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CRISPR technology: Patent & License landscapes

Final Version

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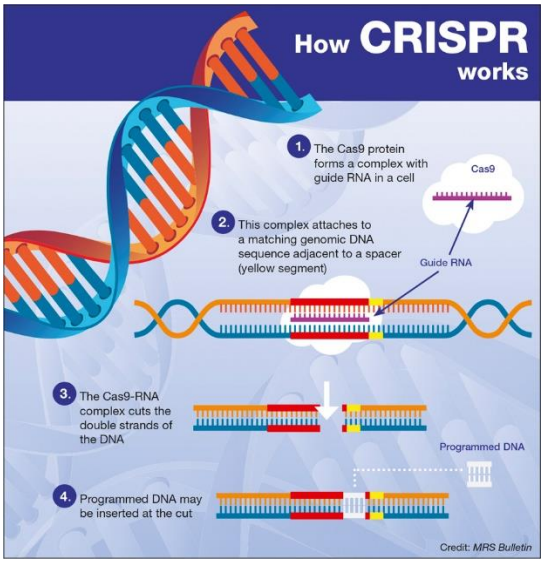
Contents

1 Introduction to CRISPR-Cas Technology: Precision Genetic Editing

CRISPR-Cas technology represents a groundbreaking tool in the field of genetic manipulation, revolutionizing our ability to edit DNA with precision and efficiency. Standing for « Clustered Regularly Interspaced Short Palindromic Repeats » (*CRISPR*) and CRISPR-associated (*Cas*) protein, this technology exploits Cas proteins and RNA molecules to achieve targeted modifications in the nucleic acid sequences, resulting in a versatile gene-editing tool. The CRISPR-Cas9 system, which is the most widely used CRISPR system, was developed in 2012 by scientists at the University of California- Berkeley and the University of Vienna, with Emmanuelle Charpentier being the primary lead. The same year, the Broad Institute of MIT and Harvard published the use of the system in eukaryotes.

At its core, CRISPR-Cas functions like a pair of molecular scissors, allowing scientists to precisely target and modify specific sections of DNA/RNA. It comprises two main components: the Cas proteins, acting as the scissors, and RNA molecules that guide these proteins to the desired location on the DNA strand.

The process commences by designing guide RNA that matches the target DNA sequence. This guide RNA then directs the Cas protein to the specific location on the DNA, where the Cas protein makes a precise cut. The cell's repair machinery then intervenes, either integrating desired alterations (*"Programmed DNA" in the scheme below*) or utilizing the cell's inherent repair mechanisms to rectify genetic anomalies. The use of a short guide RNA that can be cheaply and quickly synthesized makes it much easier to use than other gene editing techniques which can achieve similar outcomes through a much more laborious process (*ie*: TALENs).



CRISPR-Cas technology encompasses various Cas proteins, each with distinct functions and applications. Cas9, the most widely used, is an RNA-guided DNA endonuclease that precisely cleaves both strands of DNA at the location specified by the guide-RNA. Cas12 and Cas13, on the other hand, proteins that are similar to Cas9 but have unique features. Cas12 has collateral cleavage activity, enabling it to target several DNA sequences simultaneously, while Cas13 is renowned for its ability to target RNA. These diverse Cas proteins contribute to the adaptability and innovation within the CRISPR-Cas technology landscape, paving the way for more refined and specialized applications in genetic manipulation.

The applications of CRISPR-Cas technology are vast and diverse, spanning multiple fields. In agriculture, it holds the potential to more readily create crops that are more resistant to diseases,

have longer shelf lives, or even exhibit enhanced nutritional value. In medicine, CRISPR offers promising avenues for treating genetic disorders, cancer, and infectious diseases. Furthermore, it enables more accurate disease studies, targeted therapeutic development, and the prospect of personalized medicine.

However, along with its immense potential, CRISPR-Cas technology raises ethical considerations and challenges. The ability to edit the human genome raises concerns regarding unintended consequences and ethical boundaries, particularly in the realm of creating genetically modified humans. Thus, stringent ethical guidelines and regulatory frameworks are pivotal in guiding responsible usage.

Despite these challenges, CRISPR-Cas technology continues to evolve rapidly. Researchers are continuing to develop refined versions with new capabilities (such as prime editing and base editing), or improved performance (enhanced precision, reduced off-target effects), and expand the range of possible edits.

Overall, CRISPR-Cas technology is a powerful tool with far-reaching implications in a variety of fields, offering both remarkable opportunities and ethical dilemmas. Its continuing progress underlines the importance of balancing scientific progress, ethical scrutiny and regulatory oversight in order to harness its potential for the improvement of society while mitigating potential risks.

Sources: (1–9)

2 CRISPR technology: Patent Landscape

Note: this section is a patent overview in CRISPR technology with a specific focus on genetically modified plants.

2.1 Key points

- There are over 17'000 patent families covering CRISPR related technology
  - >14'000 have claims covering genome editing
- 46% of CRISPR patents have priority filings in China, and nearly 40% have them in the USA
  - Only 2 priority filings within CH
  - No extensions specifically to CH have been filed (only via the EP system)
- From 2012 to 2019, the USA lead in total priority filings, but, after a slow start, China overtook the USA in 2020
- Only 8.7% of Chinese priority filings have been extended to other countries so far (mainly via PCT)
- Most extensions occur in Canda, China, the EU, Australia, USA, Brazil, India
- the Chinese Academy of Sciences and the Chinese Academy of Agricultural Sciences are the top filers, followed by the Universities in the USA involved in the invention of CRISPR-Cas9 and its application to eukaryotes

CRISPR usage in modified plants:

- 1'387 patent families covering modified plants
  - Filings per year peaked in 2019, and have held relatively constant
  - The plant patent extension distribution was broadly similar to the overall CRISPR patent distribution
  - Most patents disclose the use of Cas9
- Corteva is by far the leader in plant patent holdings outside of China, followed by Limagrain, Benson Hill, and other major agricultural companies
  - this is in contrast to the more general CRISPR situation where public universities and institutions are the major patent holders
- These agricultural companies hold not only patents covering usage in plants, but also CRISPR patents in other areas (alternative Cas enzymes/CRISPR systems, etc)
- Outside of China, most of the main players claim undefined nucleases or legacy nucleases such as ZFN, TALENs besides CRISPR for broad protection.
  - Few Chinese patents also cover other nuclease types
  - Some also protect usage of other recent CRISPR-based technologies (*eg.* base/prime editors)
- In Chinese patents (not extended to other countries) most of the main players are still academic labs

2.2 Background

The group referred to as “CVC” is composed of the inventors of the first uses of the CRISPR-Cas9 system (primarily Doudna of the University of California- Berkeley, and Charpentier of the University of Vienna). This group has uncontested patents covering the generic use of CRISPR-Cas9 in any cell type(10). Their initial publication and patent did not disclose any application in eukaryotes, but they have argued that they have private data supporting this.

There is currently a dispute between four major groups over the use of CRISPR-Cas9 in eukaryotes. At the time of filing in the USA, the USA operated on the “first to invent” principle, and CVC attempted to obtain coverage of the usage in Eukaryotes in the USA. Courts in the USA did not find that the CVC group had presented sufficient evidence to favour their claims over the Broad Institute’s claims(11). CVC is continuing to challenge this ruling in US courts.

The second group is led by the Broad institute (of the Massachusetts Institute of Technology and Harvard University), which fast tracked their patent application and was the first to have a patent issued for the use of the CRISPR system in eukaryotes, despite not being the first to file for such a patent. It was, however, the first to publish an academic paper demonstrating the use in eukaryotes(12,13), followed closely by a Harvard group(14). In Europe, a mistake in assignment of patent rights by the inventors lead to their foundational patent covering the usage in eukaryotes being invalidated(15), leaving only the CVC foundational patents standing. Many derivative/non-foundational patents of the Broad Institute will still be valid, although some may be affected by the same issue. The exact extent of the scope of their valid patent protection in Europe is unclear.

The two remaining groups, Sigma-Aldrich and Toolgen, have both applied for patents applying CRISPR technology to eukaryotes before the Broad institute and CVC(10), and there are thus four groups competing for coverage of the use of CRISPR in eukaryotes. Currently Toolgen does not have any issued foundational patents. Sigma Aldrich has patents covering using CRISPR to lead to integration of introduced DNA in eukaryotes. Sigma-Aldrich and Toolgen’s more foundational claims on the general use of CRISPR-Cas9 in eukaryotes are still ungranted, and legal disputes are ongoing.

This dispute is by and large limited to the use of CRISPR-Cas9, and many patents now cover more generic gene editing, with additional claims enumerating more specific cases (as is typical for patents), such as the use of RNA-guided nucleases in general (without specifying a specific nuclease). It seems the “mistake” of the CVC group in not enumerating more specific usage cases (*ie*. In eukaryotes) will not be repeated, and many patents now have series of claims covering increasingly specific uses (*eg.*: eukaryotes> plants/fungi/animals> mammals> humans).

2.3 GLOBAL PATENT LANDSCAPE ON CRISPR

2.3.1 Temporal distribution of patent filings (2012-2022)

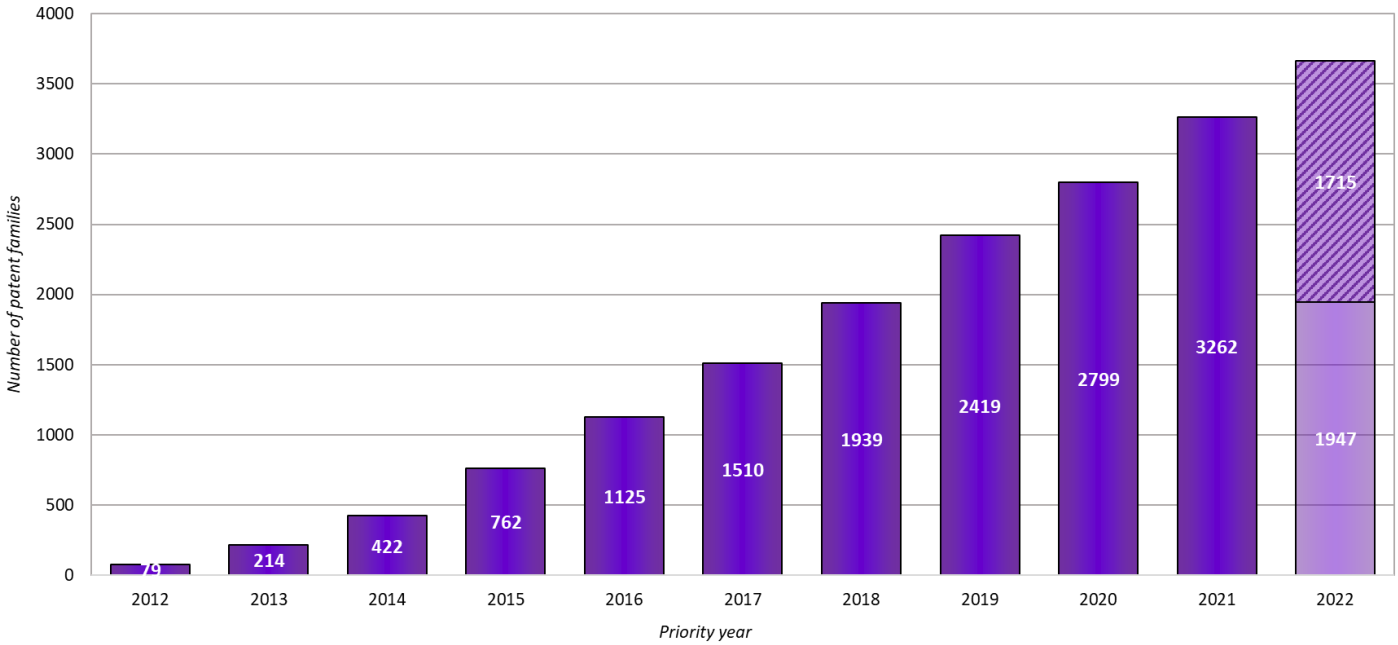


Table 2.3.1: Number of patent families by priority year

There are 17'175 patent families in the database (data from Sept.-Oct. 2023). 57 patent families filed between 2001 and 2011 are not included in this graph. Not included said patent families comprise (for instance):

- methods for typing a bacterium having a CRISPR region, such as Lactobacillus bacterial strain,
- the use of CRISPR associated with Cas genes, for modulating resistance in a cell against a target nucleic acid or providing resistance against phages, Lactococcus Crispr-Cas sequences and other historical families owned by Danisco-DuPont.
- Cas proteins covering other Cas enzymes such as Cas6, Csy4
- generating nucleic acid fragments, regulating production of a target RNA in a cell, including downregulating prokaryotic genes.
- patent members that were filed after 2012 but that are comprised in a patent family having the first priority date anterior to 2012 due to other members.

2022 is not complete and 2023 is not shown due to the delay of publication of 18 months. Therefore, an estimated 1'715 patent families were added in 2022.

2.3.2 World map of priority filings

Countries	Nb	%
CHINA	7945	46,25%
UNITED STATES	6835	39,80%
KOREA	579	3,37%
EUROPE	479	2,79%
WORLD	367	2,14%
UNITED KINGDOM	266	1,55%
JAPAN	219	1,27%
RUSSIAN FEDERATION	95	0,55%
INDIA	60	0,35%
AUSTRALIA	47	0,27%
SINGAPORE	36	0,21%
DENMARK	27	0,16%
NETHERLANDS	27	0,16%
GERMANY	18	0,10%
FRANCE	17	0,10%
SPAIN	17	0,10%
ITALY	16	0,09%
LUXEMBOURG	15	0,09%
SOUTH AFRICA	12	0,07%
SWEDEN	10	0,06%
Other countries	72	0,42%

Table 2.3.2: Number of priority filings by country, and percent of total filings

Of the 17’175 patent families filed between 2001-2023, the priority patent applications were mostly filed in the People's Republic of China (7945 – 46.25%) and in the USA (6835 – 39.80%). Priority patent applications were also filed in with the EP procedure (479, 2,79%), with the PCT procedure (367, 2,14%), and in the UK (266, 1,55%).
Countries and regions (PCT and EP) outside of the USA and the People's Republic of China represent 14.00% of the priority filings.
Only two priority filings were directly in CH, by the University of Bern in 2019 and Cytosurge in 2021.

2.3.3 Temporal distribution of priority filings (2012-2022)

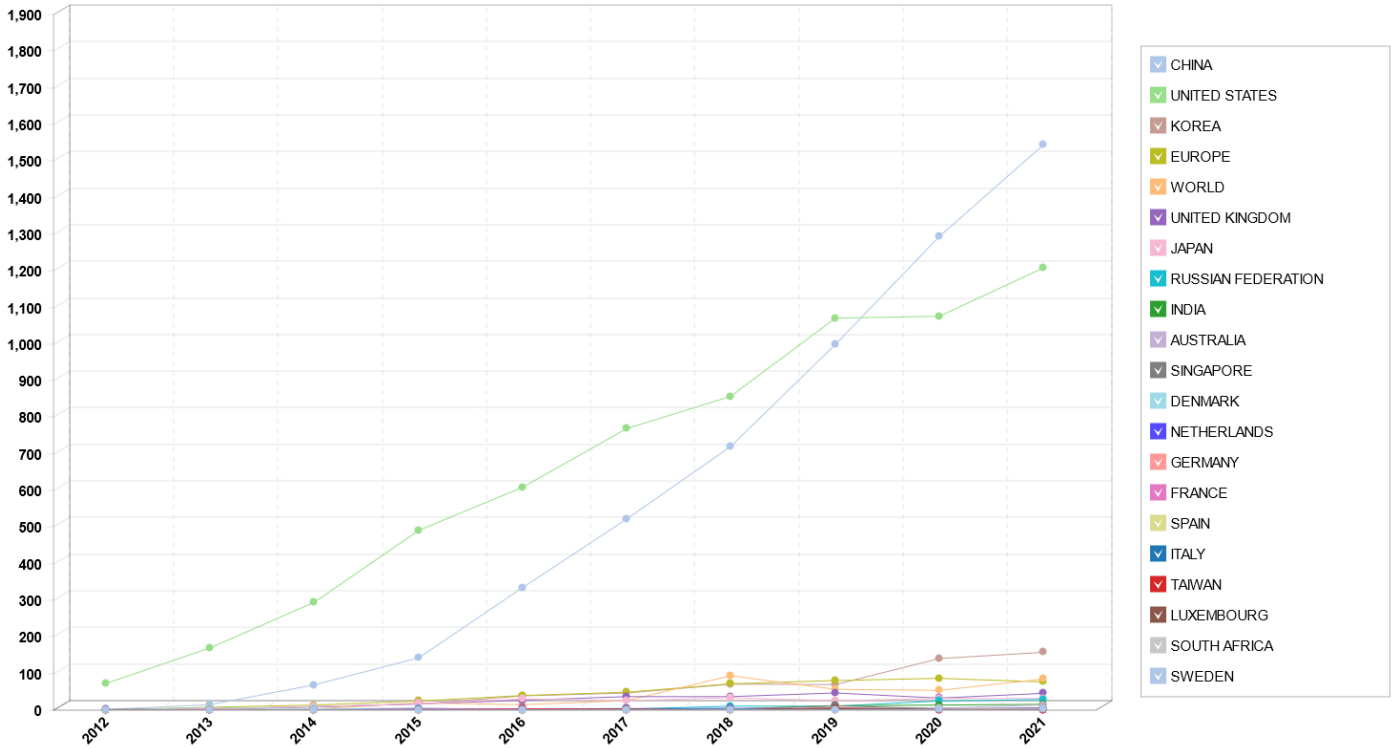


Figure 2.3.3: Temporal distribution of priority filings in each country or region having at least 10 priority filings.

Please note that 2022 and 2023 are incomplete and are therefore not shown. Chinese patent applications are published within 18 months from its filing date or within 4-6 months after the applicant files a request for early publication.
The first priority filings were in the USA in 2012 – note the strong increase of priority filings in the USA and the People's Republic of China since 2012 and 2015, respectively. The rate of increase has been faster in China, and thus China has become the leader in priority filings since 2020.

2.3.4 World map of patent extensions

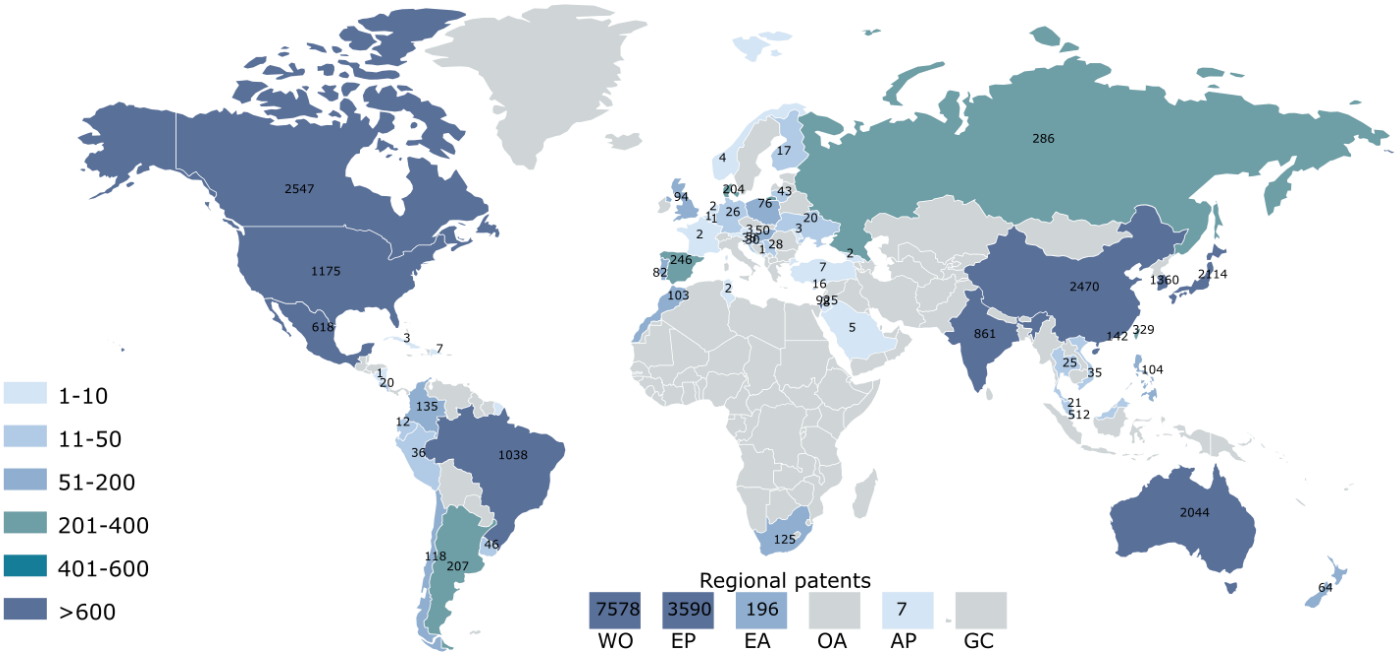


*Figure 2.3.4: The countries and regions **to** which patent protection has been extended **from** a priority filing in another country. WO = "World", ie. patents extended via the Patent Cooperation Treaty filings; EP/EA/OA/AP labels are according to https://www.wipo.int/pct/en/texts/reg_des.html. That is: EP = European Patents; EA = Eurasian patents; OA = OAPI African Intellectual Property Organization patents; AP = patent extensions via the African Regional Intellectual Property Organization; GC = Gulf Cooperation Council patents. Colours for the map (and regional boxes) correspond with the number of patent extensions (legend at the left). Switzerland is in grey, as no extensions have been filed specifically to Switzerland (but rather to the EP region).*

Note that the extension of protection from priority filings has mainly occurred via the PCT procedure (7578 patent families = 44,1%). Also note, only 704 of the 7945 Chinese priority filings (=8,7%) have been extended so far (mainly via PCT). Despite China being a leader in priority filings, few of these patents have their protection extended beyond China.

2.3.5 Main patent assignees (≥ 53 patent families)

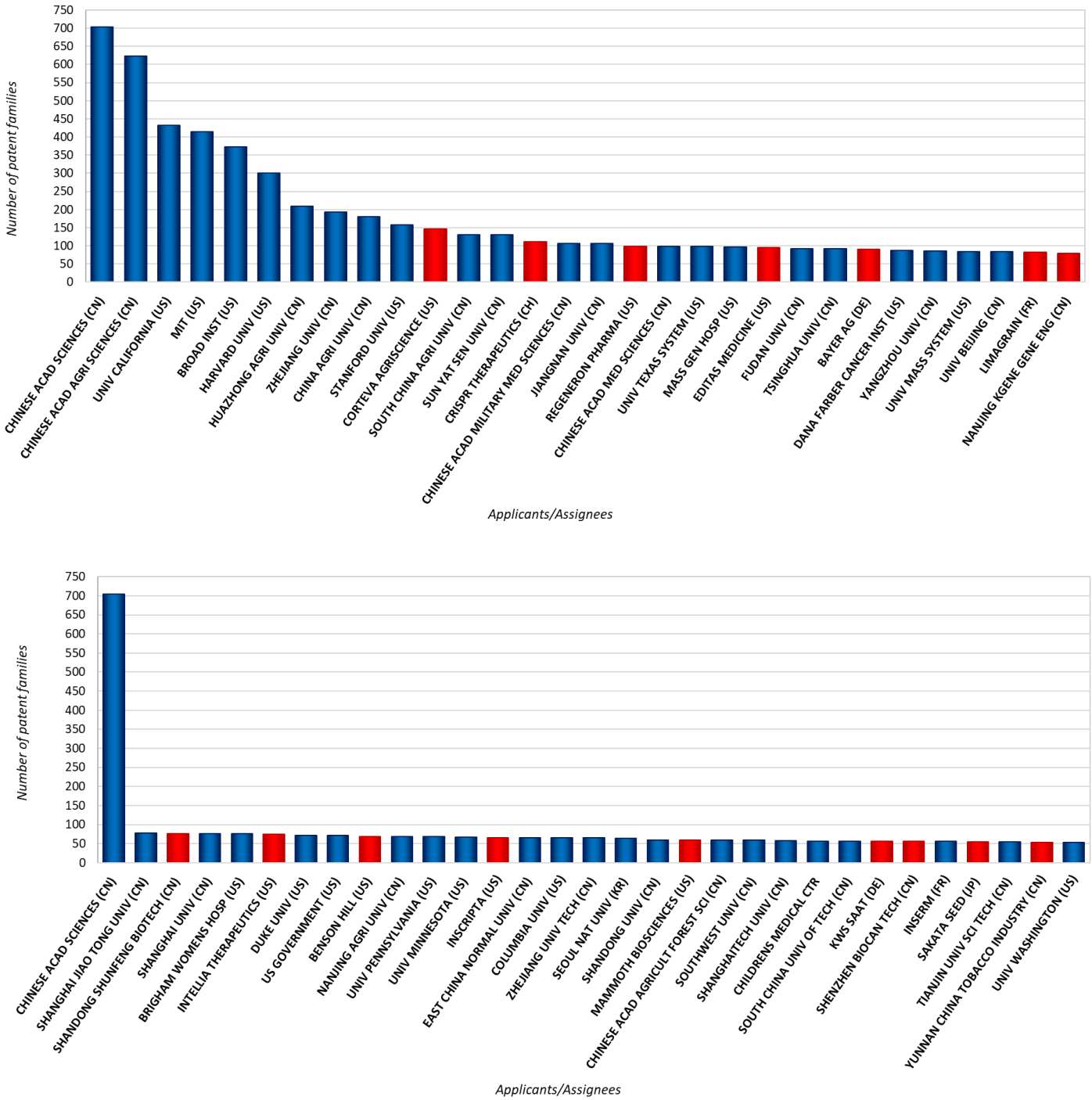


Figure 2.3.5: Top: The top 30 main patent holders/assignees. Blue indicates public entities; red indicates private entities. Bottom: The graph continued with the next top 30, and the Chinese academy of sciences shown for comparison purposes. Affiliates & subsidiaries have been gathered under their parent company (e.g. Pioneer with Corteva Agriscience). The Chinese Academy of Sciences and the Chinese Academy of Agricultural Sciences include academic labs affiliated to them. Co-filings are counted for each co-owner: a patent application co-filed between the MIT, the Harvard University and the Broad Institute is counted once for each of these assignees.

The Chinese Academy of Sciences and the Chinese Academy of Agricultural Sciences are the top players in the CRISPR Patent Landscape, illustrating the importance and the stake of Genome Editing technologies for the Chinese government.

2.3.6 Breakdown by Claim coverage of patent families - Breakdown of the patent portfolio

Please note that patent families can be classified in several categories.

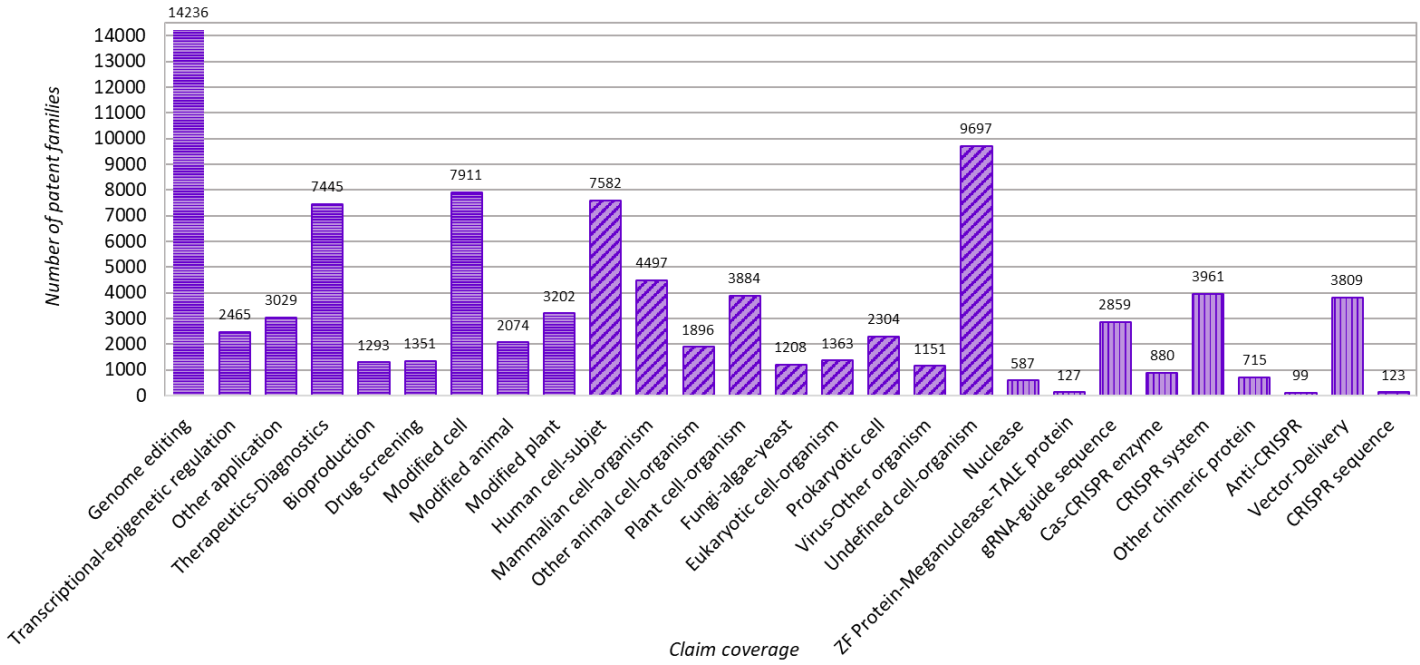


Figure 2.3.6: The number of CRISPR patent families with claims covering each enumerated area of interest.

Is seen in Fig. 2.3.6, the major areas of interest for CRISPR patents are modified organisms (plant, animal, human, cell, unidentified), and therapeutics/diagnostics, in addition to genome editing.

2.4 Modified Plants - Non-CN priority filings and CN priority filings with extensions

2.4.1 Temporal distribution of patent filings (2012-2021)

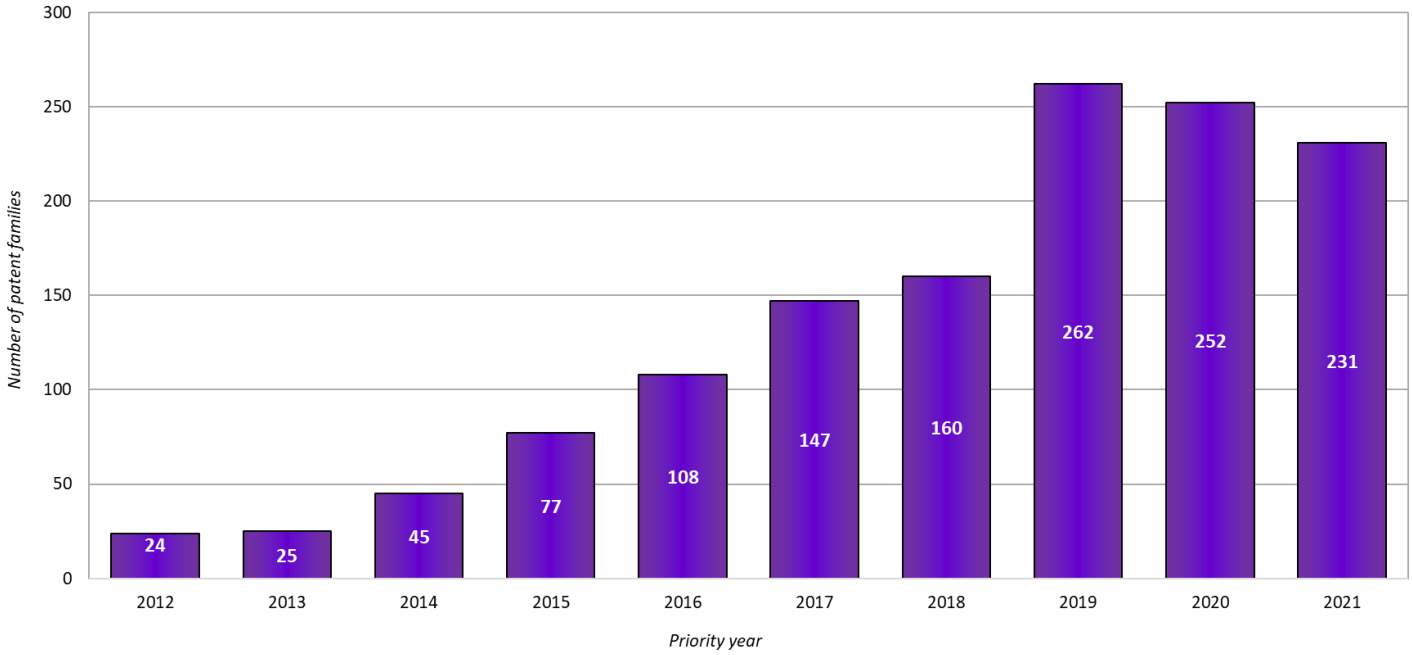


Figure 2.4: Number of patent families covering modified plants by priority year, excluding patents only valid in China (Chinese patents extended beyond China are included).

There are 1'387 patent families in this data set (data from Sept.-Oct. 2023), comprising all patent families on modified plants, except the Chinese priority filings that have not been extended outside of the People's Republic of China. The increase in 2014 primarily reflects the early adoption of CRISPR techniques following the 2013 publications.

2.4.2 World map of priority filings covering modified plants

Countries	Nb	%
UNITED STATES	862	62,15%
CHINA	147	10,60%
KOREA	122	8,80%
EUROPE	73	5,26%
WORLD	55	3,97%
UNITED KINGDOM	31	2,24%
JAPAN	24	1,73%
RUSSIAN FEDERATION	13	0,94%
INDIA	11	0,79%
NETHERLANDS	10	0,72%
GERMANY	4	0,29%
ISRAEL	4	0,29%
SOUTH AFRICA	4	0,29%
SWEDEN	4	0,29%
Other countries	23	1,66%

Table 2.4.1: Number of priority filings covering modified plants by country, and percent of total filings

Priority patent applications covering modified plants were mostly filed in the USA (862 – 62.15%) and in the People's Republic of China (147 – 10.60%). Countries and regions (PCT and EP) outside of the USA and the People's Republic of China represent 27,25 % of the priority filings.

2.4.3 World map of patent extensions

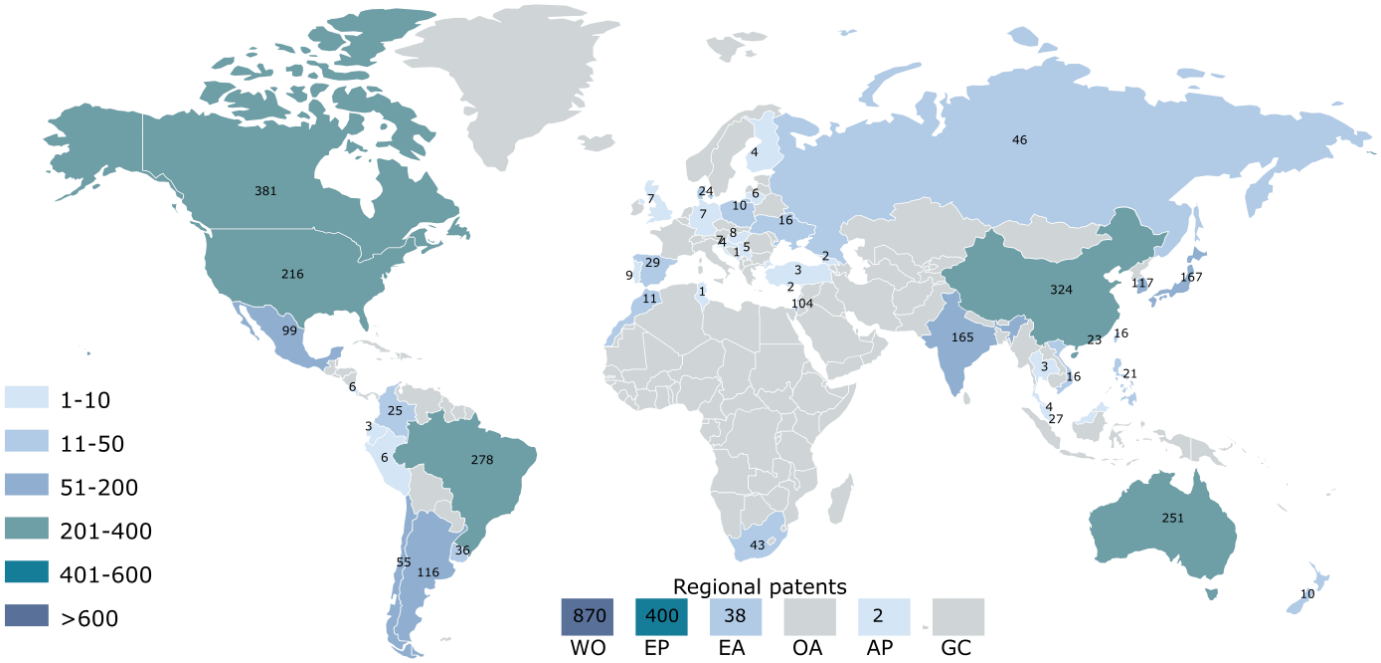


Figure 2.4.3: *The countries and regions **to** which patent protection covering modified plants has been extended **from** a priority filing in another country. WO = "World", ie. patents extended via PCT filings; EP/EA/OA/AP labels are according to https://www.wipo.int/pct/en/texts/reg_des.html. That is: EP = European Patents; EA = Eurasian patents; OA = OAPI African Intellectual Property Organization patents; AP = patent extensions via the African Regional Intellectual Property Organization; GC = Gulf Cooperation Council patents. Colours for the map (and regional boxes) correspond with the number of patent extensions (legend at the left). Switzerland is in grey, as no extensions have been filed specifically to Switzerland (but rather to the EP region).*

Figure 2.4.3 shows the extension of priority filings for CRISPR patents covering modified plants or plant cells. The extensions occurred mainly via the PCT procedure (870 patent families = 62,73%) and the EP extension policy (400 patent families = 28,84%). Most extensions were to Canada (381 patent families = 27,47%) and to the People's Republic of China (324 patent families = 23,36%).

2.4.4 Main patent assignees (≥ 6 patent families)

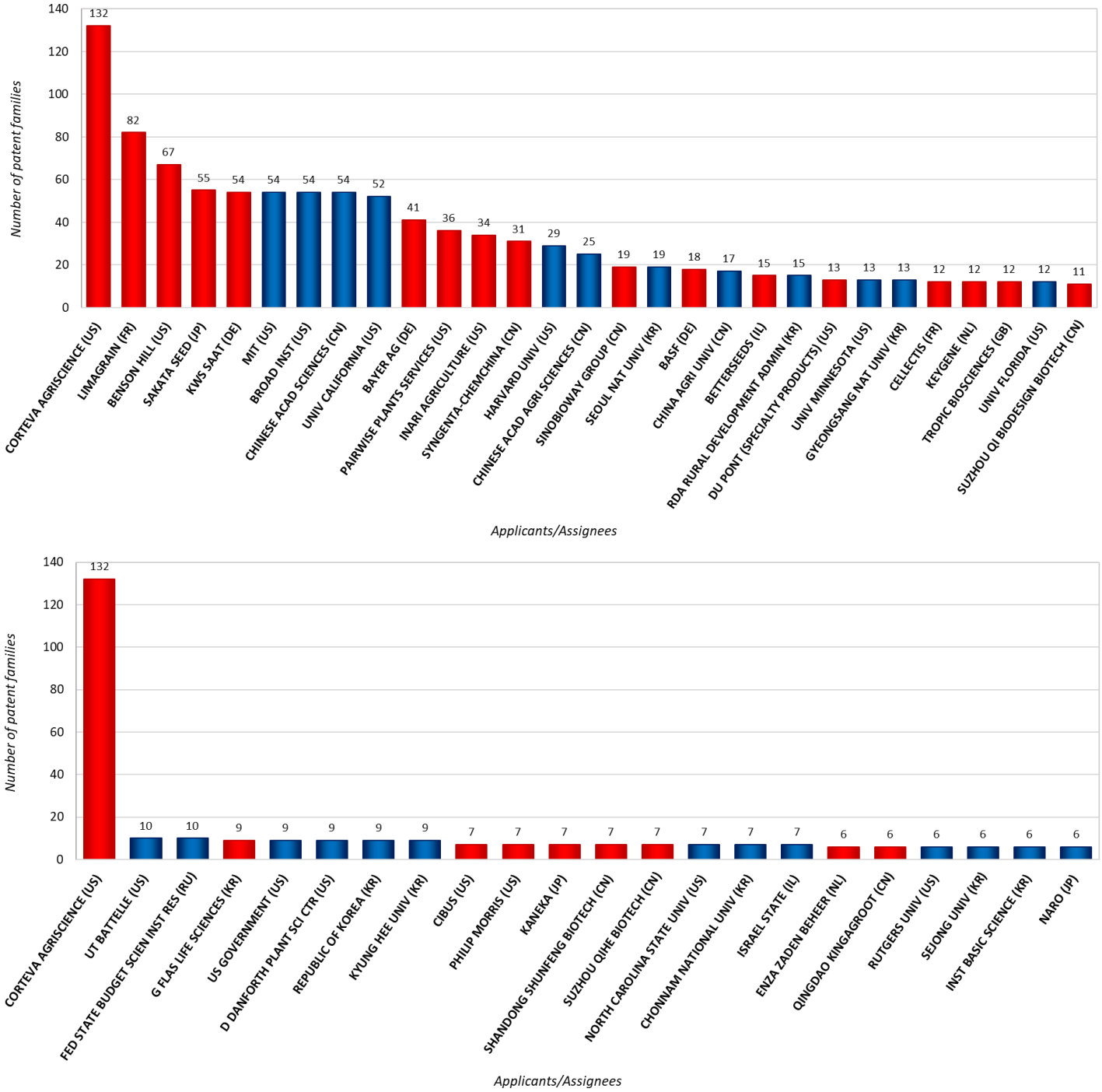


Figure 2.4.4: Top: The top 19 main patent holders/assignees for patents covering modified plants. Blue indicates public entities; red indicates private entities. Bottom: The graph continued with the next top 21, Corteva Agriscience is shown for comparison purposes. Affiliates & subsidiaries have been gathered under their parent company (e.g. Pioneer with Corteva Agriscience). Co-filings are counted for each co-owner: a patent application co-filed between the MIT, the Harvard University and the Broad Institute is counted once for each of these assignees.

The MIT, the Broad Institute of MIT and Harvard, the University of California, the Harvard University have patent portfolios covering some key pioneer patent families on CRISPR-Cas9 and more globally CRISPR enzymes and CRISPR systems for various applications, including plant engineering.
Note the presence of the major agricultural companies: Corteva Agriscience, Limagrain, Sakata Seeds, etc.

2.4.5 Breakdown by Claim coverage of patent families - Breakdown of the patent portfolio

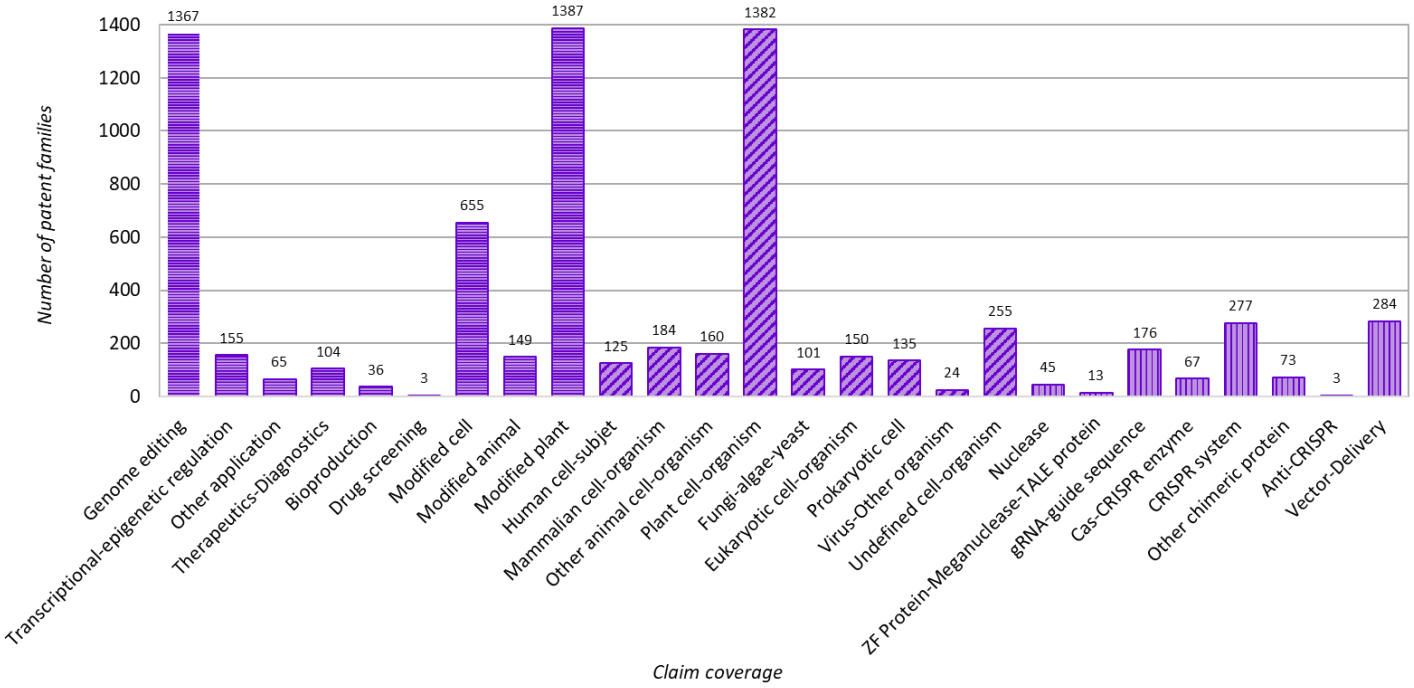


Figure 2.4.5: The number of CRISPR patent families relating to modified plants with claims covering each enumerated area of interest.

This graph shows this data subset is about the use of CRISPR for genome engineering of plants or plant cells. Unsurprisingly, modified plants plant cells are the leading claim categories, in this modified plant subset. Aside from the more generic “genome editing” and “modified cell” categories, note the significant protection of guide RNAs, CRISPR systems, and vectors for such modifications.

2.4.6 Breakdown by Claim coverage of patent families - Positioning of main applicants/assignees (≥ 6 patent families)

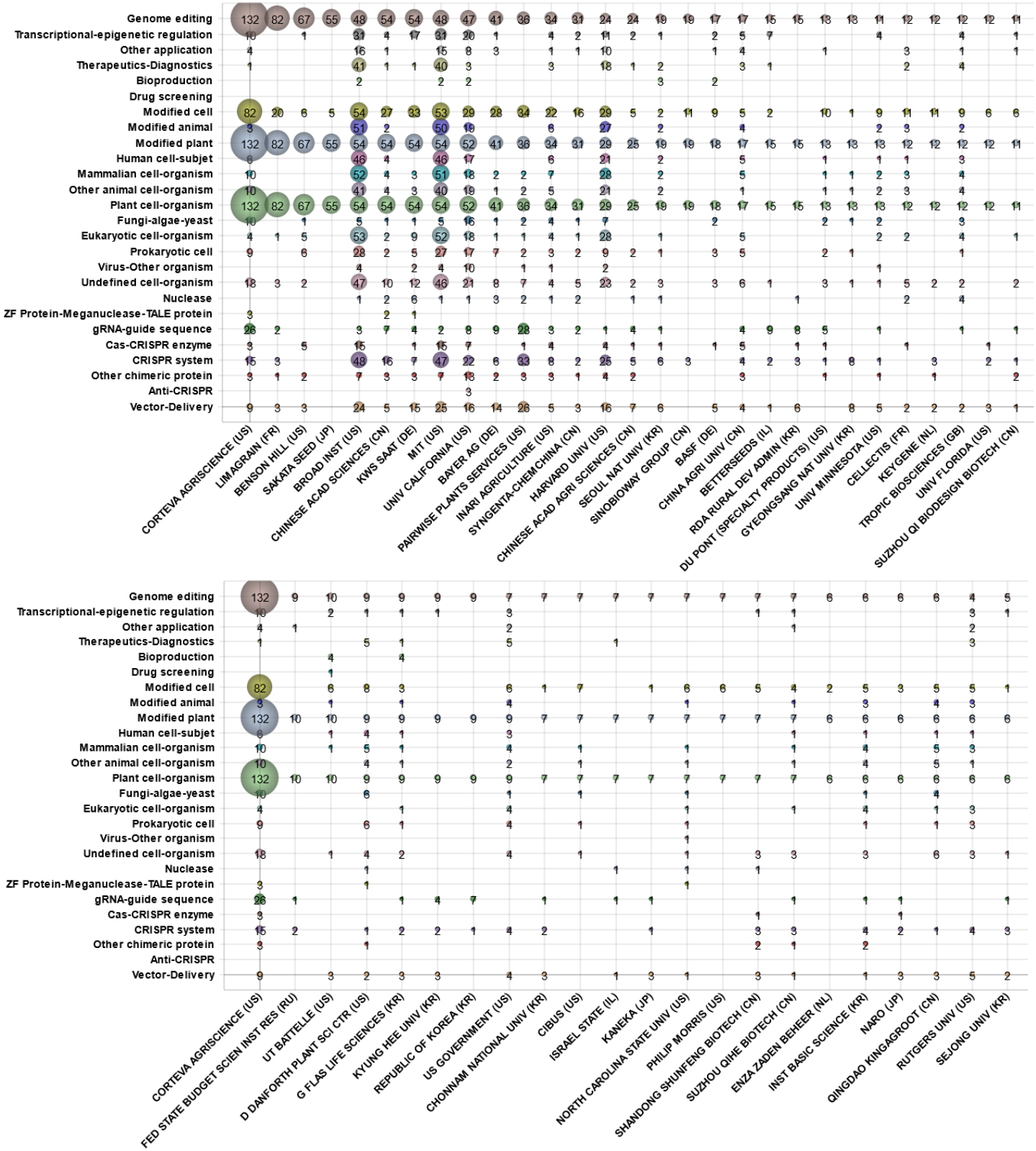


Figure 2.4.6: Top and bottom: a breakdown by claim coverage of patent families by the top patent holders, in order (left to right, then top to bottom) of patent families held. Corteva is shown again in the bottom section for comparison purposes

The main agricultural companies: Corteva Agriscience, Limagrain, Sakata Seeds, etc. own patent families protecting the use of CRISPR for modifying plants. A few of these patent families additionally cover gRNA, and/or CRISPR enzymes and/or CRISPR systems, such as the patent portfolio owned by Pairwise Plant Services.

2.4.7 Breakdown by Components of patent families - Breakdown of the patent portfolio

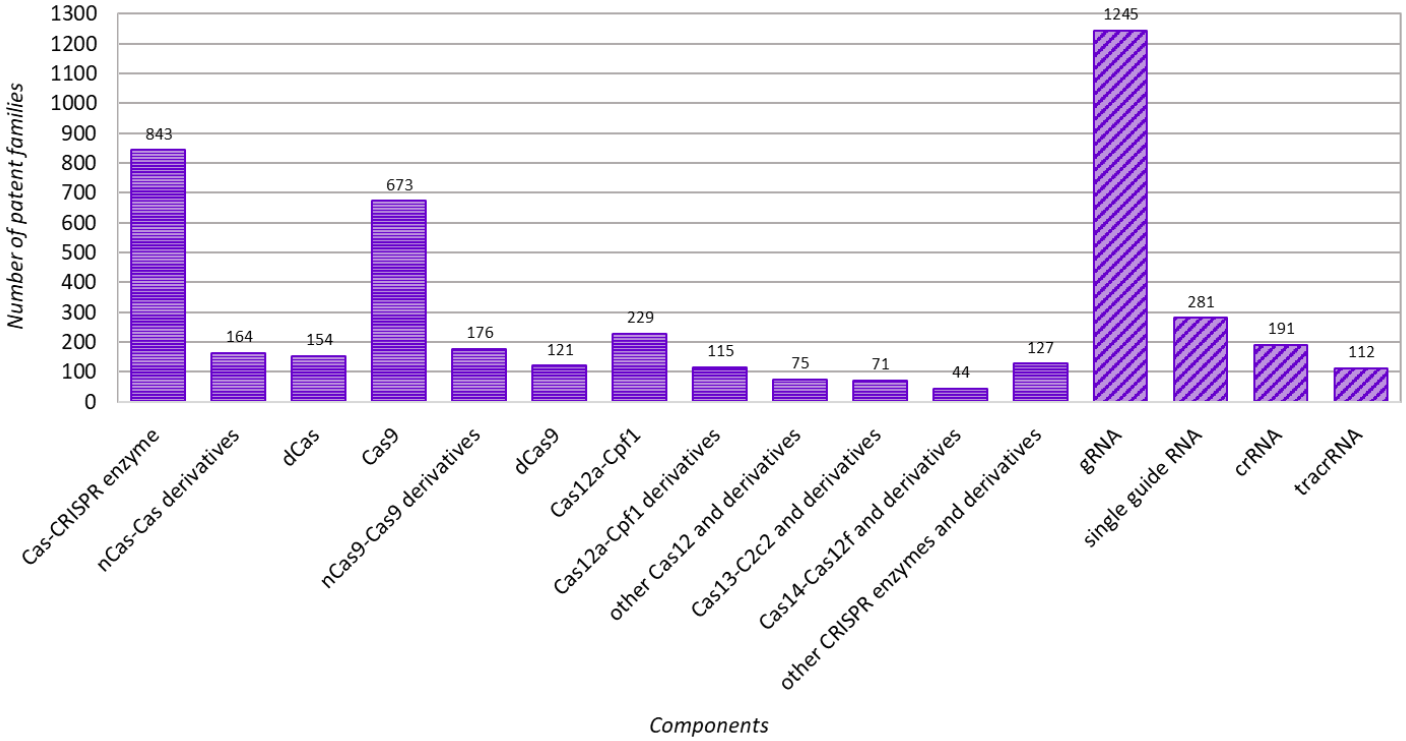


Figure 2.4.7: Number of patent families relating to modified plants with specifications disclosing the use of each enumerated component

Note the most common component covered by these patents is a guide RNA, and most disclose the use of Cas9, but other nucleases are mentioned. Cas12a-Cpf1 is the next most common Cas protein mentioned after Cas9.

2.4.8 Breakdown by Components of patent families - Positioning of main applicants/assignees (≥ 6 patent families)

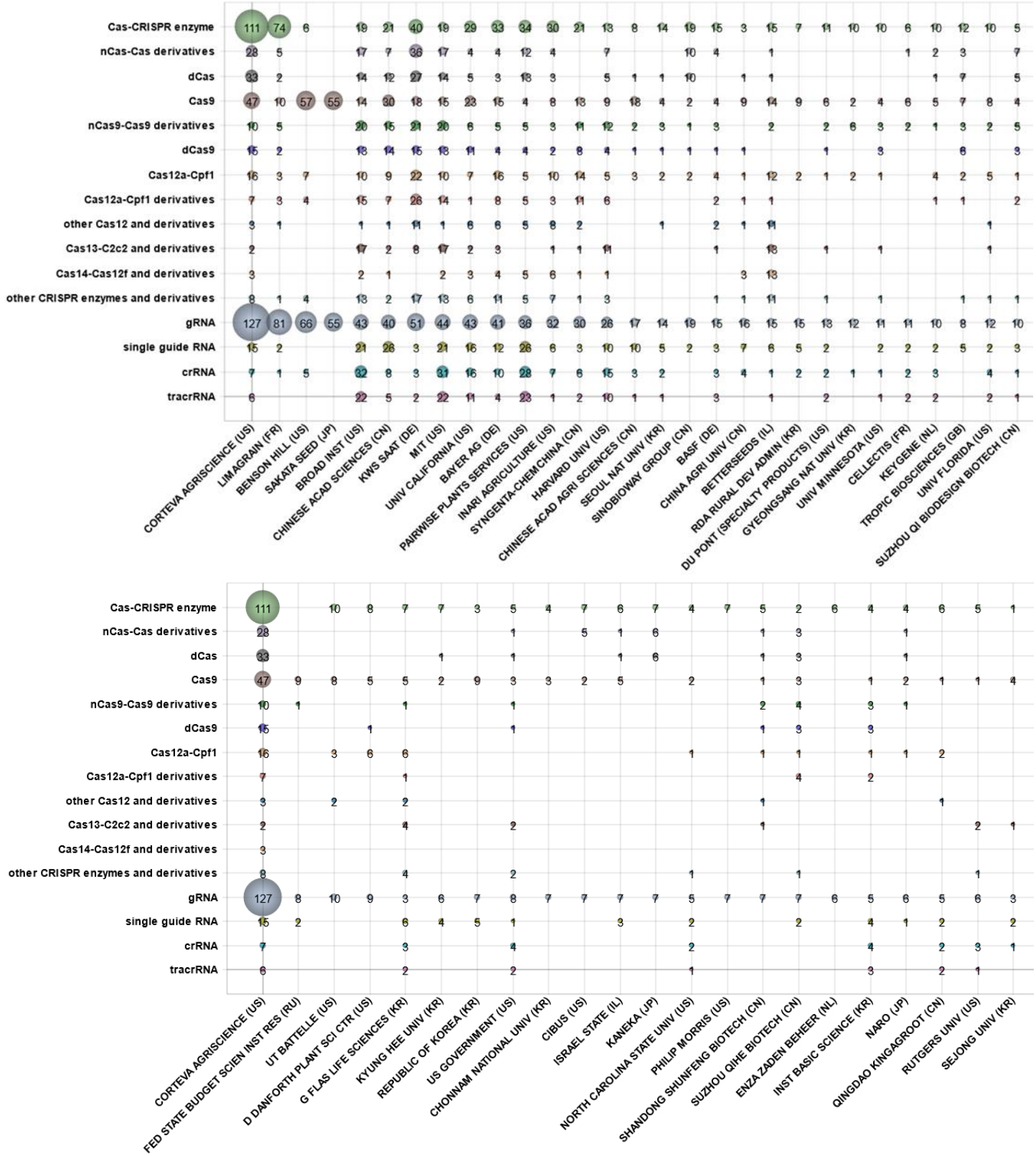


Figure 2.4.8: Top and bottom: a breakdown by components of patent families relating to modified plants by the top patent holders, in order (left to right, then top to bottom) of patent families held. Corteva is shown again in the bottom section for comparison purposes.

2.4.9 Breakdown by Chimeric proteins of patent families - Breakdown of the patent portfolio

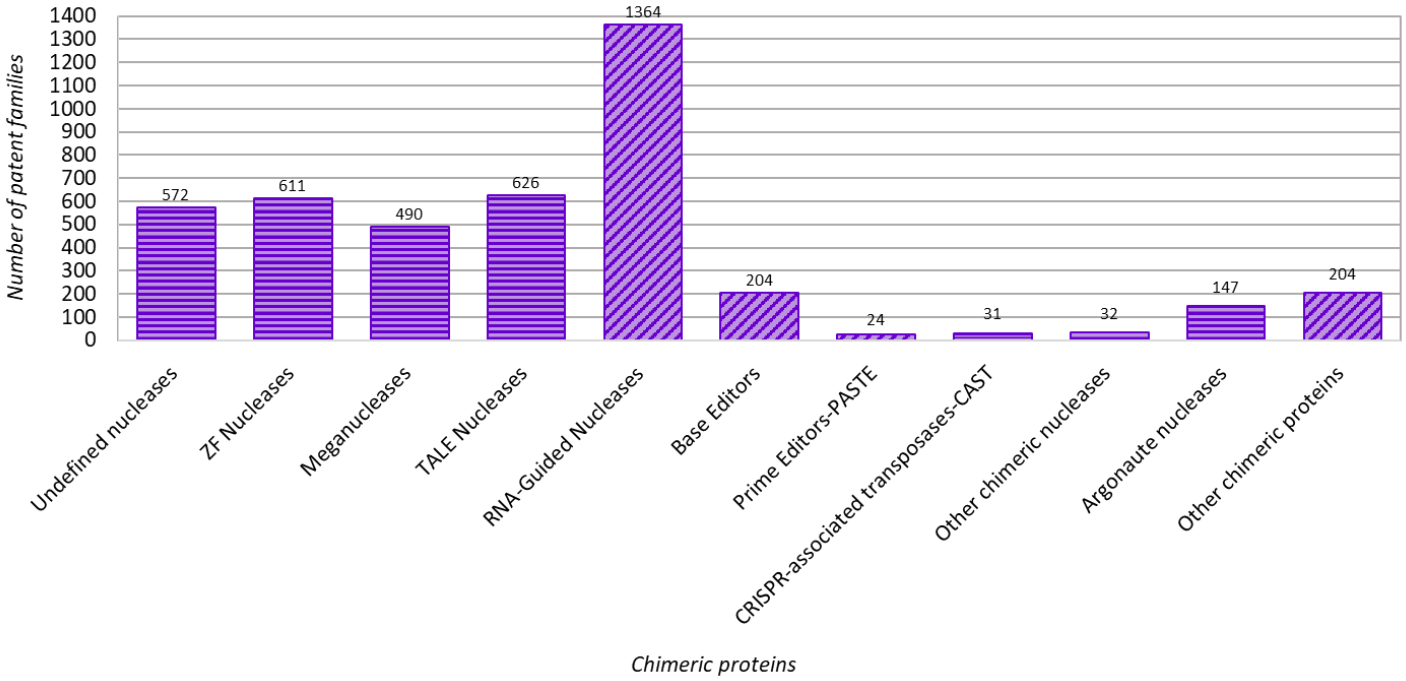


Figure 2.4.9: Number of patent families relating to modified plants with specifications disclosing the use of each enumerated type of chimeric protein

Players in this data set claim the use of CRISPR for modifying plants but also legacy nucleases such as ZFN, TALENs besides CRISPR. Some of them also protect the use of other recent technologies based on CRISPR such as Base Editors or other non-nuclease chimeric proteins such as artificial transcription factors). Note the high number of families generically covering RNA-guided nucleases.

2.4.10 Breakdown by Chimeric proteins of patent families - Positioning of main applicants/assignees (≥ 6 patent families)

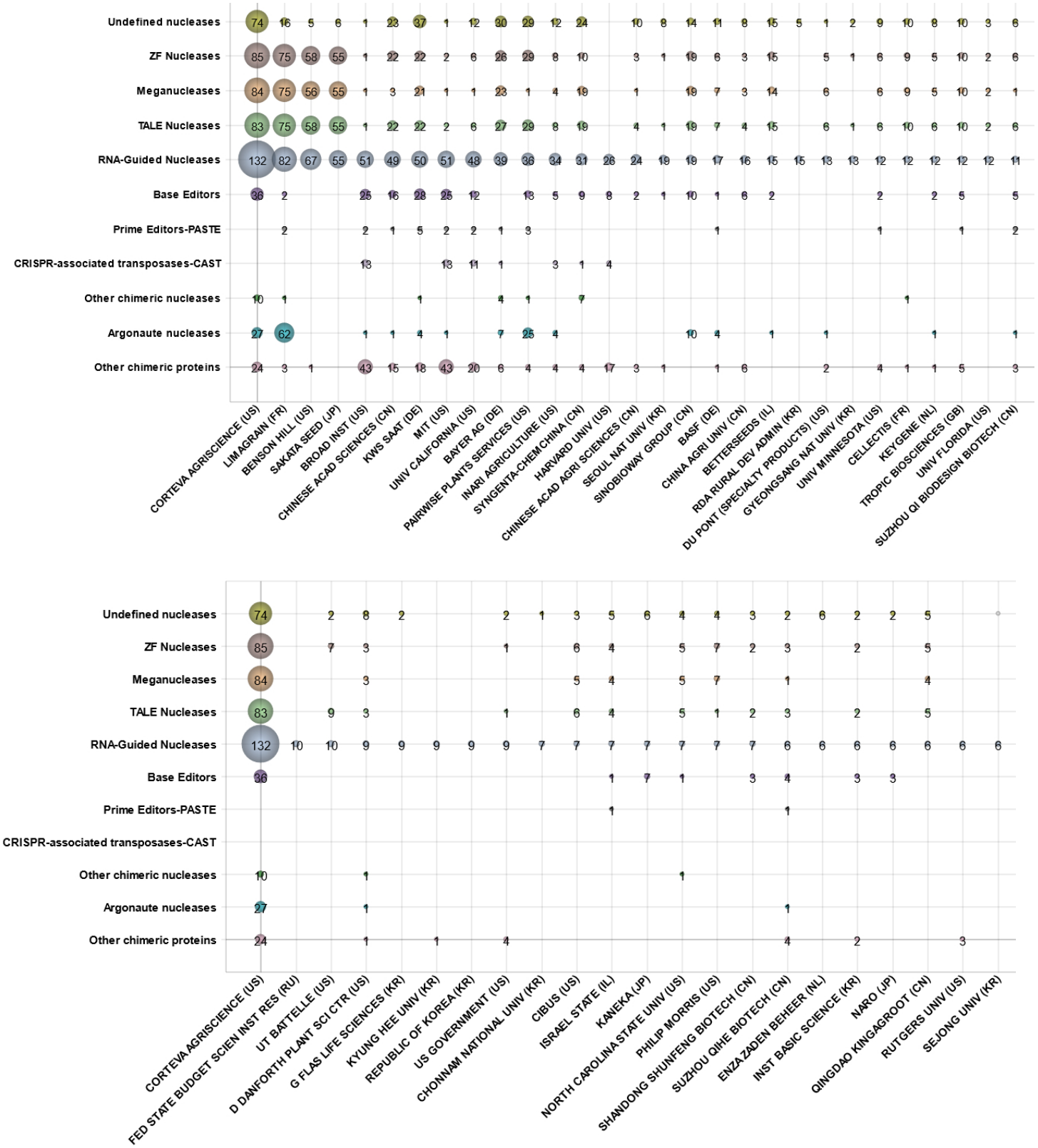


Figure 2.4.10: Top and bottom: a breakdown by chimeric proteins of patent families relating to modified plants by the top patent holders, in order (left to right, then top to bottom) of patent families held. Corteva is shown again in the bottom section for comparison purposes.

Most of the main players claim undefined nucleases or legacy nucleases such as ZFN, TALENs besides CRISPR. Some of them also protect the use of other recent technologies based on CRISPR (Base Editors, Prime Editors, CAST or other non-nuclease chimeric proteins such as artificial transcription factors), such as Corteva Agriscience with 36 patent families, KWS SAAT (28) or Pairwise Plants Services (13) on Base Editors.

2.4.11 Breakdown by Technology cluster and Portfolio size

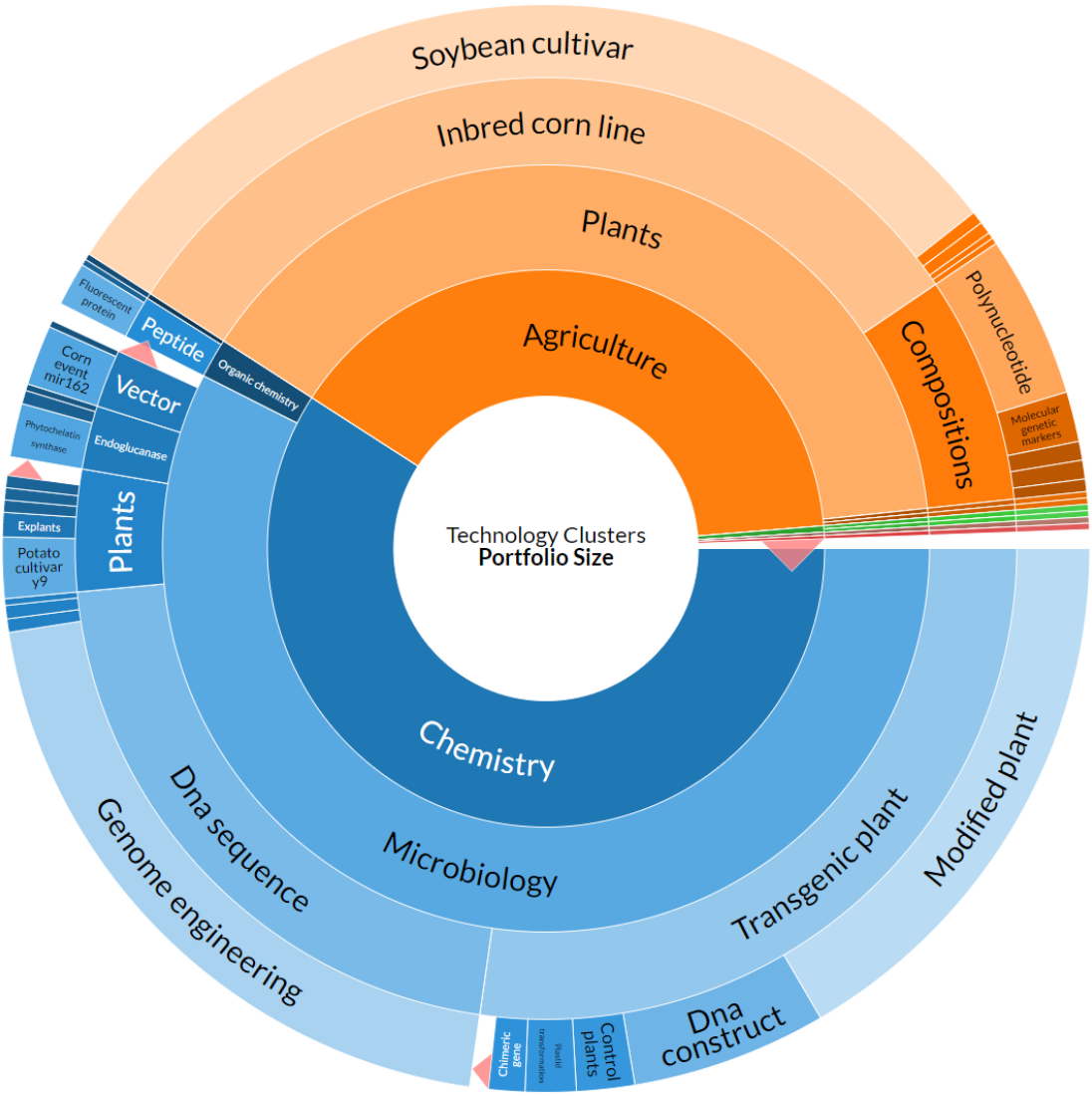


Figure 2.4.11: The portfolio sizes for each technology cluster for the patent portfolios of the major plant agriculture players.

Among the main plant agricultural players, soybean cultivars were a very prominent technology cluster covered their portfolios, highlighting the importance of CRISPR technology to soybean cultivation.

2.4.12 Breakdown by Patent Asset Index

Top Owner by Patent Asset Index

Modified plant (CRISPR Plants Main players 538)

	Owner	Patent Asset Index	Portfolio Size	Competitive Impact	Technology Relevance	Market Coverage
1	Corteva	336	116	4,6	2,4	1,6
2	KWS Saat	165	41	4,0	2,1	1,8
3	Benson Hill	149	57	2,6	1,2	1,2
4	Monsanto (in: Bayer)	147	37	4,0	1,8	2,2
5	Cellectis	128	7	18,2	10,1	1,6
6	Syngenta (in: Sinochem Holdings)	124	31	4,0	2,0	1,9
7	PAIRWISE PLANTS SERVICES	115	32	3,6	1,8	2,1
8	TROPIC BIOSCIENCES UK LIMITED	89	12	7,5	3,0	2,3
9	INARI AGRICULTURE INC	78	27	2,9	1,7	1,7
10	Limagrain	78	69	1,1	1,0	1,1
11	Keygene	52	10	5,2	2,5	2,1
12	Cibus Global	33	7	4,7	2,5	2,0
13	BETTERSEEDS	21	11	1,9	1,1	1,9
14	BENSON HILL HOLDINGS	20	1	19,9	7,0	2,9
15	Sakata Seed	19	53	0,4	0,4	1,0
16	SINOBIOWAY BIO AGRICULTURE GROUP ...	18	19	0,9	0,7	1,3
17	University of Tennessee	16	10	1,6	1,4	1,2
18	Enza Zaden	11	6	1,9	0,8	2,1
19	Battelle	11	8	1,4	1,4	1,0
20	G FLAS LIFE SCIENCES INC	5	6	0,9	0,8	0,5
21	HM CLAUSE S	3	4	0,8	0,8	1,0
22	KEYGENE NV	3	1	2,8	1,0	2,7
23	PAIRWISE PLANTS SERVICES INC	3	1	2,7	1,0	2,7
24	SAKATA SEED CORP	2	3	0,6	0,6	1,0
25	HM CLAUSE INC	1	2	0,7	1,0	0,7
26	SAKATA SEED COPRORATION	0	1	0,4	0,4	1,0
27	BETTERSEEDS LTD	0	1	0,1	1,2	0,1

Figure 2.4.13: Top owners by Patent Asset index for the major players in the plant agricultural field (excluding patents only valid within China). Patent Asset Index is an indicator of the patent portfolio strength. It is calculated at the patent portfolio level as the sum of the Competitive Impacts of all patent families within the portfolio. Competitive Impact is calculated by multiplying the Technology Relevance (measured by citation of the art) by the Market Coverage.

When assessing patent portfolios by the Patent Asset index, it is clear that Corteva holds a commanding lead in the use of CRISPR technology in plant agriculture.

2.5 CRISPR PATENT LANDSCAPE: Modified Plants - CN priority filings with no extension

2.5.1 Temporal distribution of patent filings (2012-2022)

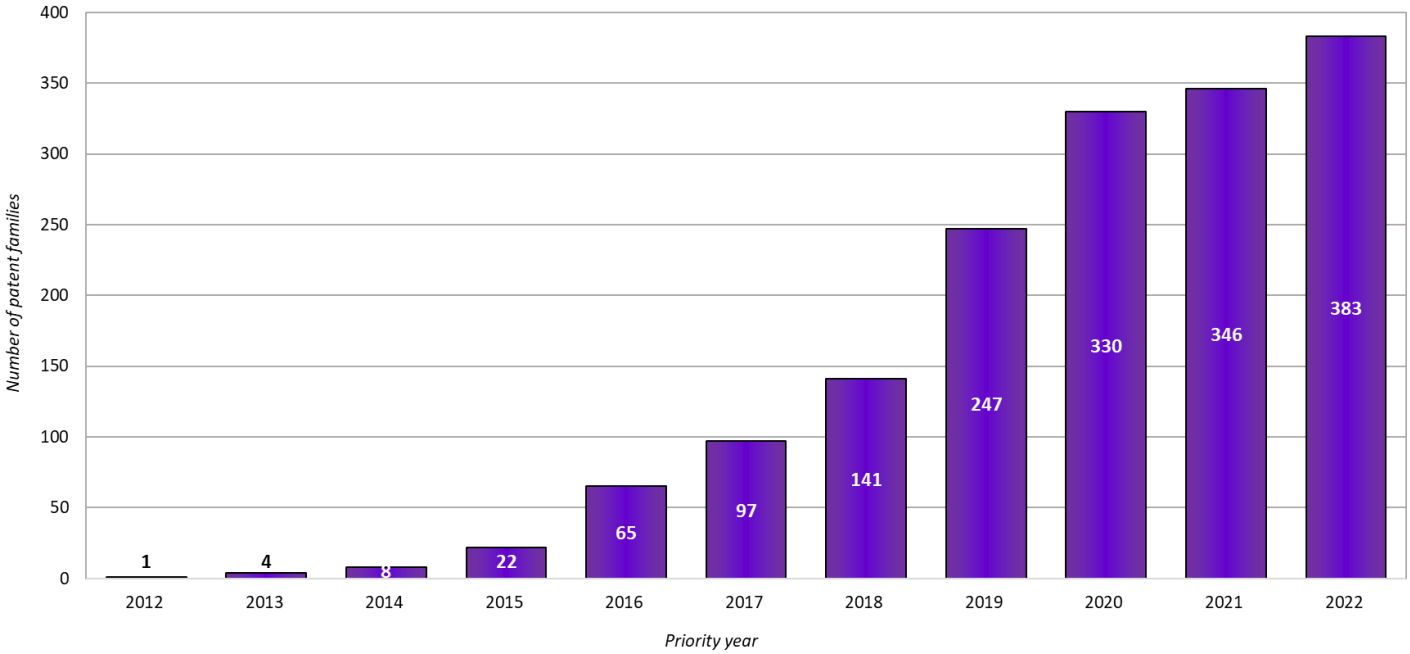


Figure 2.5: Number of patent families covering modified plants by priority year, for patents only valid in China (Chinese patents extended beyond China are excluded).

There are 1’808 patent families covering modified plants in this data set (data from Sept.-Oct. 2023), that are only valid in China (Chinese priority filings that have not been extended outside of the People's Republic of China).

2.5.2 Main patent assignees (≥ 11 patent families)

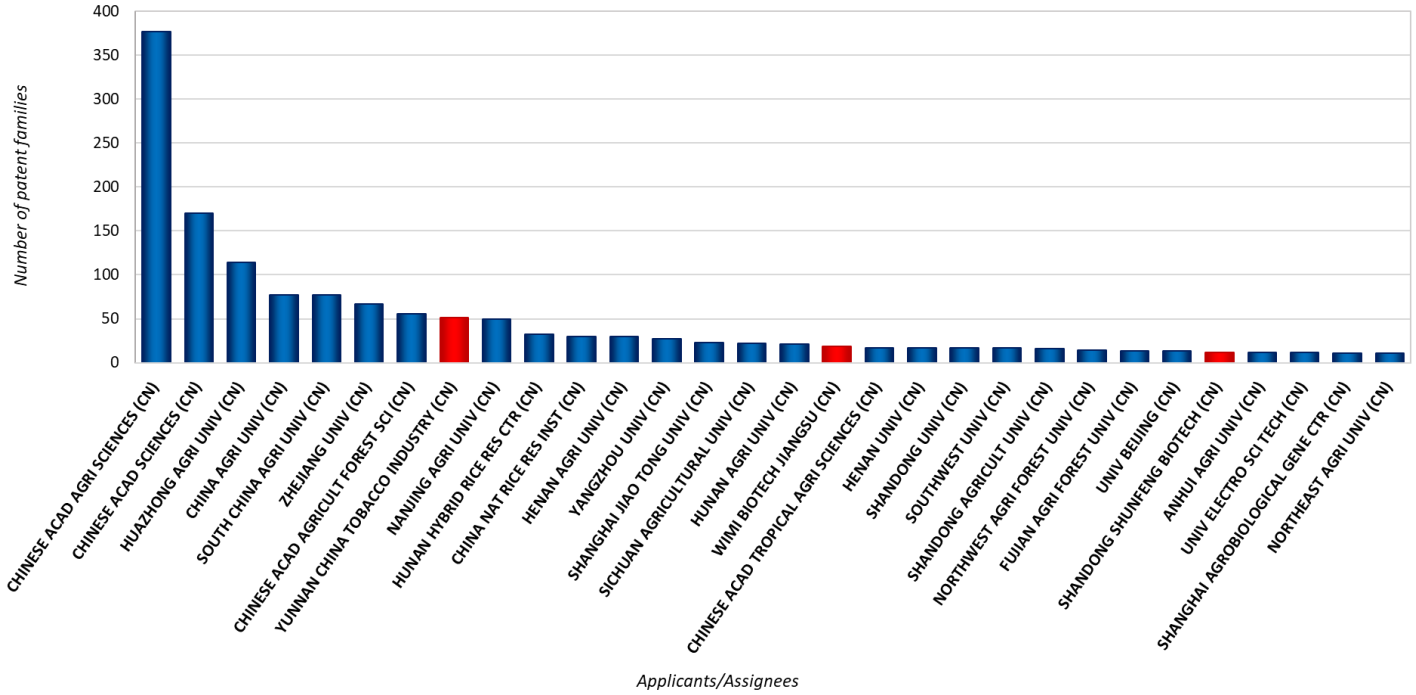


Figure 2.5.2: Number of patent families valid only in China by assignee. Blue indicates public entities; red indicates private entities. Affiliates & subsidiaries have been gathered under their parent company (e.g. Pioneer with Corteva Agriscience). Co-filings are counted for each co-owner. The Chinese Academy of Sciences and the Chinese Academy of Agricultural Sciences include academic labs affiliated to them.

The Chinese Academy of Sciences and the Chinese Academy of Agricultural Sciences are the top players in the CRISPR modified-plant Patent Landscape in China, illustrating the importance and the stake of Genome Editing technologies of plant modification by the Chinese government.
Most of the main players are public entities/academic labs in contrast to the situation outside of China, where the main players are agricultural companies.

2.5.3 Breakdown by Claim coverage of patent families - Breakdown of the patent portfolio

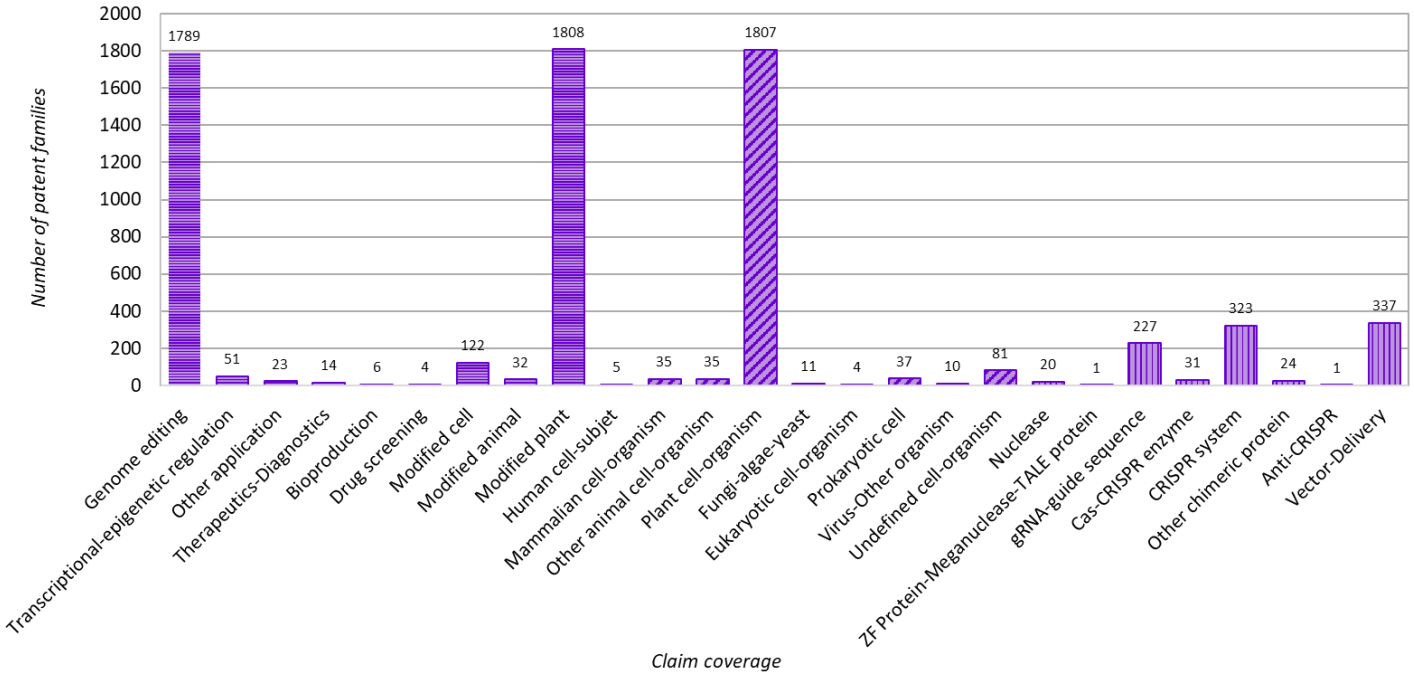


Figure 2.5.3: The number of CRISPR patent families, valid only in China, relating to modified plants with claims covering each enumerated area of interest

This graph shows this data subset is about the use of CRISPR for genome engineering in plants. Of note, some players have also protected guide RNA or CRISPR systems, or vectors for such modifications.

2.5.4 Breakdown by Claim coverage of patent families - Positioning of main applicants/assignees (≥ 11 patent families)

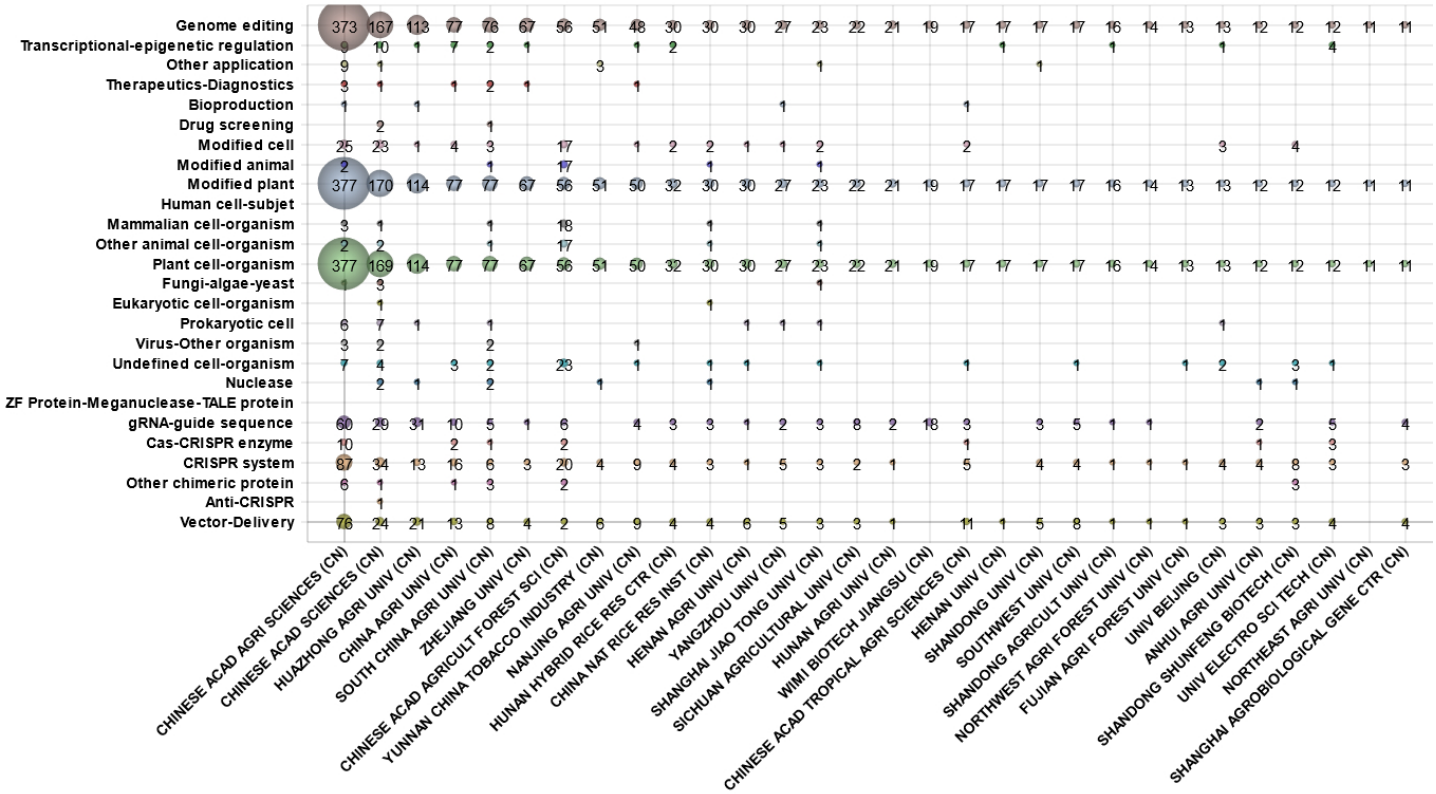


Figure 2.5.4: A breakdown by chimeric proteins of patent families, valid only in China, by the top patent holders, in order (left to right) of patent families held.

As discussed earlier, some players have protected plants and methods of producing such plants but also guide RNA or CRISPR systems for such modifications.

2.5.5 Breakdown by Components of patent families - Breakdown of the patent portfolio

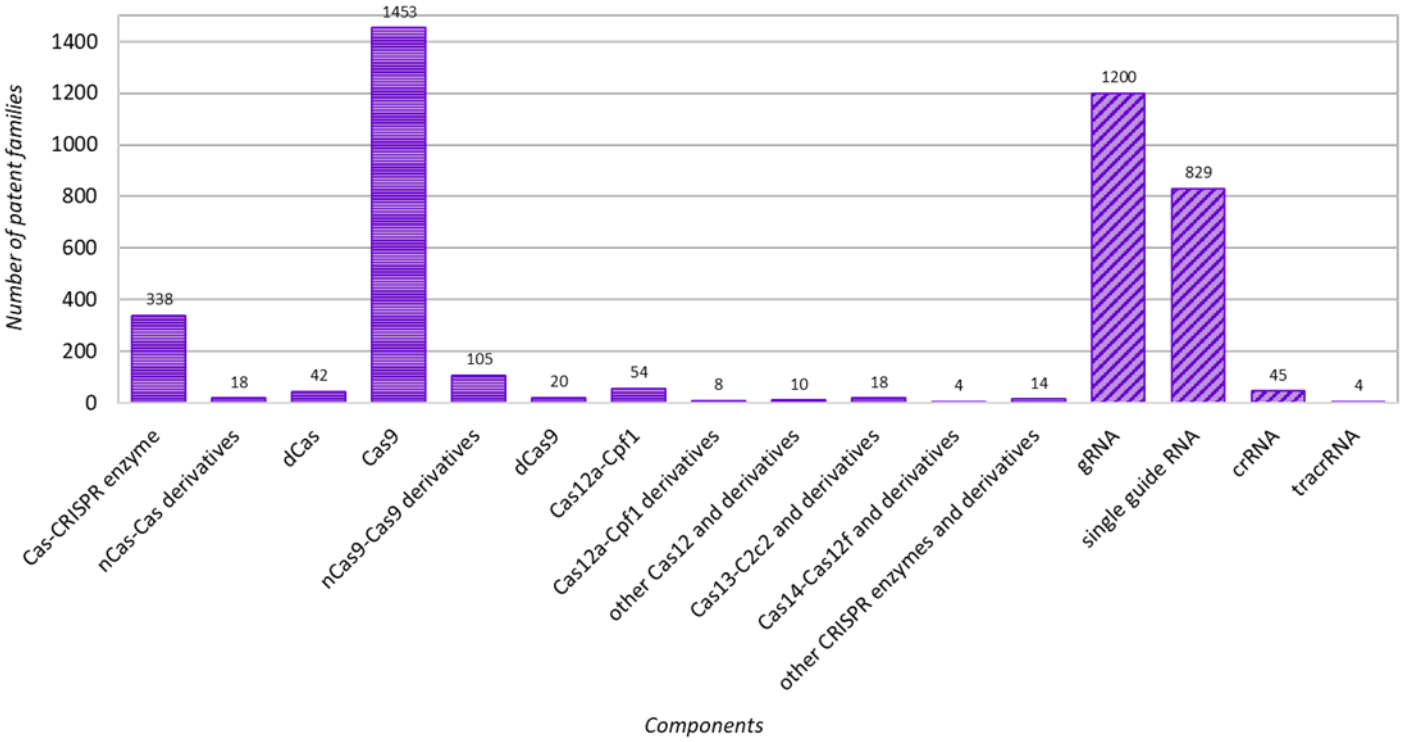


Figure 2.5.5: Number of patent families, valid only in China, relating to modified plants with specifications disclosing the use of each enumerated component

Cas9 is the main claimed CRISPR enzyme in this focus. (80.37% of 1'808 patent families having Chinese priority filings that have not been extended outside of the People's Republic of China). Chinese players mainly claim a guide RNA (gRNA) or single guide RNA (sgRNA), but sgRNA is also often defined as gRNA in the definition sections of the descriptions. Again, Cas12a-Cpf1 is the next most commonly referenced Cas protein, but to a lower extent than the patent families outside of China.

2.5.6 Breakdown by Components of patent families - Positioning of main applicants/assignees (≥ 11 patent families)

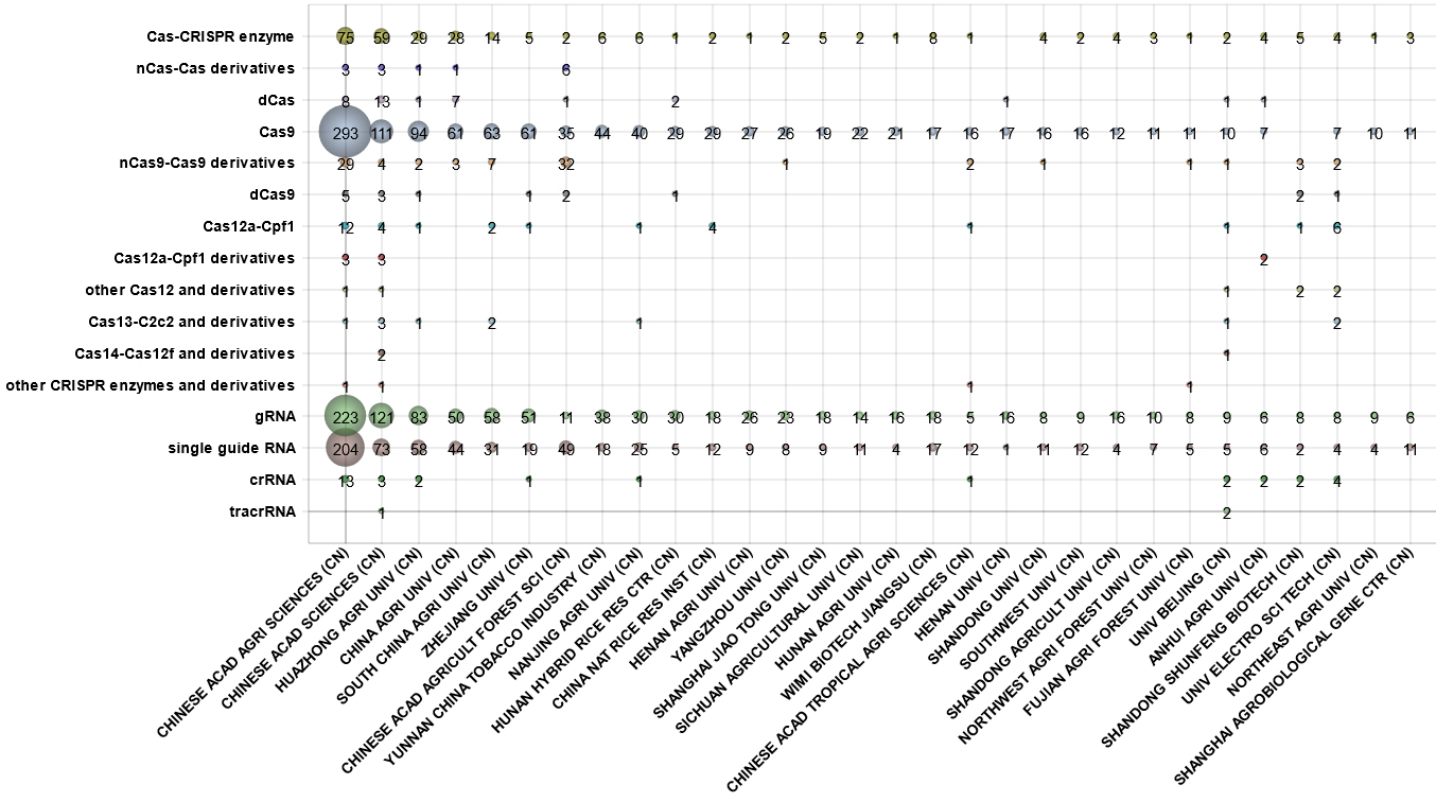


Figure 2.5.6: A breakdown by chimeric proteins of patent families relating to modified plant, valid only in China, by the top patent holders, in order (left to right) of patent families held.

A few players among the top players also cover other CRISPR enzymes such as Cas12a (*eg.*: Chinese Academy of Agricultural Sciences, University of Electronic Science Technology of China).

2.5.7 Breakdown by Chimeric proteins of patent families - Breakdown of the patent portfolio

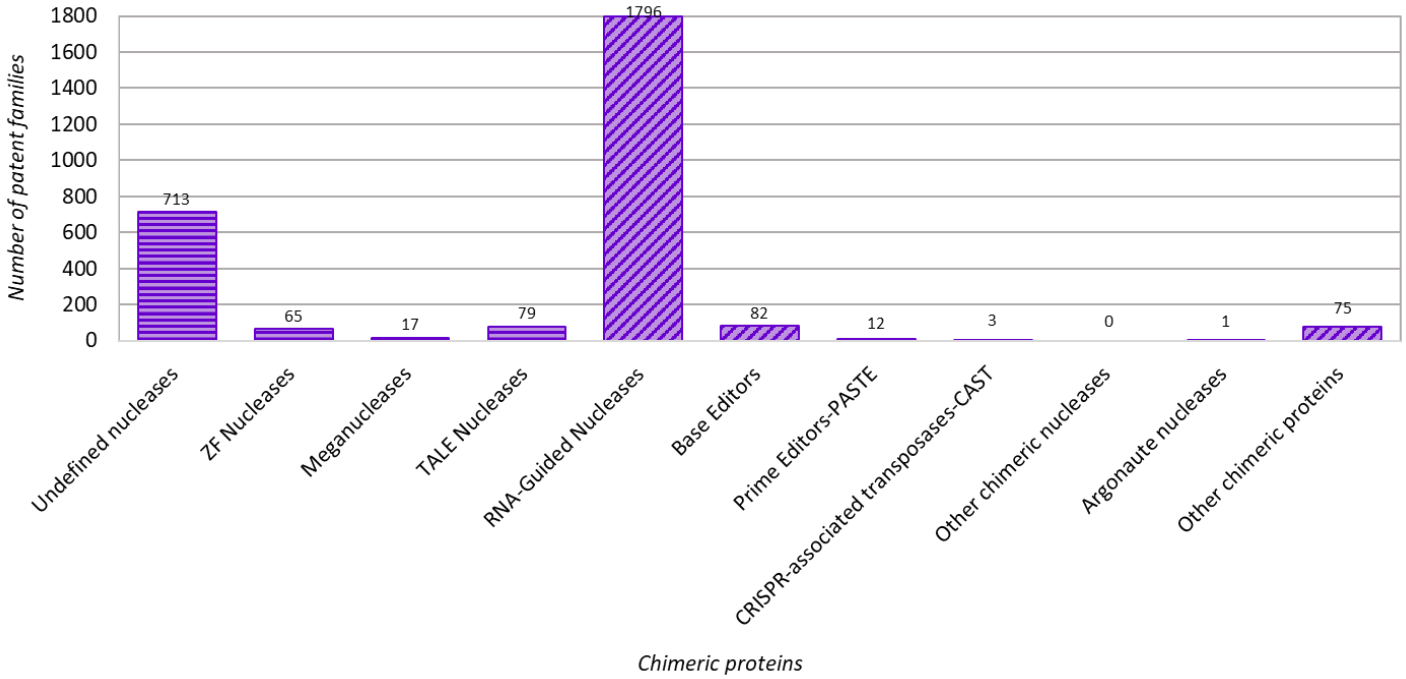


Figure 2.5.7: Number of patent families, valid only in China, relating to modified plants with specifications disclosing the use of each enumerated type of chimeric protein

Most of these Chinese Players claim RNA-guide nuclease for producing genome editing in plants and eventually an undefined nuclease. Of note, other recent technologies based on CRISPR (Base Editors, Prime Editors, CAST or other non-nuclease chimeric proteins such as artificial transcription factors) are barely covered in the plant related CRISPR patents in the People's Republic of China, in contrast to the situation outside of China.

2.5.8 Breakdown by Chimeric proteins of patent families – Positioning of main applicants/assignees (≥ 11 patent families)

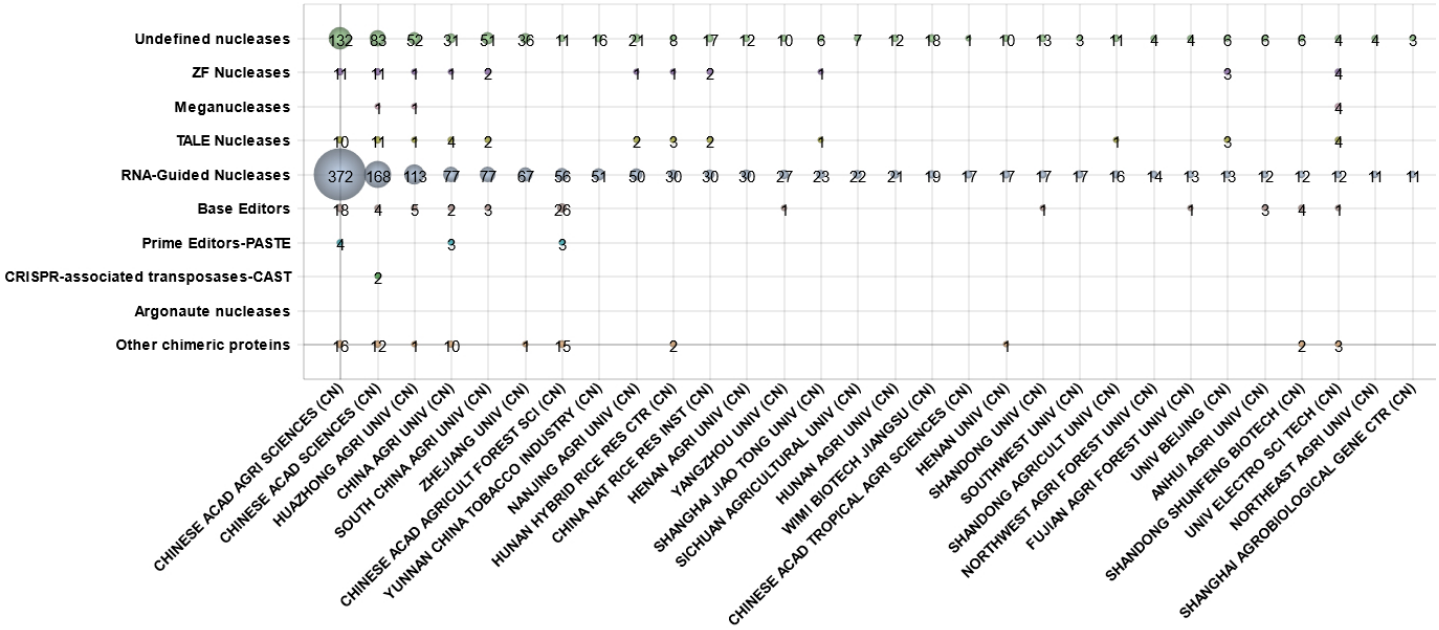


Figure 2.5.8: a breakdown by chimeric proteins of patent families, valid only in China, relating to modified plants by the top patent holders, in order (left to right) of patent families held.

Compare with section 2.4.10 and note the paucity of coverage extending also to other nuclease types (ZF, Mega, and TALE nucleases). Also note that the Chinese Academy of Agricultural Sciences leads the base-editing category with 26 patent families on the use of Base Editors in plants, despite being far behind in the total patent number (and RNA-guided nucleases in particular).

3 CRISPR technology: License Landscape

Note: this section primarily explores licensing within the agricultural domain

3.1 Key points

- Two groups ("CVC" and "Broad") hold issued foundational CRISPR-Cas9 patents
    - Broad's patent protection applies only to eukaryotes, is subject to multiple challenges, and has a reduced scope in Europe
- Two groups (Toolgen and Sigma Aldritch) have pending patent applications covering usage in eukaryotes, before Broad and CVC,
    - Sigma Aldrich's granted foundational patents only cover integration/insertion of DNA within eukaryotes with Cas9
    - Sigma Aldrich and Broad have conclused cross-licensing agreements
- The CVC group holds unchallenged patents on the use of Cas9 generically in any cell
    - 4 groups (CVC, Broad, Sigma-Aldrich, toolgen) are competing for the use specifically in eukaryotes
    - CVC patent protection in eukaryotes is subject to multiple challenges, and is not valid in the USA.
- Agricultural applications of Cas9 would likely require licenses from CVC and at least one other group
- The majority of granted licenses are non-exclusive licenses.
    - Broad only grants exclusive licenses for human therapeutics
    - CVC has granted exclusive licenses in the field of Agriculture, particularly to Corteva
    - No regional or national restrictions have been noted, except for the CVC license to Regional Fish Institute, which is limited to the Asia-Pacific region
- Broad does not grant exclusive licenses in the agricultural field (only in the field of human therapeutics)
    - No license is needed from Broad for non-Commercial/academic/governmental research
    - No license is needed from CVC for academic research (governmental research policy is not specified)
- The CVC group has granted some exclusive licenses (thus a legal monopoly) in specific areas of the agricultural field, primarily to Corteva
    - Corteva does grant sub-licenses
    - Corteva has non-exclusive licenses from the Broad group
    - Licenses for CRISPR-Cas9 are not needed for purely academic research
    - Licenses for alternatives like Cas12 are still obtainable from other players
- There are multiple systems similar to CRISPR, and alternative CRISPR systems to CRISPR-Cas9
    - The CVC group's foundational patents cover only Cas9
    - Broad leads in the identification of alternative CRISPR systems
    - The widely used TALEN system patents will expire soon
- The exclusive licenses are not problematic given the plethora of Cas9 alternatives
    - Sub-licenses are given
    - The existence of these exclusive licenses encourages the invention of these other systems – the patent system is thus encouraging innovation

3.2 Background

The international licensing situation is made more complex by the dispute between four major groups:
The first group, “CVC”, is composed of the inventors of the first uses of the CRISPR system (primarily Doudna of the University of California- Berkeley, and Charpentier of the University of Vienna). In 2016 the groups of the University of California and the University of Vienna, and the respective inventors (Doudna, Charpentier) and associated companies (ERS genomics, Caribou Biosciences, CRISPR Therapeutics, Intellia Therapeutics) announced that they “have entered into a global cross-consent and invention management agreement for the foundational intellectual property covering CRISPR/Cas9 gene editing technology”(16). Thus these companies and inventors can be largely treated as a single unit for most licensing purposes.
The second group, “Broad”, is led by the Broad institute (of the Massachusetts Institute of Technology and Harvard University), which was the first to have a patent issued for the use of the CRISPR system in eukaryotes.
The two remaining groups, Sigma-Aldrich and Toolgen, have both applied for patents applying CRISPR technology to eukaryotes, and there are thus four groups competing for coverage of the use of CRISPR in eukaryotes. Currently Toolgen does not have any issued foundational patents. Sigma Aldrich has patents covering using CRISPR to lead to integration of introduced DNA in eukaryotes. Sigma-Aldrich and Toolgen’s more foundational claims on the general use of CRISPR-Cas9 in eukaryotes are still ungranted, and legal disputes are ongoing.
In Europe, Broad’s foundational patents were invalidated over issues with the assignment of patent rights by the inventors(15), leaving only the CVC foundational patents standing. Many of Broad’s derivative/non-foundational patents will still be valid, and the exact extent of the scope of their patent protection in Europe that will be upheld is unclear. In the USA, Broad’s patents were upheld, requiring parties to license the patents from both CVC (for the general use of the CRISPR technology) and from Broad (for the use in eukaryotes, and thus in plants)(11). If the cultivation of genetically modified or edited plants is is expanded in Europe, this difference would likely lead to the need to conclude separate licensing agreements for the sale of CRISPR modified plants/seed in different locations. Please see table 3.2.1 below for an overview of the major patent holders and the fields covered by their patents.

Company	IP claimants	Applications
ERS Genomics	Emmanuelle Charpentier	Animal Models, Drug Discovery, Industrial Biology, Research Tools
CRISPR Therapeutics		β-Thalassemia, Cystic Fibrosis, Muscular dystrophy, Sickle Cell Anaemia
Caribou BioSciences	University of California, Berkeley	Agriculture, Drug Discovery, Industrial Biology, Livestock, Research Tools
Intellia Therapeutics		α-1 Anti-Trypsin, CART Cells, Stem Cells
Editas Medicine	Broad Institute	α-1 Anti-Trypsin, β-Thalassemia, CART Cells, Cystic Fibrosis, Leber Congenital Amaurosis, Muscular dystrophy, Sickle Cell Anaemia, Stem Cells
Broad Institute		Agriculture, Animal Models, Drug Discovery, Research Tools

Table 3.2.1, An overview of the major companies, holders of IP, and areas of exploitation of the CRISPR patents(17)

Regardless of this dispute, the sheer amount of patents will require any commercial actor to obtain licenses for multiple patents from multiple groups. There is no true patent pool to simplify the process of licensing.

3.2.1 CRISPR-Cas9 and Alternatives

Many of the patents held by Corteva apply only to Cas9 and the use of a single guide RNA, and there are many other suitable Cas proteins aside from Cas9. This leaves considerable opportunities

for systems using alternative nucleases or dual-guide RNAs. Much of what is done by CRISPR-Cas9 is also achievable, *mutatis mutandis*, with other RNA guided systems such as CRISPR-Cas12, Fanzor/OMEGA proteins (which are evolutionarily related to CRISPR-Cas9); with DNA-guided systems such as Argonaute proteins; and with protein only systems such as TALENs and Zinc-Finger-Proteases.
Some chimeric nucleases have been paired with the CRISPR-Cas system, such as the *Cas-CLOVER* system developed by Demeetra, with an apparent goal to circumvent the CRISPR-Cas9 patents. The system in question makes use of a catalytically inactive derivative of the Cas9 protein, leading to questions of what is covered by the CRISPR-Cas9 patents – as Demeetra recently concluded a licensing agreement with the CVC group(18), it seems the question has been settled and such derivatives are covered.
The TALEN system is older (although it requires more time and labour to use) than the CRISPR-Cas9 system, thus the foundational TALEN patents will expire earlier. In the USA TALEN-modified plants occupy a large share of the market, and this system should be kept in mind. The CRISPR system's main advantage over the TALEN system is that it uses a guide RNA that can be rapidly and easily synthesized, in contrast to the TALEN system which requires a slower and more labour-intensive assembly of a plasmid from a module library. The CRISPR system is thus much more suitable than the TALEN system for high throughput applications.
The great variety of near-interchangeable systems opens many possibilities to acquire licenses for a suitable technology. This relatively large supply of suitable licenses would be expected to drive down the licensing costs. Furthermore, it would also be possible to use a reduced scope license to carry out preliminary research using CRISPR, and then switch to using an older technology such as TALENs in the later development stages when the most suitable candidates have already been selected and high through-put is no longer needed.
In recognition of the near-interchangeability of CRISPR-Cas9 with these other systems, the trend has been for more recent, non-foundational patents, to reference all these systems (or a generic system capable of cutting/modifying specific nucleic acid sequences) in the claims when appropriate.
Additionally, Broad has been striving to identify alternative Cas9 proteins and systems, and is currently the leader in the identification of these alternatives(19) – recently publishing a paper which identified 188 CRISPR-linked gene modules. Despite the aforementioned wide variety of suitable systems, it remains possible that most of them will end up being held by only a few entities. This, combined with the trend for non-foundational patents to cover all systems similar to CRISPR, may mitigate the effects of the large variety of suitable systems and only lead to a modest drop in licenese costs.

3.3 Licensing policies

"Are licenses only granted to large organizations or also to public research institutions and SMEs or even micro-enterprises?"

The exact terms of licensing agreements are rarely made public, and when public announcements of licensing agreements are made public, the details are often quite vague. Public descriptions of the scope of the rights granted rarely specify if the rights are restricted to systems using the Cas9 nuclease or not, nor what the exact conditions or use are.
Licenses are generally granted (or not even needed) for public research institutions. One major patent holder, the Broad Institute, has publicly clarified its licensing policy (Table 3.3)(20). That policy specifically states: "*For academic and non-profit research use, no written license is necessary […] to the extent such research does not include the production or manufacture of products for sale or offer for sale or performance of commercial services for a fee*".

	Broad Institute			
Use	Academic/non-Profit/Government research	Reagents and kits for genome editing	Non-human use/research	Human Therapeutics
Licensing policy	No license needed	Non-exclusive licenses sold	Non-exclusive licenses sold	Exclusive* licenses sold

*Table 3.3: Broad institute licensing policies. *Exclusive licenses are sold under the "inclusive innovation model" described in the text below*

The Broad Institute explicitly states that they generally will offer exclusive licenses for Human therapeutics in order to encourage the necessary level of investment. It is unclear if exclusive licenses will be deemed suitable for any other applications, as company policies can change. The Broad Institute describes an "inclusive innovation model" in which exclusive licenses are granted only for specific genes. Under their model, third parties may be issued a license, after a predefined period of time, "for use against genes that are not being pursued by the primary licensee".
The Sigma-Aldritch licensing policy is broadly similar to that of the Broad institute(21):

- academic and non-commercial research does not require a license
- reagents and kit production licences are non-exclusive
- human therapeutic uses may be exclusive "as necessary"
- other commercial licenses may be "field-exclusive or disease or trait indication-exclusive based on availability for research, production, therapeutic and agricultural uses"

In contrast, the CVC group's publicly available licensing policy is less specific. Like the Broad institute, "purely academic" use does not require a license. The CVC group (ERS genomics) has stated that it may require a license for other types of research and cautions academic groups about selling products "even to other academic institutions", and transferring CRISPR modified organisms to non-commercial entities(22–24). They state that "ERS genomics offers affordable licensing for incubators and startups". They further encourage any group to contact them first to clarify the situation.
More generally, the publicly available data on the license landscape indicates that the major patentholders are willing to grant exclusive licenses, but these licenses are generally restricted to narrow applications and/or species, generally in accordance with the licensee's ability to exploit the scope of the license (as described in detail above for the Broad institute's publicly stated policies). Vilnius University and the University of Vienna are notable exceptions, having granted exclusive licenses for all agricultural applications.

3.4 Comparison with other fields

As mentioned above, except for human therapeutics, the general policy of the major CRISPR IP holders is to grant non-exclusive licenses. Similarly, basic research and development for non-commercial purposes does not need a license. The licensing policies here are in line with all other fields for commercial research and production.

3.5 Agricultural and non-Agricultural license landscapes

3.5.1 Agricultural license landscape

Table 3.5.1 below gives an overview of the licensing status in the field of agriculture and aquaculture.

Fundamental Patent Holder	Licensee	Field	Type
Broad, Harvard, MIT (Zhang)	Bayer-Monsanto	Seed development	Non-Exclusive
	BASF	All Agricultural Applications	
	Corteva		
	Syngenta		
	Pairwise		
	Harpe Bio	Bioherbicides	
	Vilmorin & Cie	Agricultural use (seeds), Cas9 and Cpf1	
	International Rice Research Institute	Rice variety development	
	JR Simplot	Spoiling resistant crops, Cas9	
	Yield10 Bioscience	Crop research, Cas9	
	Amfora	Crops with more protein, Cas9	
	Sustainable Oils	Camelina for Biofuels	
	Bioresource Intl.	enzyme feed additives	
University of California, Berkeley (Doudna, Caribou Biosciences) – CVC	*Corteva*	Major Row crops	Exclusive
		Agriculture/ industry applications	Non-Exclusive
	Genus	Livestock	Exclusive
	Regional Fish Institute	Fish, other non-mammalian marine animals	Non-Exclusive
	TreeCo	Tree Agriculture	Exclusive
	Harpe Bio	Bioherbicides	Non-Exclusive
	Vilmorin & Cie	Agricultural use (seeds), Cpf1 and Cas9	
	International Rice Research Institute	Rice variety R&D with Cas9	
	JR Simplot	Spoiling resistant crops, Cas9	
	Yield10 Bioscience	Crop research, Cas9	
	Amfora	Crops with more protein, Cas9	
	Sustainable Oils	Camelina for Biofuels	
	Bioresource Intl.	enzyme feed additives	
University of Vienna (Charpentier, ERS Genomics) – CVC	Evolva	Flavor/scent products/ fungal biomanufacturing	Non-Exclusive
	Corteva	All uses in plants	Exclusive
Vilnius University	Corteva	All Applications	Exclusive

Table 3.5.1: (expanded from (25) *for accuracy, presentation). Overview of the license landscape for agricultural uses. Company names in italics have licenses from multiple foundational patent holders.*

The license landscape is dominated by Broad and CVC. Of these two, only the ERS genomics (CVC) has issued exclusive licenses in the agricultural field (although rarely), whereas Broad has reserved such licenses for human therapeutics. ERS genomics claims to have over 100 licensees, although most are not named. Notably, the USA is the largest producer of genetically modified crops, and the foundational Broad patents are valid there (unlike in Europe), and thus rights to patents from both groups are needed for most agricultural uses in the USA. In Europe, the scope of Broad's patent protection is much smaller, but the limited adoption of genetically modified plants in agriculture limits this impact.
When the technology is specified in licensing agreements, it is almost always CRISPR-Cas9. Notably, the CRISPR-Cas9 specific patents have led many companies, including agricultural companies, to develop alternative CRISPR nucleases, which may then be used in other fields such as human therapeutics.

Agricultural Collaborations

Corteva, which has licenses from both CVC and the Broad instutite, has announced collaborations with the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT), International Maize and Wheat Improvement Center, the International Rice Research Institute (IRRI), and the Donald Danforth Plant Science Center. These agreements are described as collaborations, and are generally aimed at improving food security but do include licensing agreements.

Agricultural Companies with exclusive licenses

Corteva Agriscience is a major agri-biotech company that separated from DowDupont in 2019. It was formed from DuPont Crop Protection, DuPont Pioneer and Dow AgroSciences. It has been granted exclusive licenses from CVC for agricultural applications in many major crops(26), while the University of Vienna granted it(Dupoint Pioneer) exclusives licenses for all uses in plants, and Vilnius University broadly granted it (Dupoint Pioneer) an exclusive license for all applications(27). Recently in 2023, Corteva overtook Bayer-Monsanto as the dominant player in the soybean market(28). More generally, in terms of market share, it is the 2nd largest seed company worldwide(29,30). Despite the exclusive licenses of Corteva, it is notable that Coretva itself has granted licenses to numerous other companies, thus the exclusive licenses held by Corteva do not neccesarily stop other companies from making use of the technology.

Genus plc. Is a British agri-biotech company specializing in cattle and pig products. It has been granted an exclusive license by Caribou Biosciences (CVC) for livestock uses.

TreeCo (https://tree-co.com/) is a smaller agribiotech/plant breeding company which uses CRISPR to introduce edits in tree varieties, with an exclusive license from Caribou Biosciences.

Agricultural Companies with non-exclusive licenses

Monsanto, a subsidiary of Bayer chemical following its acquisition in 2018, is a major agri-biotech company, producing hybrid and genetically modified seeds. It has been granted non-exclusive licenses from Broad for seed development applications(31). It obtained non-exclusive patent rights from ERS genomics, but the details of the areas covered are not disclosed(32). It has also licensed patents from Toolgen(33). Notably it has also received exclusive licenses to the (non-foundational) portfolio of Pairwise plants for agricultural applications in wheat, corn, soybeans, canola, and cotton(34). By 2005, Monsanto controlled 24% of the vegetable seed market within the EU(35). By 2014 in the USA, it controlled 80% of the Maize seed market, and 90% of the soybean market(36). As of 2016 it controlled 23% of the worldwide seed market. In terms of total seed market share, it is currently the largest seed company worldwide(29,30).

BASF (Badische Anilin- und Sodafabrik) is a European multinational chemical company, headquartered in Germany. It is the largest chemical producer in the world. It has licensed CRISPR technology for agricultural applications. Many of its agricultural products are focused on "crop-

protection" (herbicides, fungicides, pesticides), but biological controls are also within its portfolio. Often crop protection solutions involve generation of plants resistant to a treatment, such as a herbicide. In terms of market share, it is the 5th or 6th largest seed company worldwide(29,30).

Corteva Biosciences, as mentioned above, has also been granted non-exclusive licenses by the Broad institute in the field of agricultural applications. Notably, due to the nature of the claims held by Corteva and Broad (where and when Broad patents are valid), licenses/patent rights from both patent holders are needed to use the CRISPR-Cas9 system in plants/agriculture.

Syngenta is a Chinese-held company headquartered in Switzerland. Like BASF, its primary products are crop protection products, sales of which account for approximately 75% of its revenue (about 11 billion CHF). Hybrid and genetically modified seeds are its next major source of revenue. Syngenta has substantial cross-licensing agreements with DOW agrochemical in the field of genetically modified plants. It is also active in biofuel research. In term of market share, it is the 3rd largest seed company worldwide(29,30).

Regional Fish institute – A Japanese company which has licensed CRISPR technology for aquaculture of non-mammal marine animals, primarily fish. They use genetic engineering to assist in developing new fish breeds. Notably, they induce small targeted changes that could be accomplished by normal mutation in the course of natural evolution. Foreign DNA/RNA is not introduced, thus all of their products would be permitted genetic modifications under the proposed new EU regulations. The scope of the non-exclusive license is restricted to the asia-pacific region, and thus is not particularly relevant for Europe and Switzerland.

Evolva is a Swiss company that mainly produces specific chemical compounds, such as flavors and fragrances, reservatrol, etc, through a fermentation process. Many of these products are destined for consumption in foods. They make use of genetically modified fungus/yeast, which may be able to produce compounds normally only produced by plants or other organisms. Revenue in 2022 was approximately 15 million CHF.

Harpe BioHerbicide is an American company specializing in weed control. The licensing deal with Corteva and Broad was announced in September 2023(37), and is thus a very new player in the market. The aim of the licensing deal is to develop crops resistant to Harpe's Bioherbicides.

Vilmorin & Cie is a French seed company owned by the industrial agriculture industrial company Groupe Limagrain. It has licensed the use of CRISPR-Cas9 from Corteva as well as the use of CRISPR-Cpf1 and Cas9 from the Broad institute(38). In term of market share, it is the 4th largest seed company worldwide(30).

Sustainable Oils, Inc., is a renewable fuel company that uses the oil from camelina seeds as the primary input material for biofuel production. It has concluded non-exclusive licensing agreements with with Corteva Agriscience, the Broad Institute of MIT, and Harvard for CRISPR-Cas9 and related gene IP to develop improved varieties of camelina. They are interested in traits such as increased oil yield, faster maturation, and drought tolerance. Biodiesel is the primary fuel product, but other fuel types may be produced, such a jet fuel.

JR Simplot is an agricultural company headquartered in the USA that is notable for the production of browning and bruising resistant potatoes. It signed agreements with Corteva and Broad in 2018(39).

Comparison with other fields/countries

As noted, while the licensing policies here are in line with all other fields for commercial research and production, there are some significant differences with regard to license requirements in different jurisdictions.

Countries like the USA, which allow organisms (not just traits, methods, etc.) to be patented, are outliers. Despite being an outlier, the USA is the leading market for genetically modified agricultural products due to its overall agricultural output and the looser regulations on the use of genetically modified organisms in agriculture.

Despite this difference, similar protections for most cases would be granted in other countries through mechanisms such as protection of plant varieties. The major differences in licensing requirements is that within the EU and Switzerland the breeder's exemption and farmer's privilege apply. No licensing agreement is needed to make use of these two exemptions. It is also worth noting that while breeder's exemption does not require a license to derive new varieties from a CRISPR edited organism, a license would be needed to use CRISPR technology in the production of those derivatives. For this particular case, Swiss law provides for a compulsory licence for research tools (Art. 40b PatA).

3.5.2 Non-Agricultural license landscape

The key players in the non-agricultural CRISPR-Cas9 license landscape are quite similar to those of the agricultural license landscape: A group comprising the Broad institute; one comprising the University of California, Berkely, Emmanuelle Charpentier and the University of Vienna (CVC); Toolgen; and Sigma-Aldrich Life Sciences. Notably, Sigma-Aldrich and the Broad institute have concluded cross-licensing agreements for Cas9, where both entities can grant access to their shared IP.

Some of these key players also negotiated together. The agreements between the major player are as follows:

Caribou Biosciences, ERS Genomics, CRISPR Therapeutics, Emmanuelle Charpentier, University of Vienna: a Global cross-consent and invention management agreement in 2016.

The Broad Institute of MIT, Harvard & Sigma-Aldrich Life Sciences reached a cross licensing deal in 2019(40). Sigma-Aldrich was then aquired by Merck KGaA (MilliporeSigma) in 2015. Merck, the Broad Institute, and Harvard signed a non-exclusive CRISPR license framework in 2019.

Regarding Dupont, the company has licenses from: Vilnius University (2015), Caribou Biosciences (2015), ERS Genomics (2017).

Other notable CRISPR-Cas9 licensing agreements are as follows:

Licensor	Licensee	Date
Broad Institute	Transposagen	2016
Broad Institute	Rockefeller Uni. MPEG-LA	2017
CVC	Bayer	2016
CVC / Broad / Sigma	Horizon Discovery	2017/ 2014 /2022
Sigma Aldrich	Horizon Discovery	2022
CVC and Broad	Thermo Fisher	2018
Merck (Sigma)	Integrated DNA Technologies	2018
Merck (Sigma)	genOway	2018
Merck (Sigma)	Promega	2019
Broad/ MIT /Harvard /CVC	Thermo Fisher	2018
CVC	Demeetra	2023
Integrated DNA Technologies	Graphite Bio	2021
Harvard	Colossal	2021

The ThermoFisher license example is likely the most common form of licensing, where licenses from both the Broad and CVC groups will be needed.

Another notable example is that of Horizon discovery, which has licensed CRISPR-Cas12a technology in addition to CRISPR-Cas9 - Mammoth Biosciences (Doudna, University of California, Berkeley) licensed its CRISPR-Cas12a patents to Horizon Discovery in 2020 & 2021. The Demeetra licensing agreement is also notable, as they had previously argued that such a licensing agreement was not needed: "*The constraints placed by organizations that govern CRISPR/Cas9 licensing have forced many researchers to look to other solutions entirely. Our Cas-CLOVER technology, which edits genes more precisely than CRISPR, is covered by patents that are distinct from those of CRISPR, so our commercial users can wield greater freedom*."(41) Their technology in fact used an inactive Cas9 derivative fused to another nuclease. This still illustrates the demand for Cas9-independent CRISPR methods. Licensing agreements for non-Cas9 based systems include:

In Pharma:

Licensor	Licensee	Date
Emendo	Takeda	2019
Mammoth Biosciences	Bayer	2022
Metagenomi	Moderna	2021
Life Edit Therapeutics	Novo Nordisk	2023
ERS genomics	Algenscribe	2023

In Ag/plants:

Licensor	Licensee	Date
Benson Hill Biosystems	Ricetec	2019
	Novozymes	2018
	Agribody	2018
	Bioheuris	2023
	Embrapa	2018
Inari	Eden Enterprise	2021
Cibus	GDM seeds	2021

3.6 Licensing conclusion

The most impactful litigation related to CRISPR involves disputes with Broad, primarily from CVC. The core of these disputes centre on a dispute between these two groups, Sigma-Aldrich, and Toolgen over the use of CRISPR-Cas9 in eukaryotes(10). The dispute between the Broad Institute and CVC appears to be over in the USA. Sigma-Aldrich and Broad have concluded cross-licensing agreements(40), so a dispute seems unlikely even in the event additional patent claims are granted to Sigma-Aldrich. Toolgen still has pending patent claims, which may lead to further disputes if it is not resolved internally through a similar cross-licensing agreement.

So far there has been no indication that any of the patent-holders are substantially deviating from rational behaviour or are unwilling to license their patents to third parties. The major patent holders are all willing to grant licenses to small entities and modify their pricing accordingly. Thus, licensing requirements costs should generally not be overly burdensome for most small entities.

It is important to note the large and diverse scope of application for CRISPR-Cas gene editing, and the limited timeframe that companies have to exploit their patents. Assuming all the entities continue to behave as rational actors, it is in their interest to extend licensing agreements on reasonable terms, as they will not have sufficient resources to exploit all the possible application of the CRISPR-Cas gene editing technology within the lifetime of their patents.

In cases where there are exclusive licenses, there are alternatives such as Cas12. There are also alternatives such as licensing CRISPR-Cas9 or Cas12 only for research and development purposes in high throughput screens to identify the ideal gene edits to be made. Once such edits have been identified, an older more laborious technology (such as TALEN) which can achieve the same results may be used to make the final modified plant for commercial purposes.

Uncertainty resulting from the status of the still pending foundational Toolgen and Sigma-Aldrich patent applications may also result in some hesitation from investors to license patents. In the field of human therapeutics, this has not held back companies like Vertex from proceeding to bring therapeutics to the market.

4 CRISPR related litigation

4.1 Inventory

- CVC's Eukaryote claims and Broad-CVC interference proceedings
- Rockefeller University – Broad Institute inventorship dispute and European invalidation
- Broad inventor issue
- Synthego wins its petition with the USPTO to invalidate Agilent's patents on chemically modified RNA
- Corteva-Inari seed dispute
- Toolgen patent claims

4.2 CVC claims of CRISPR-Cas9 use in Eukaryotes, Broad interference proceeding

After Broad published a paper describing the use of CRISPR-Cas9 in eukaryotes and filed a patent covering the same, CVC sought to invalidate Broad's patent. On the basis of their earlier patent covering the use of CRISPR-Cas9 in cells generically (and with publications showing its use in prokaryotes), they initiated an interference proceeding against Broad with the Patent Trial and Appeal Board (PTAB) of the U.S. Patent and Trademark Office. The board found that the two patents covered different inventions (one generically covering the use in any cell, and another concerning the application in eukaryotes specifically), and could co-exist.
At the time of the filing of the foundational CVC and Broad patents in the USA, the USA operated under a "first to invent" principle, rather than the now-standard "first to file system". CVC then initiated another proceeding with the PTAB and attempted to prove to that they had been the first to invent the use of CRISPR-Cas9 in eukaryotes. In September 2020, the PTAB found their evidence unconvincing and ruled against CVC and in favour of Broad. This ruling was confirmed in another case in 2022(11). As the rest of the world operated on the first to file principle at the relevant time, this dispute was limited to the USA and appears to be settled.

4.3 Rockefeller University and the Broad Institute dispute

Dr. Luciano Marraffini of Rockefeller University was listed as a co-author, alongside authors from Broad, on the first scientific paper describing the use of CRISPR-Cas9 in eukaryotes.
Bizarrely, conflicting patent applications were filed that were identical except for differing lists of inventors.
In the USA, Rockefeller University and the Broad institute agreed to submit the matter to binding arbitration. In 2018 that arbitration process resulted in the inventorship remaining excluding Dr. Marraffini and the ownership resting with Broad. Notably, the two groups are co-owners of other CRISPR related patents, and Dr. Marraffini is listed as a co-inventor on applications related to use of CRISPR in prokaryotes(42).
When they filed the extension to the EPO, Dr. Marraffini was not listed as an inventor, but the EP application claimed the priority date of the application which included Dr. Marraffini as an inventor.
As a result of European rules about the listing of inventors on patents, the European patent office revoked the foundational patent held by the Broad institute covering the use of the CRISPR-Cas9 system in eukaryotes in 2018(15).

4.4 Synthego-Agilent RNA modification dispute

In May 2023, the USPTO PTAB invalidated all 63 claims of two patents (0,337,001 and 10,900,034) held by Agilent(43). These patents were both directed towards the use of chemically modified guide RNAs for Cas proteins. The claims were invalidated on the grounds that they were obvious in view of prior art (*i.e.*: the invention was not "non-obvious"). This is essentially equivalent to finding that

there was a lack of an inventive step (in the parlance of the EPC). The extensions to the EP are still pending, but it is possible that the EU similarly find that they a lack of inventive step.

4.5 Corteva-Inari seed dispute

This dispute does not necessarily involve CRISPR-modified plants nor the CRISPR technology. Given the extensive use of CRISPR-Cas9 technology used by Corteva and the nature of the dispute it is nonetheless relevant and is thus included here.
In 2023, Corteva filed a lawsuit against Inari, alleging that “Inari purloins high quality seeds, including Corteva’s protected seeds, and makes slight genetic modifications to those seeds […] then seeks patent protection for the resulting modifications [and] intends to commercialize seeds containing these modifications”(44)
Corteva alleges that Inari acquired “hundreds of varieties of Corteva’s protected seeds”, although which varieties these are, and whether or not they include CRISPR modified varieties is unclear.
The only specific variety mention concerns the seeds of transgenic maize covered under Corteva’s US patent No. 8,575,434, which included patent protection of the seeds. Note that Breeder’s exemption does not apply to US patents, which can protect the seeds themselves. Corteva alleges that Inari illegally obtained the seeds through ATCC and exported them to Belgium (where such patent’s on the seeds themselves are not valid, and Breeder’s exemption applies). Corteva notes that ATCC made the protected seeds available for public inspection but expressly prohibited using those seeds for commercial purposes.
This lawsuit is ongoing. While it does not concern CRISPR specifically (or perhaps at all), it illustrates the type of disputes that may equally arise for CRISPR modified varieties. This dispute mainly results from the different exemptions to patentability in the USA compared to Europe, and Breeder’s rights.

4.6 Toolgen patent claims

A principle issue with Toolgen’s patent claims are that they stem from a provisional patent application filed in the USA, which was generally not up to normally standards(45). In Australia, Toolgen has been unsuccessful at linking their patent applications to the earlier provisional application (i.e.: they were unable to claim the priority date of the provisional application for the later application)(46).

5 Expected patent and licensing landscape trends

Conventional CRISRP-Cas systems (such as CRISPR-Cas9) utilize an RNA template (guide RNA) to direct the Cas nuclease to a DNA sequence, where it induces a double strand break. This break is often repaired by cellular processes such as non-homologous end-joining (NHEJ). This type of DNA modification is useful for knocking out genes. When a donor template is added, the double strand breaks can be repaired by homologous recombination to introduced targeted changes and insertions, including large insertions of transgenes. These more conventional methods are often less efficient or specific than desired. This led to the development of more advanced CRISPR based techniques.

Base Editing uses a guide RNA to bring a base editing enzyme (deaminase fused to a Cas enzyme, such as a Cas nickase) to a specific nucleotide of DNA. Notably, no DNA is cut. This class of enzyme is capable of making four kinds of changes: C to T, T to C, A to G, and G to A. This type of targeted change can introduce very specific DNA changes, without the randomness of NHEJ or the relatively low efficiency of homologous recombination, and is ideal for correcting or introducing point mutations. A downside is that it is not capable of making all possible nucleotide substitutions (C to A, for example). It also sometimes causes off-target effects, where bases other than the intended target are deaminated.

A newer method was developed called Prime Editing. This method uses a modified Cas protein is only able to cause single strand “nicks” rather than double strand breaks. The modified Cas protein

is fused to a reverse transcriptase which allows it to introduce new DNA sequences into a specified site. This chimeric protein uses a prime editing guide RNA (pegRNA) to simultaneous specifies the target site and serve as a template for the reverse transcriptase to introduce the desired edit. This method is capable of inserting up to 200 bases at a time, or deleting over five thousand bases at a time, with greatly reduced off-target effects. When paired with recombinases, insertions of over five kilobases are also possible.

Yet another method involves CRISPR-associated transposases or CAST (Cas enzymes, such as catalytically inactive Cas fused to transposase). The basis for this system was the discovery that some transposons had nuclease-deficient CRISPR–Cas systems for RNA-guided integration into the genomes. Soon enough similar systems were engineered to use the CRISPR system to direct integration of DNA. On-target efficiencies using this system approach 100%, and the system is capable of introducing very large (over 11 kilobases) DNA sequences. The system can also be used to knock-out genes by targeted gene disruptions.

These recent strategies have been recently developed for various applications, including for genome engineering of plant cells and organisms. Applications of Base Editors, Prime Editors and CAST in plants respectively comprise 286, 36 and 34 patent families. Some companies have already positioned themselves on these emerging technologies by filing dedicated patent families: Pairwise Plants Services (Base Editors, Prime Editors), Syngenta-Chemchina (Base Editors), Limagrain (Base Editors, Prime Editors), KWS SAAT (Base Editors, Prime Editors), Bayer/Monsanto (Prime Editors, CAST), Bioray Laboratories (Base Editors) or Suzhou Qi Biodesign Biotech (Prime Editors). Academic players have been also involved in these technologies: laboratories affiliated with the Chinese Academy of Sciences (Base Editors, Prime Editors), the Chinese Academy of Agricultural Sciences (Base Editors, Prime Editors), China Agricultural University (Base Editors, Prime Editors), Hanyang University & Korea University (Base Editors), or Shanghai University (CAST) to name a few.

Regarding the use of CRISPR technologies for human therapeutics, there has been notable progress in the development of new drug delivery methods and technologies such as nanoparticles (e.g. Lipid Nanoparticles especially since the Covid crisis) or Recombinant Adeno-associated Viruses (AAV) for gene therapy purposes. Anticipating potential emerging signals in the Plant field, similar trends are expected in the development of delivery technologies for introducing desired alterations in specific loci in plant cells or organisms. For instance, this includes optimized Agrobacteria-based vectors or microparticles coated with nucleic acids such as a CRISPR system.

Moreover, digitalization and automation are currently very hot topics in Biotech and Life Sciences. For instance, the future of agriculture and farming is shifting towards a world supported by mobile platforms, including robots. Therefore, anticipation lies in the integration of more digital and automated technologies. A recent patent family has been identified. For instance, a recent patent family has been identified, covering means and methods for the precise differentiation of crop plants and weeds, which can be utilized by automated weeding platforms.

6 Possible applications to plant breeding and agriculture in the EU and Switzerland

6.1 A note on farmer's privilege and breeder's exemption

The Farmer's privilege and breeder's exemption are still valid, and nothing in the CRISPR patents interferes with them. It is also worth reiterating that while breeder's exemption is still valid, a license would be still be needed to make use of CRISPR breeding methods for commercial purposes. For this particular case, Swiss law provides for a compulsory licence for research tools (Art. 40b PatA). Deriving new breeds from CRISPR edited plants by traditional methods would still be allowed,

however the commercialization of a derived breed containing the patented trait would still be a patent violation, and thus would require a license.
Indirectly, the technical ease and efficiency of CRISPR based techniques may render more traditional, non-patent protected methods, uncompetitive. While CRISPR-Cas gene editing is relatively easy to use compared to earlier gene editing techniques, the up-front costs of setting up an appropriate laboratory environment to carry out CRISPR-assisted plant breeding is still greater than that of more traditional breeding methods. Therefore, small plant-breeding entities may still not make use of the CRISPR-Cas technologies for reasons unrelated to licensing.

6.2 Possible Applications

Given that there is currently a moratorium on the cultivation of genetically modified plants for horticultural, forestry or agricultural purposes in Switzerland, and only limited cultivation of such plants is allowed in the EU due to a stringent certification process, without any changes to the law, CRISPR technology would only have a very limited applications to agriculture in Europe and Switzerland. However, it appears likely that the law may change to allow certain forms of gene editing/modification in plants.

Many forms of modification can be enumerated, and the following list is not definitive:

Transgenes- On one end of the spectrum “unlimited” modification may be allowed, wherein entirely foreign genes are inserted into plant genomes – an example of this is *Bt* corn which expresses genes from *Bacillus thuringiensis.*

Allele swaps- A more restrictive rule could allow inclusion of DNA from the same species. In this case entire genes could be swapped between two varieties of the same species, to more rapidly produce a plant variety that could also be obtained by traditional methods after numerous crossings of the two varieties.

Base editing- An even more restrictive rule would allow for targeted edits of single bases or just a few bases. Commonly cited justifications for such a rule invoke the possibility of such changes occurring naturally – this form of editing would simply be a faster method of obtaining the same thing that is obtainable by selecting naturally occurring mutations

Deletions- The law could be changed to allow only deletions/knockouts/inactivation of an organism’s DNA/genes.

A commonly proposed rule would be that no trans-genes would be allowed. In such a case, base editing and deletions would be allowed. It is unclear if allele swapping would be allowed, that is if genes from the same species would be legally considered transgenes.

The following is a non-exhaustive list of agricultural products commercialized or in development, and what modification categories they would fall under:

Transgenic Plants

Company	Method/transgene	Description
Norfolk Health produce	Snapdragon transcription factors	Increased antioxidant tomato (Purple tomato)
		Purple tomato’ with high GABA
Okanagan Specialty Fruits	Agrobacterium tumefaciens- plasmid RNA interference	Non-browning apples (Fuji, Granny, Gala, Pink and Honey and Golden varieties)

Base editing

Company	Method	Description
Corteva	CRISPR	Higher yield waxy corn
		Corn with extra starch
		Drought-resistant maize
BetterSeeds	CRISPR	Mechanized harvesting compatible cowpea
		Allergen free nuts
		Heat and herbicide resistant tomatoes
		Reduced “growing and harvesting” cost cucumbers
Agrisea/Alora	CRISPR	Salt resistant rice
Nexgen Plant	CRISPR	Virus resistant tomato
Covercress	CRISPR	High yield pennycress
Calyxt	TALEN	Mildew-resistant wheat
		Improved-quality alfalfa
		Soybean oil with 20% less saturated fatty acids
		Soybean oil with no trans-fat
		High-fibre wheat
		Non-browning potato
Cold Spring Harbor	CRISPR	High-yield tomato, more fruit and fewer leaves and branches
Yield10 Bioscience	CRISPR	Camelina with increased oil content
		Camelina with enhanced omega-3-oil content
University of Minnesota	CRISPR	Drought- and salt-tolerant soybean
Iowa State University	TALEN	Disease-resistant rice

Deletions

Company	Method	Description
GreenVenus	CRISPR	Non-browning avocado
		Non-browning lettuce
Pennsylvania State	CRISPR	Non-browning mushrooms
Pairwise	CRISPR	Less pungent mustard greens
Corteva	CRISPR	Amylopectin enriched waxy corn,
VitisGen3	CRISPR	Powdery mildew resistant grapes

The agricultural applications within Europe and Switzerland due to the adoption of CRISPR-Cas9 would vary depending on how the law is changed. the law, would thus be the effects of adopting of

these (and similar) plants. Note that no transgenic plants have been identified using CRISPR technology.

Note that the majority of applications involving gene editing or deletions/knockouts make use of CRISPR technology, although there are a substantial number of TALEN modified plants as well. Many of the new varieties can reduce food waste by reducing food spoilage before reaching the market. Others are directed at adapting plant varieties to warmer, drier climates.

7 Conclusion

Between 2014 and 2019, the rate at which CRISPR related patents were filed increased sharply, and has remained high since 2019. The majority of these patents are filed in the USA and China. When looking specifically at patents on CRISPR modified-plants with validity outside of China, the USA is the clear leader.

Few exclusive licenses for CRISPR- related patents are given outside the field of human therapeutics, but Corteva holds exclusive licenses in certain agricultural areas. The foundational patents mainly focus on CRISPR-Cas9, but there are alternatives which render these exclusive licenses easy to circumvent via use of alternative Cas nucleases. In particular, agricultural companies have developed some of these alternative systems as a result.

The most impactful litigation related to CRISPR revolves around a dispute between four groups and the use of CRISPR-Cas9 in eukaryotes. The dispute between the Broad Institute and CVC appears to be over in the USA. Sigma-Aldrich and Broad have concluded cross-licensing agreements, so a dispute seems unlikely in the event additional patent claims are granted to Sigma-Aldrich. Toolgen still has pending patent claims, which may lead to further disputes.

The effects on agriculture in Switzerland and Europe are currently very limited due to laws restricting or prohibiting cultivation of genetically modified plants for horticultural, forestry or agricultural purposes. It seems likely that these laws will change to allow targeted edits or deletions of genes, causing changes that could occur naturally and be selected for by traditional methods over a much longer period of time.

Allowing such edits would likely lead to the reduction in food waste by adopting varieties that are resistant to spoilage. Many crops in development also have improved heat and drought tolerance, and will likely play an important role in adapting to the warming climate.

Overall, the intellectual property landscape surrounding CRISPR is complex due to the multitude of applications for this revolutionary technology and its potential financial benefits. Given the complex nature of animal and plant organisms, their extensive genetic make-up and the vast possibilities offered by CRISPR, any player involved has the potential to carve out a niche in this dynamic environment. The major players in the agri-food sector have rapidly established their position through strategic patent filings and licensing agreements. This has led the scientific community - including university laboratories and smaller companies - to develop alternative systems to the conventional Cas9 and Cpf1 systems, to negotiate licenses, to navigate between potentially problematic patents and to engage in patent filings - in short, to drive innovation.

Therefore, the patent system plays a crucial role in disseminating technical information and promoting technology transfer. This underlines the fundamental role of the patent system: to stimulate technological innovation by providing incentives for research and development.

8 CONSULTED DATABASES

Scopus

Global collection of peer-reviewed scientific publications

Scopus uniquely combines a comprehensive, expertly curated abstract and citation database with enriched data and linked scholarly literature across a wide variety of disciplines.

Scopus quickly finds relevant and authoritative research, identifies experts and provides access to reliable data, metrics and analytical tools.

PubMed, Google Scholar

Pubmed and Google Scholar were also used for further research, as well as scientific magazines/websites.

FamPat

Global collection of patent families

Coverage: Patent families in all disciplines made up of documents published by 77 offices. Questel-Orbit has developed a definition of family which combines the EPO's strict family rule with additional rules which allow applications filed beyond the 12 months fixed by the Paris Convention (intellectual families) to be taken into account, the different definitions of patent offices of what an invention is, in particular for Japanese publications, the links to the parent EP and/or PCT application and the links between provisional US applications and published US applications.

Priority: Bibliographic data for the United States and most of Europe from the early 1920s. Other data, including abstracts, from the early 1970s.

(Last viewed on 09.01.2024.)

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