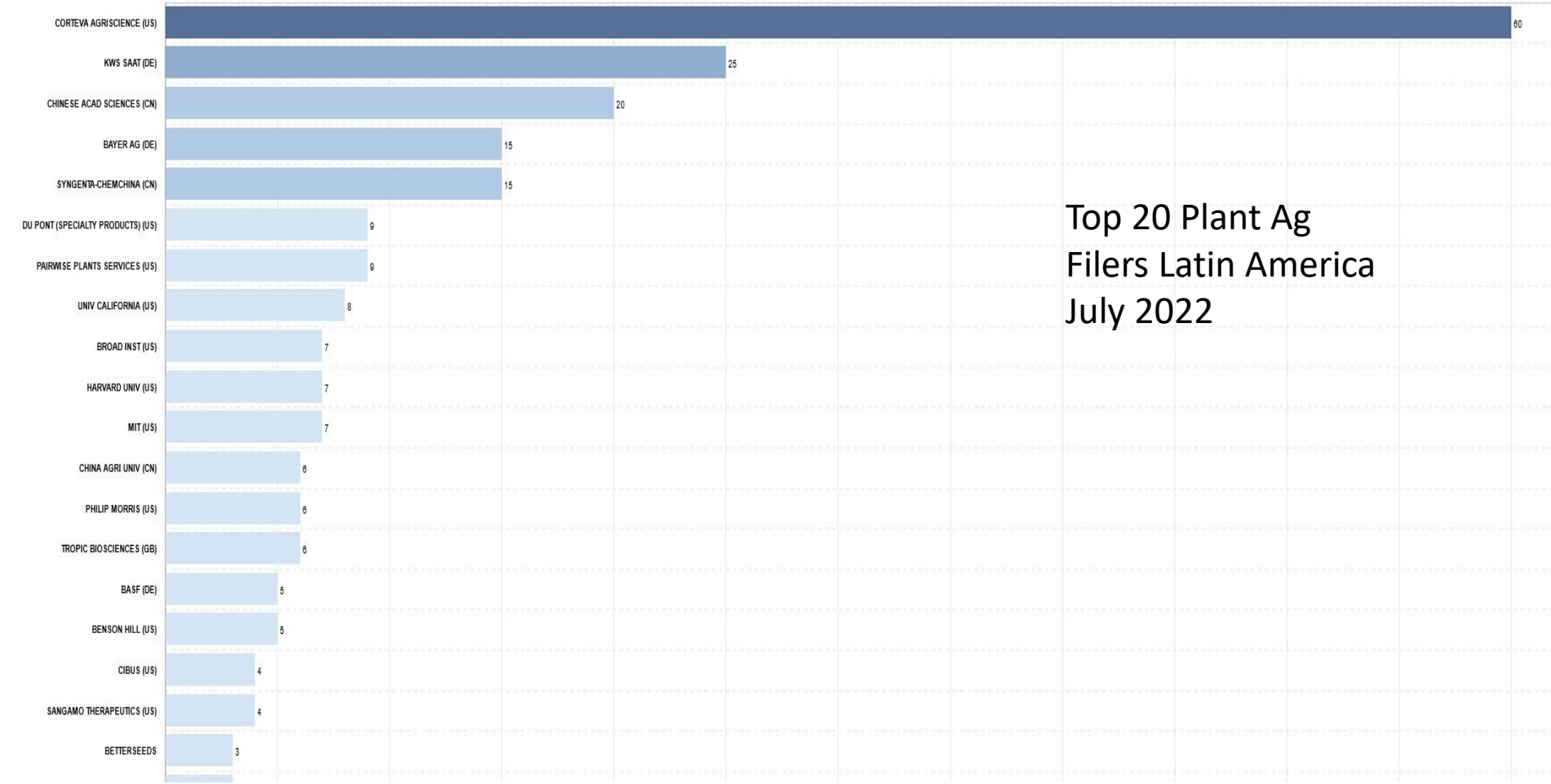




Top 20 Plant Ag Filers Worldwide July 2022

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

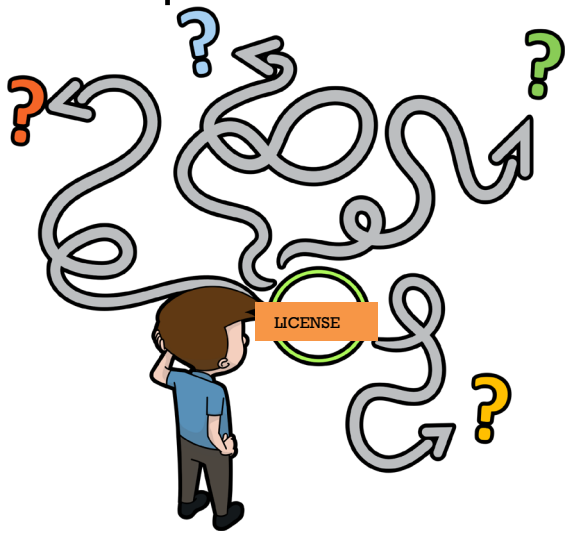




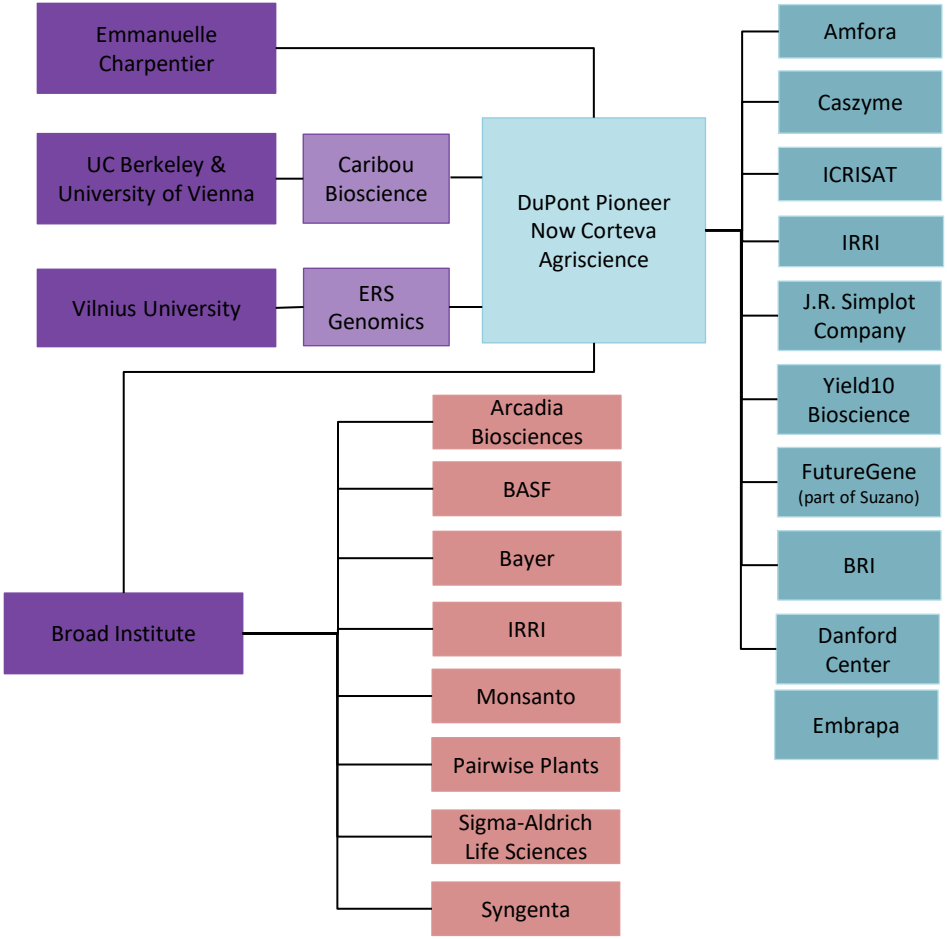
Top 20 Plant Ag
Filers Latin America
July 2022

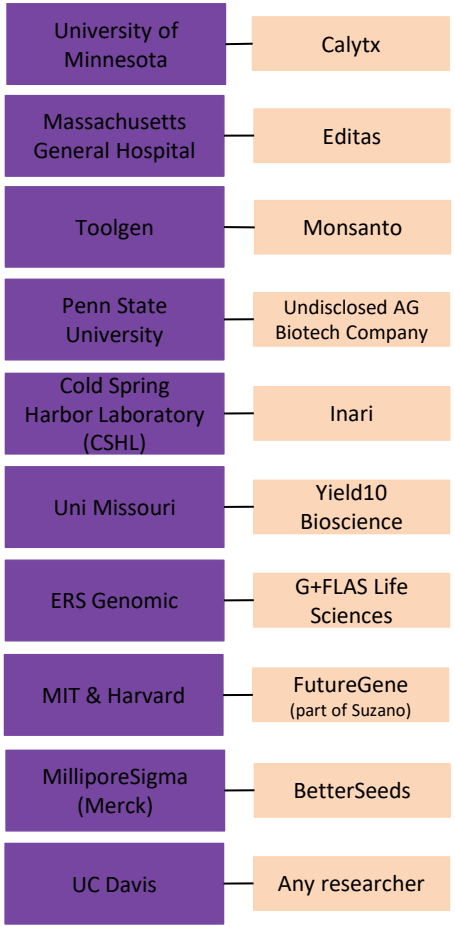
CRISPR Patent Licensing Protocols

The landscape is extremely complex, likely impossible to know all the possible patent owners one might need to seek a license from (because of later researchers to patent non-obvious improvements).



"Navigating the CRISPR IP thicket can be extremely confusing. And, unfortunately, it is likely to become even more so." *Synbiobeta*





Reported CRISPR-Cas9 Licenses in Plant Agriculture

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.

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;
    - Create terminator seeds; or
    - Produce tobacco products for human consumption.

CRISPR-Cms1, 12a2 (CRISPR 3.0): Benson Hill Biosystems

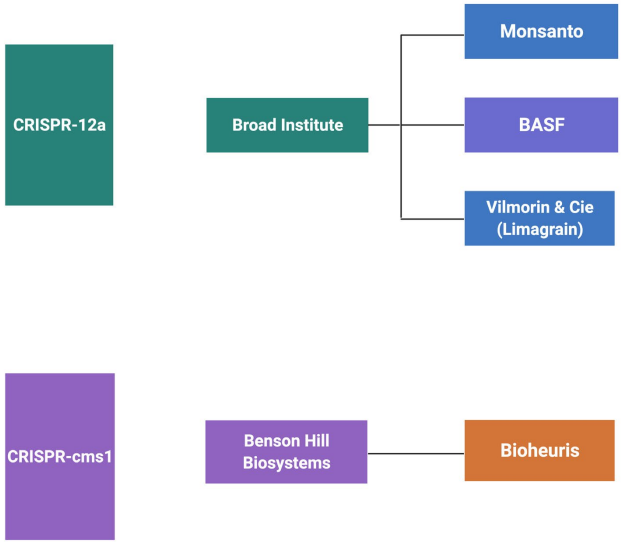
- May be able to offer lower cost licenses and greater clarity regarding patent rights.
- Agreements are individually negotiated.

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.
- Also identified new CRISPR-12a2 nuclease
  - This smaller size allows for more compact system for precision genome editing.
  - (but new focus on ingredients business, maybe less on licensing?)

Reported CRISPR-12a and CRISPR-Cms1 Licenses/Collaborations in Plant Agriculture

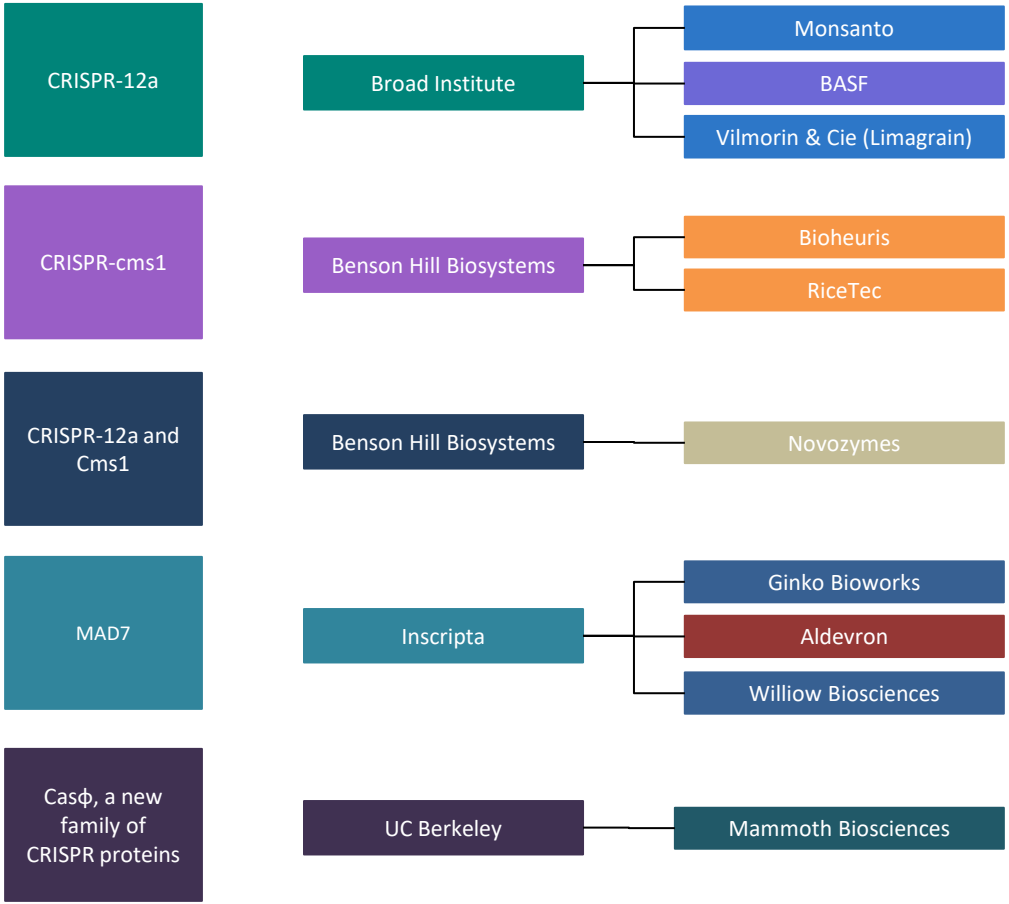


(All of these relationships may not involve CRISPR licenses)

Benson Hill empowers innovators that are advancing food and agriculture

Embrapa, BECK'S, Simplot, UF University of Florida, SmartBarley, CTC, USB United Soybean Board, RiceTec, University of Minnesota Driven to Discover, Donald Danforth Plant Science Center, GDM, BTI Boyce Thompson Institute, VIB, Washington State University, MARS, mahyco, National Corn Growers Association, OMRF, Wisconsin University of Wisconsin-Madison, inholland university of applied sciences, Fibria, Americot cotton seed, NC State University, University of Maryland, novozymes Rethink Tomorrow, BIOHEURIS, Brownseed Genetics, Fresh Kampo, Sime Darby

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



First reported Chinese CRISPR License in Plant Agriculture

CRISPR gene editing for molecular design in corn
(first Chinese license)

Origin Agritech — China Agricultural University

Through collaboration agreement

China Agricultural University — Origin Agritech

Pairwise Use of CRISPR Licenses

(Pairwise US20220243217A1 (application)

1. A plant or plant part thereof comprising at least one non-natural mutation in an endogenous gene encoding an AGAMOUS clade MAD S-box transcription factor. . . .

"Our innovation began **with exclusive licenses in plants** to base editing and high-fidelity enzymes from Harvard and Massachusetts General Hospital. From there, our team has developed a whole portfolio of proprietary systems for which we own the foundational IP. Plus, our founders - David Liu, PhD, Feng Zhang, PhD, and J. Keith Joung, PhD - are thought leaders in the field of CRISPR and gene editing, as well as skilled in bringing tech-enabled products to market across an array of crops and sectors." *Pairwise*

Conclusions

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 in certain instances so seeking a license is still advisable.

Entities seeking to commercialize products using CRISPR/Cas9 should consider obtaining research licenses in **early research stages** to possibly obtain more favorable commercial licensing terms.

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.

Entities in the LAC region should consider **collaboration and information sharing on license terms and strategies**, where possible, as well as **obtaining patent protection** on CRISPR inventions they develop.