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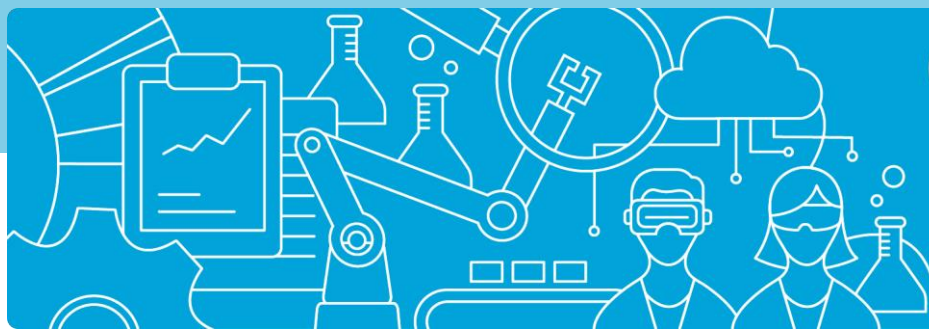

Samantha Zyontz

Mapping CRISPR Research, Innovation, and Diffusion Activities in Agriculture – Cross-national

Herausgeberin: Expertenkommission Forschung und Innovation (EFI)

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ABSTRACT

This report updates and expands the paper, patent, and company datasets collected for Zyontz and Pomeroy-Carter (2021) through 2022. Particular attention is paid to worldwide CRISPR activity in plant applications. The results from the databases updated for this report reveal a number of important trends in the global CRISPR plant ecosystem. First, China dominates in CRISPR plants, but there are many countries that innovate in this space, including the United States and European Union. Second, innovation strategies in CRISPR plants are still influenced by the existing academic, business, and cultural environments at the time CRISPR was introduced. Third, Germany produces very high quality scholarship in CRISPR plants and has a number of well-established companies that patent, but there is little evidence of university-company co-creation that helps to translate ideas into products and create new ventures.

ACKNOWLEDGEMENTS

I would like to thank Saranya Singh for her extraordinary work on putting together the updated CRISPR companies database. The original data through 2018 – 2019 was collected by the incredible efforts of my team, Cassidy Pomeroy-Carter, Yvo Sandjideh, and Orly Salik. Rebecca Grunberg provided excellent support in creating the original natural language processing algorithm used for classifying papers and patents into application categories that was then modified for the updated databases. All errors are my own.

I. UPDATING THE COLLECTED DATA ON THE RESEARCH, INNOVATION, AND DIFFUSION ACTIVITY OF CRISPR ACROSS COUNTRIES OVER TIME

The data collection methods for the updated datasets build on and reference the original Report on CRISPR activity (Zyontz and Pomeroy-Carter 2021). To identify the research, innovation, and diffusion activity of CRISPR, with particular focus on Agriculture, three datasets of key measures were updated: (1) CRISPR publications; (2) CRISPR patents; and (3) CRISPR companies. Each database measures global CRISPR activity at different stages of the technology lifecycle. The CRISPR Papers Database captures the creation of fundamental understanding of the CRISPR tool and some of the earliest ideas developed by academic and corporate scientists. The CRISPR Patents Database illustrates the organizations and countries who may be interested in commercializing the tool. The CRISPR Companies Database tracks the companies active in using, developing, or selling CRISPR-based products. Agriculture is one of the smaller categories of CRISPR use, so datasets containing only Plants and Farm Animals/Aquaculture are about 15% or less of all CRISPR activities. The development and updating of each dataset is discussed below.

A. CRISPR PAPERS DATABASE (2012 – 2022)

To collect CRISPR publications, data was extracted from one of the most commonly used bibliographic databases, Web of Science (WoS).[1] The WoS Core Collection includes over 21,000 academic journals worldwide in over 250 areas in the sciences, social sciences, humanities, and arts.

A topic search was conducted for the term "CRISPR" in the WoS Core Collection from 2012 through 2021. This searches for the term "CRISPR" in the title, abstract, and keywords of each document. "CRISPR" is a distinct term used by CRISPR pioneers to describe the data editing tool, and since 2012 the term has rarely been used to refer to anything other than the system. Further, scientists developing or using the tool have every incentive to include the term "CRISPR" in their titles or abstracts in order to be cited and participate in the rapidly moving conversation. Accordingly, searching for the term "CRISPR" in papers published 2012 and later is a reasonable way to collect relevant publications (Zyontz 2016). Past work has compared early sets of CRISPR articles in WoS to the set of articles that cited to the early Doudna (Jinek 2012), Zhang (Cong 2013), and Church (Mali 2013) papers. Almost every subsequent CRISPR article cites to at least one of those three fundamental papers (Zyontz 2016).

[1] Web of Science, Clarivate Analytics, www.webofknowledge.com.

To find new published ideas on CRISPR tools and applications, the CRISPR Paper Database was restricted to academic articles only, excluding other publication types.[2] Data was restricted to articles published after July 2012 but before January 2023. This allows capture of articles published after Doudna and Charpendier (Jinek 2012) (generally considered the first CRISPR paper) while mitigating problems with reporting truncation.

For each article, the following information was collected:

- Article Title
- Abstract
- Date Published
- Journal Title
- WoS Categories and Research Areas (pre-determined fields from WoS)
- WoS and Author Keywords
- Country of Authors
- Organizations of Authors
- Author Names
- Number of Forward Citations

For tables of German and US organizations, institutions were grouped and names harmonized manually.

Each article was also classified by an application category. This classification has been updated since the 2021 Report to break out the Agriculture/Livestock category into Plants and Farm Animals/Aquaculture. Martin-Laffon et al. (2019) manually categorized 2,072 CRISPR patent families into six main categories: Technical improvements (general), Industrial applications, Medical, Plants, Farm animals/aquaculture, and Other *in vitro* uses. To better use the same categories across all databases in the report and to separate out Plants, these were simplified to five: Plants, Farm Animals/Aquaculture (the previous Agriculture/Livestock category), Health/Medicine (combining Medical and the pharmaceutical applications in Industrial applications), Industrial Applications (the remaining Industrial applications), and Technical Improvements (combining Technical improvements and Other in vitro uses).

[2] WoS creates consistent categories of document types. To restrict our data to academic articles only, documents categorized as Meeting Abstract, Review, Editorial Material, Book Chapter, Book, Book Review, News Item, Letter, Proceedings Paper, Bibliography, and Reprint were dropped.

These categories were then used along with the titles and abstracts of the patent families identified by Martin-Laffon et al. (2019) to create a training set for a support vector machine (SVM) algorithm.[3] This natural language processing algorithm was applied to the titles, abstracts, and keywords of the WoS CRISPR articles. The training set was used to determine factors in the patent abstract and title texts that help identify each category and then applied those factors to the articles in order to predict each paper's best fit. Each paper is assigned to one of the five categories. The accuracy of the categorization was verified with manual checks.

Finally, data from WoS InCites Journal Citation Reports was used as a proxy for journal quality. Quality was calculated as the journal impact factor from 2012 (the journal quality prior to CRISPR) for journals that existed before CRISPR. For more recent journals, the five-year average impact factor from 2019 or 2023 was used depending on when they were founded. Journals that had no reported impact factor were omitted from quality analyses.

For Figures that include aggregations of countries, the United Kingdom (UK) includes England, Wales, Scotland, and Northern Ireland. The European Union includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lativia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Potugal, Romainia, Slovakia, Slovinia, Spain, and Sweden. It does not include the UK. The Rest of the World (ROW) includes papers that have authors outside of the already listed countries in the relevant Figure.

The dataset contains 26,560 academic articles published globally from Q3 2012 – Q4 2022 that include data on the year of publication, country of authors, and abstract or keywords. There are 2,263 Papers categorized as Plants or Farm Animals/Aquaculture.

B. CRISPR Patents Database (Earliest Priority Date as of December 31, 2021)

Again, because interest is in the number of independent inventions created with CRISPR, the focus is patent families. The update of the database of worldwide patent families that describe CRISPR inventions again follows the methodology outlined in Martin-Laffon et al. (2019). Martin-Laffon et al. (2019) found 2,072 patent families worldwide with over 5,000 applications or granted patents with the earliest priority dates through December 2017. The extended the CRISPR patent families database uses their methodology for

[3] Python code available with the author.

patent families with the earliest priority date by December 31, 2021. The data stops at this date to avoid truncation issues due to differing patent application publication times around the world.

Worldwide CRISPR patent families were collected from the Lens.org.[4] Lens.org is an extensive source of patent metadata that is open to the public and linked to academic articles; as of October 2023, it included 151.3 million patent records (both applications and grants) and 85.9 million simple families in 106 jurisdictions.[5] The jurisdictions include the USPTO, EPO, WIPO, and the Chinese Patent office (CNIPA), among many others.[6]

For patent families with the earliest priority date of December 31, 2018 the same initial search strategy as Martin-Laffon et al. (2019) was used, applying the search string [CRISPR OR Cas9 OR Cpf1 OR gRNA* OR sgRNA* OR "RNA* guide*" OR "guide* RNA*"] to the titles, abstracts, and claims of patent applications and granted patents published worldwide.[7] Patent families with earliest priority dates from January 1, 2019 – December 31, 2021 were searched using the string [CRISPR OR Cas9 OR Cpf1 OR Cas12 OR Cas13 OR CasX OR CasY OR gRNA* OR sgRNA* OR "RNA* guide*" OR "guide* RNA*"] to make sure the most common new CRISPR enzymes were included. After identifing all possible CRISPR patent families, they were manually reviewed, checking for duplicates and removing patent families that were not directly related to the CRISPR system. The CRISPR patent families identified in Martin-Laffon et al. (2019) were also verified in the Lens.org database.

For each patent family, the following information was collected:

- Patent Family Title
- Abstract
- Earliest Priority Date (for patent families)
- Priority Number(s)
- Inventors' Names
- Applicant/Assignee
- Applicant/Assignee Country
- Patent Family Size

[4] https://www.lens.org/
[5] https://www.lens.org/lens/search/patent/structured
[6] https://www.lens.org/lens/search/patent/structured (under Jurisdiction/Groupings)
[7] The search string is robust to adding other terms for newer Cas proteins like Cas12. The terms "CRISPR" and the variations on "guide RNA" drive the results.

Each new article was also classified by application category in the same way as the CRISPR Paper Database. Martin-Laffon et al. (2019) manually categorized 2,072 CRISPR patent families into six main categories: Technical improvements (general), Industrial applications, Medical, Plants, Farm animals/aquaculture, and Other *in vitro* uses. To better use the same categories across all databases in the report and to separate out Plants, these were simplified to five: Plants, Farm Animals/Aquaculture (the previous Agriculture/Livestock category), Health/Medicine (combining Medical and the pharmaceutical applications in Industrial applications), Industrial Applications (the remaining Industrial applications), and Technical Improvements (combining Technical improvements and Other in vitro uses).

These categories were then used along with the titles and abstracts of the patent families identified by Martin-Laffon et al.(2019) to create a training set for a support vector machine (SVM) algorithm.[8] This natural language processing algorithm was applied to the titles and abstracts of the CRISPR patent families. The training set was used to determine factors in the patent abstract and title texts that help identify each category and then applied those factors to the new families in order to predict the best fit. Each patent family is assigned to one category. The accuracy of the categorization was verified with manual checks.

For Figures that include aggregations of countries, the United Kingdom (UK) includes England, Wales, Scotland, and Northern Ireland. The European Union includes Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lativia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Potugal, Romainia, Slovakia, Slovinia, Spain, and Sweden. It does not include the UK. The Rest of the World (ROW) includes patent families that have applicants outside of the already listed countries in the relevant Figure.

The dataset contains 9,718 CRISPR patent families with published applications and grants around the world with earliest priority dates by December 31, 2021 or earlier.[9] There are 1,480 patent families categorized as Plants or Farm Animals/Aquaculture.

[8] Python code available with the author.
[9] Worldwide patent families are often identified by the collection of patent applications they claim priority to, so I chose to follow Martin-Laffon et al. (2019) by reporting the year as the earliest priority date for the family. This can lead to some priority dates before CRISPR's introduction (27 families), but the family members for CRISPR patents are published in 2012 and after.

C. *CRISPR COMPANIES DATABASE (THROUGH Q2 2023)*

Sources of firms and their activities vary widely in their coverage and content, so there are a number of methods used to compile a list of the most publicly active commercial firms in CRISPR. The database began with a list of names from academic articles on active companies in CRISPR licensing, patenting, and commercialization (Egelie et al. 2016, Brinegar et al. 2017, Contreras and Sherkow 2017, Samy 2018, and Ferreira et al. 2018). This includes the companies associated with the earliest CRISPR patents and their licensees. Then, in Q2 2020 and Q2 2023, Google searches on each company were run. Any additional licensees, parent companies, strategic partners, and other companies associated with the CRISPR work were added to the list.

Next, the search was broadened using the search strings "CRISPR companies" and "(CRISPR and (firm or company)) or agreement or license or venture or acquire" and "CRISPR and (license or agreement or "joint venture" or alliance)" in Google. This search was designed to capture companies that publicly mentioned CRISPR in company websites, press releases, other public filings, or industry news sources but that may not have been mentioned in the academic articles or may not publish or patent. This search included information from the U.S. SEC EDGAR system for public filings,[10] Crunchbase,[11] AngelList,[12] and GenomeWeb.[13] The term "CRISPR" was also searched for directly in Crunchbase and GenomeWeb to find new biosciences and biotech companies claiming to use CRISPR. Companies on the Germany-Biotech Company List[14] were also searched for to ensure all possible German CRISPR companies were captured.

Finally, any corporations that appeared in CRISPR Patents Database that were not already listed from the initial searches were considered. The same sources as above were used to find information on these companies with the exception of Chinese firms where international company data in LexisNexis was used. These additional companies from the CRISPR Patents Database were more difficult to find, often did not have data, and did not describe how they used CRISPR beyond what was in the patent. These companies were not included in the CRISPR Company Database.

[10] https://www.sec.gov/edgar.shtml
[11] https://www.crunchbase.com/
[12] https://angel.co/
[13] https://www.genomeweb.com/
[14] https://biopharmguy.com/links/country-germany-all-location.php. This list did not result in the inclusion of German companies that could not be found through the same sources used for all other countries. It was included as a check on the initial search and does not bias the results towards German companies due to oversampling. The full database is still biased towards companies that publicly associate themselves with CRISPR as described in the text.

Based on conversations with bioscience firms, a number of companies may be using or developing CRISPR but may not be obviously public about their actions due to uncertainty regarding the ongoing patent litigation or other secrecy concerns. Since it is only possible to rely on publicly observable information, such firms will not be included in the database. Thus, the database may not be comprehensive; instead, it contains publicly active, known firms.

For each company, the following information where available were collected:

- Company Name
- Company Type (Public Company; Private Company, established; Private Company, startup; Private Company, acquired)
- Location of Headquarters
- Description of How the Organization Uses CRISPR
- Founder/CEO/President/PI Name
- Number of Employees
- Date Founded
- Company Value

The data collected represents the most recent available as of Q2 2023, when the database was most recently compiled. Some information may be outdated, particularly if it was not updated in the sources used to research the company.

Finally, each company was manually categorized into the same application categories used in the CRISPR Paper Database and the CRISPR Patents Database (Agriculture/Livestock, Health/Medicine, Industrial Applications, and Technical Improvements) based on how the company reported using CRISPR. Agriculture/Livestock was kept together since it was not always possible to tell whether a company was using CRISPR for Plants, Animals, or both. Two added additional categories for corporate activities that are not found in patents or papers were also added. Specifically, many companies either license CRISPR technology or offer CRISPR-based products or services for research purposes ("Research Services"). Other organizations are included in the Database because they own subsidiaries working on CRISPR or have otherwise invested in strategic partnerships or joint ventures ("Ownership"). Companies were assigned to multiple categories if their activities did not fit solely into one.

For Figures that include aggregations of countries, the United Kingdom (UK) includes England, Wales, Scotland, and Northern Ireland. The European Union includes Austria, Belgium, Bulgaria, Croatia,

Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Lativia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Potugal, Romainia, Slovakia, Slovinia, Spain, and Sweden. It does not include the UK. The Rest of the World (ROW) includes companies that are headquartered outside of the already listed countries in the relevant Figure.

The Dataset contains 397 CRISPR companies that are publicly active, known firms with sufficient data worldwide as of Q2 2023. There are 57 Companies involved in Agriculture/Livestock CRISPR activities.

II. RESULTS

A. CRISPR PAPERS DATABASE FOR PLANT APPLICATIONS

i. Worldwide Publications

Since 2012 increasing interest in CRISPR for agriculture applications can be seen in **Figure 1**. **Figure 1a** is the trend for all agriculture applications and **Figure 1b** shows the trend for plants and livestock/aquaculture applications separately. Articles on agriculture applications grew at a 159.75% rate for a total of 2,263 by the end of 2022. The majority of these focused on using CRISPR for new plant applications (2,204). The remaining discussion in this section will focus on these plant-specific articles.

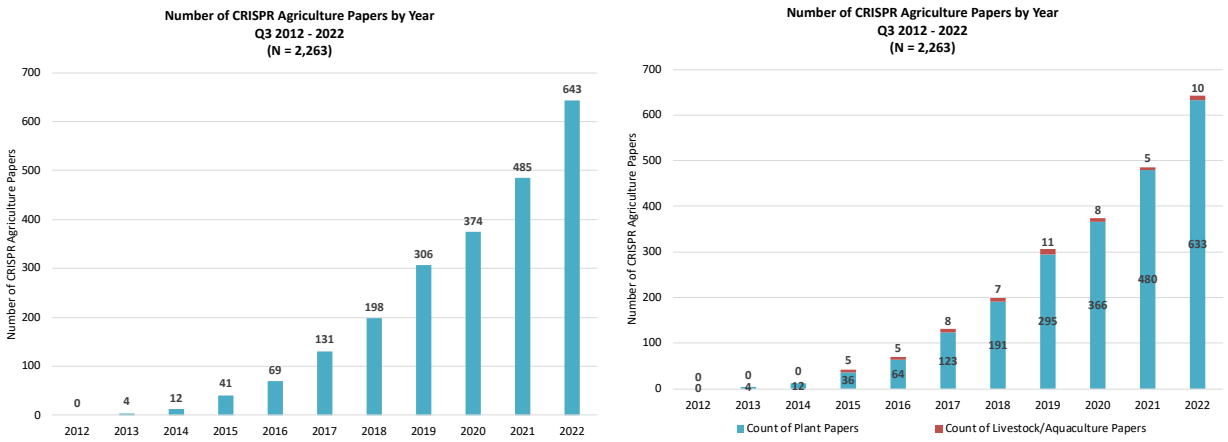

Figure 1a-b: Count of CRISPR agriculture (a) and plant versus livestock/aquaculture (b) academic articles in Web of Science by publication year

As with CRISPR in general, academic publications in plant applications that use CRISPR have a geographical bias (**Figure 2**). Academic teams from all over the world contribute to the advancement of CRISPR plant research, but China far and away dominates all other countries with at least one co-author on 53.8% (1,186/2,204) of all plant papers published between 2012 – 2022. The European Union and

United States co-authors represent 23.5% (519/2,204) and 23.0% (508/2,204) of plant papers respectively. German scientists, appearing in 6.7% (148/2,204) of all plant papers.

China's dominance in agriculture may be in part due to China's 13th Five-Year Plan (2016-2020) which emphasizes becoming a global leader in innovation and technology by focusing resources on more scientific research and scientific degree holders (Koleski 2017 and Central Committee of the Communist Party of China 2016); if successful, this should have a positive effect on CRISPR publications during this period.

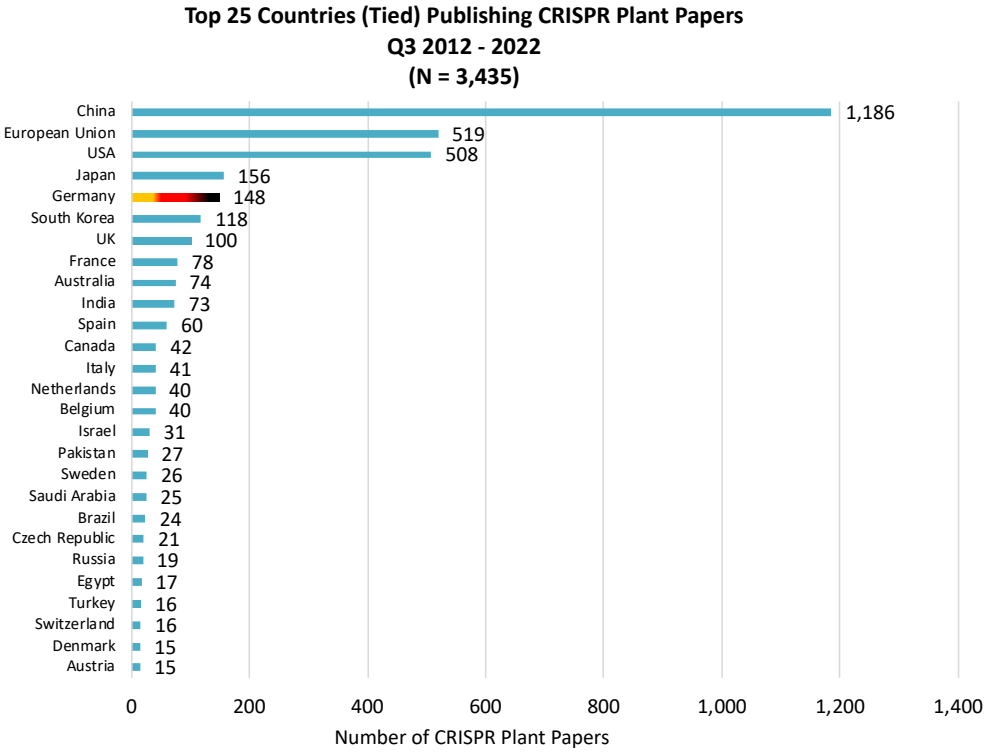

Figure 2: Count of CRISPR plant academic articles in Web of Science by the top 25 countries or country groups (tied)

Notes: Papers can have authors in more than one country, and the paper is counted once for each country represented, so some papers will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

ii. Publication Quality

As with CRISPR papers in general, there is still concern that the rapid publication of articles could compromise the quality of the research conducted on plants. Restricting attention to CRISPR plant articles published in the highest ranked journals can help to clarify in which countries the highest quality papers appear. Only considering plant papers in the top 10% of journals by impact factor from the set of journals

where CRISPR plant articles are published, results in 239 papers, or 10.8% of the 2,204 total CRISPR plant papers. The subset of 239 papers are called "Top Papers." In the Top Papers, the same countries appear as the most prolific publishers, although Germany gains on Japan (**Figure 3**).

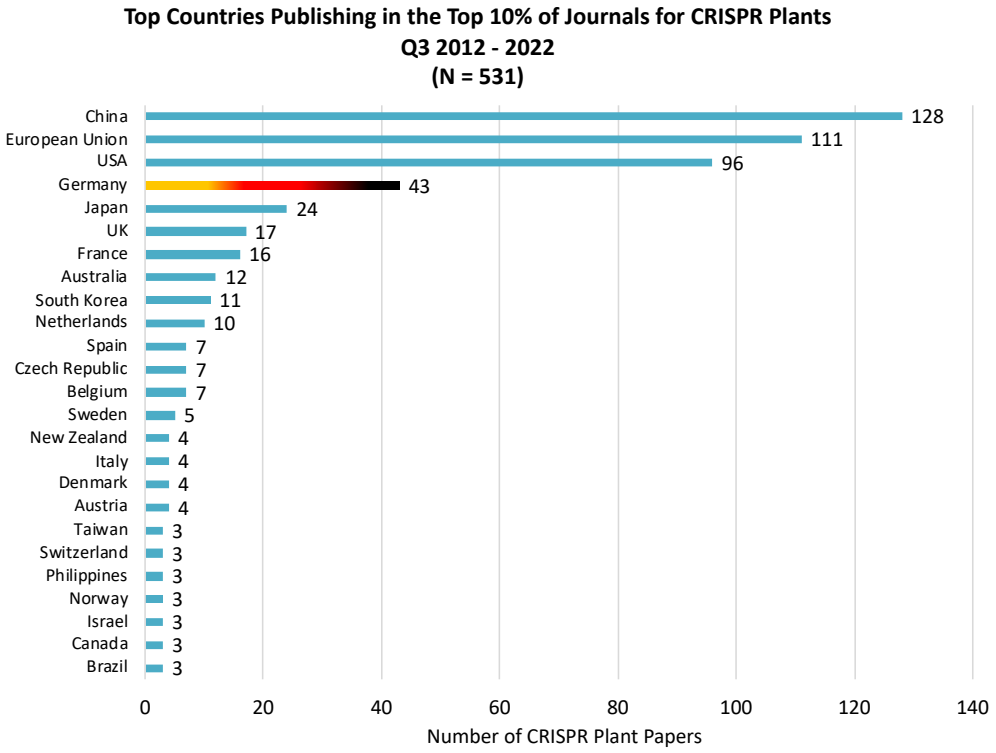

Figure 3: Count of CRISPR plant academic articles in the top 10% of journals where plant papers are published by impact factor in Web of Science by the top countries

Notes: Papers can have authors in more than one country, and the paper is counted once for each country represented, so some papers will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

To explore the relationship between total CRISPR papers and Top Papers for plant applications, **Figure 4** highlights plant Top Papers as a percent of total plant CRISPR papers for each country as long as they have 40 or more total plant articles to make sure there is a sufficient base. Here, Germany has the highest proportion of high quality CRISPR plant articles with 29% (43/148). The United Kingdom and United States are behind with 21% (111/519) and 19% (96/508) respectively. China, despite its dominance in publishing plant articles, has only 11% (128/1,186) in top journals. This may be because Chinese scientists tend to publish in Chinese journals that are not highly ranked worldwide.

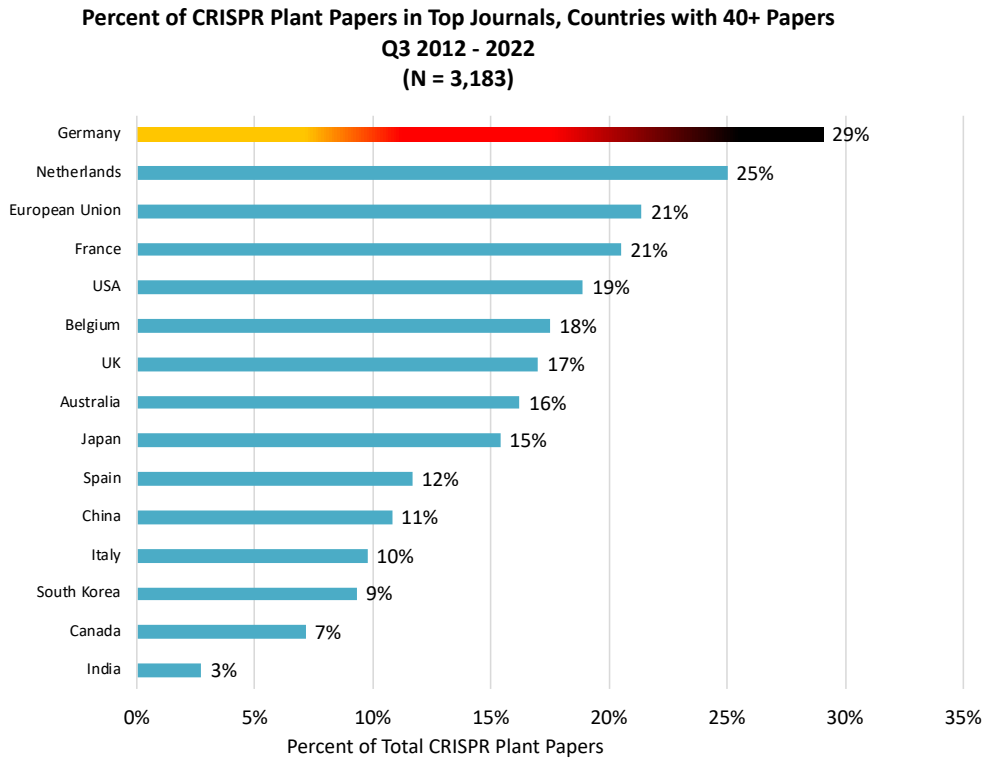

Figure 4: Top Papers for plants as a percent of all CRISPR plant papers in the country.

Notes: Countries must have published at least 40 plant articles to be included. Top Papers are those CRISPR plant papers in the top 10% of journals where plant papers are published by impact factor. Papers can have authors in more than one country, and the paper is counted once for each country represented, so some papers will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

iii. Papers by Application Category

To put the number and growth of plant articles in perspective, this section updates and expands the CRISPR Paper Database described in Zyontz and Pomeroy-Carter (2021). CRISPR papers were now classified into five categories: Health/Medicine (including medical applications), Plants, Livestock/Aquaculture, Industrial Applications (including biofuels and food manufacturing), and Technical Improvements (improvements made to the CRISPR tool, including new delivery mechanisms). Papers are in mutually exclusive categories as described in Section I.

Figure 5 shows the proportional breakdown of the categories for all CRISPR publications through 2022. Consistent with much of the basic science research in CRISPR, especially early on, 40% of the papers focus mostly on Technical Improvements. These include enhancements to the CRISPR tool, new uses of CRISPR such as screening, or improvements to delivery mechanisms. Another 50% of papers primarily address

Health/Medicine. These capture research on new model organisms, treatments, genetic therapies, drugs, and similar uses,. Plant applications, like creating new and better crops, account for 8% of papers. The remaining 2% of papers focus on Industrial Applications, such as biofuels and Livestock/Agriculture such as hornless cattle.

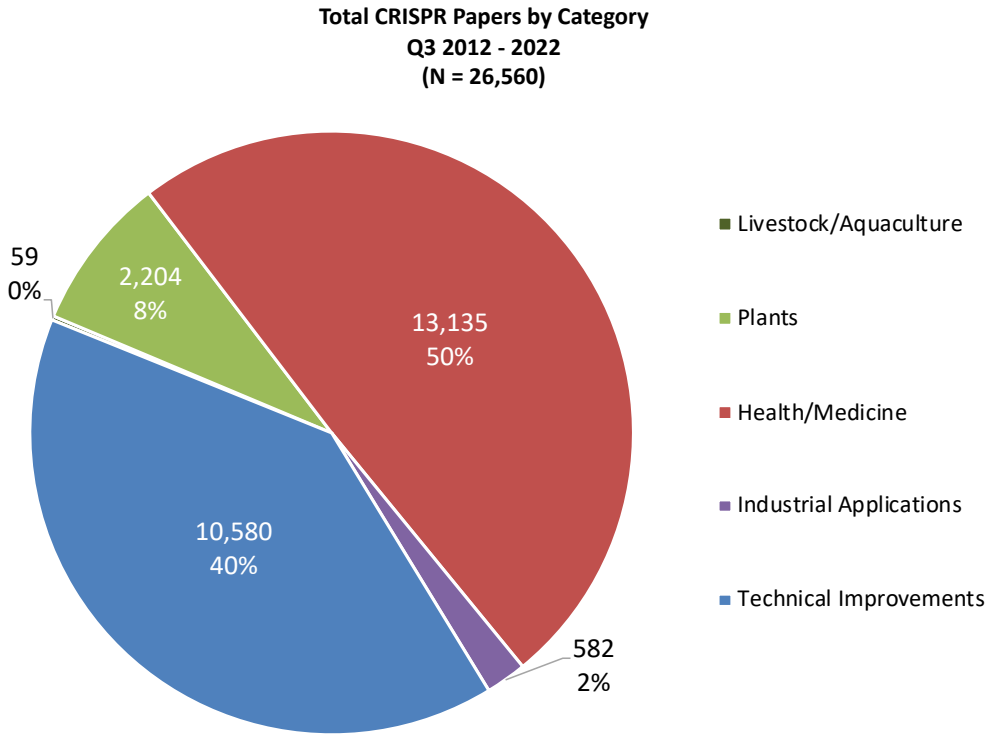

Figure 5: Percent of CRISPR academic articles in Web of Science by Application Category

Over time, publications in certain application areas have increased quickly (**Figure 6**). As might be expected with new breakthrough technologies like CRISPR, Technical Improvements papers appear first, but are starting to grow more slowly around 2019. In contrast, Health/Medicine applications took a little longer to appear as scientists began to apply the tool, but continue to rocket in growth, surpassing Technical Improvements in 2018. Some of the growth in Health/Medicine in 2020-2021 is due to research applying CRISPR to COVID-19 solutions. Plants has a smaller growth trajectory, but interest will continue since there will be needs for climate robust crops that produce higher yields. It is also the case that agriculture companies may be more interested in patenting their inventions than publishing papers for commercialization purposes.

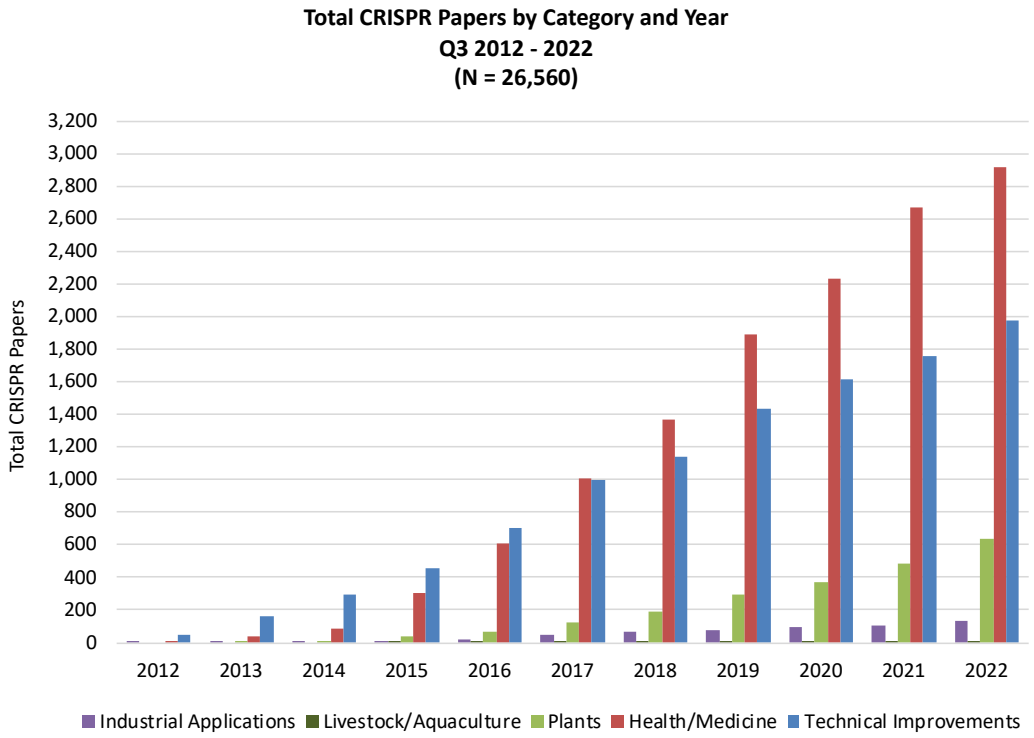

Figure 6: Count of CRISPR academic articles in Web of Science by Application Category and Year

iv. CRISPR Plant Articles in Germany

With 148 papers in CRISPR plant applications, Germany a top contributor to new ideas in the field. Still, its rate of publications is slower than its larger counterparts (**Figure 7**). Germany's compound annual growth rate for plant publications is 29.7%, due to a slow-down in 2021-2022. Over the period examined, plant publications in China grew 54.5%. It is still possible to see the delayed start but quick catch-up to the United States mentioned in Zyontz and Pomeroy-Carter (2021). The Rest of the World (papers with co-authors not in the United States, European Union, China, Germany, and Japan) also make up a substantial portion of the plant articles. This is mostly due to the United Kingdom not being included in the European Union for these calculations, but also because South Korea, Australia, and India round out the top 10 countries. There are also 59 different countries outside of the United States, European Union, China, Germany, and Japan that published at least one CRISPR plant paper from 2012 – 2022.

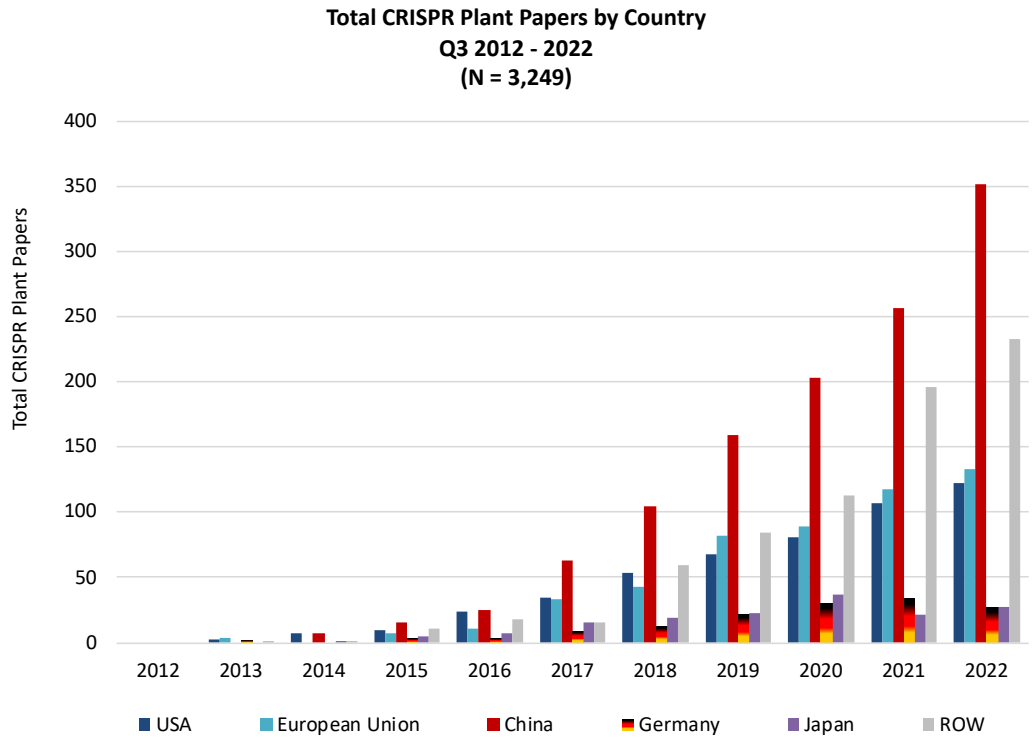

Figure 7: Count of CRISPR plant academic articles by publication year and country

Note: Papers can have authors in more than one country, and the paper is counted once for each country represented, so some papers will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

The German organizations publishing most frequently in CRISPR plant applications shown in **Table 1**. They primarily include universities and research centers.

Publishing Organization	# Papers in Plants
Max Planck Institute	49
Leibniz Institutes	21
Freie Universität Berlin	9
Leibniz University Hannover	9
Technical University of Munich	9
Georg-August-Universität Göttingen	9
Heinrich Heine University	8
Karlsruhe Institute of Technology	8
Martin Luther University Halle-Wittenberg	8

Table 1: Most prolific German organizations publishing CRISPR plant articles

For comparison, there are many more organizations that publish CRISPR plant articles in the United States, but the most prolific also tend to be universities and research organizations (**Table 2**).

Publishing Organization	# Papers in Plants
University of Minnesota	76
University of California - Davis	61
Cornell University	54
University of Florida	52
Iowa State University	47
University of Maryland	47
USDA - Department of Agriculture	45
Penn State University	32
Purdue University	32
University of Missouri	31
University of Georgia	26
University of California - Berkeley	25
Texas A&M University	23
University of Nebraska	23
Donald Danford Plant Sci Ctr	20
University of California - San Diego	20
University of Wisconsin	20

Table 2: Most prolific United States organizations publishing CRISPR plant articles

B. CRISPR Patents Database for Plant Applications

i. Worldwide Patent Families

The rapidly increasing interest in CRISPR for plant applications can also be seen in patents filed worldwide as seen in **Figure 8**. **Figure 8a** is the trend for all agriculture applications in filed patent families and **Figure 8b** shows the trend for plants and livestock/aquaculture applications in filed patent families separately. The number of CRISPR patent families that can be traced to the earliest application (earliest priority date) in 2021 is 104 times greater than those that rely on an application from 2012. Patent families are a more appropriate measure of distinct ideas here, although families can have more than one associated application across several patent jurisdictions. Because jurisdictions have different publishing delays for applications, 2022 is incomplete for countries that have longer delays. To avoid this truncation problem, the remaining analyses focus on families with an earliest priority date of December 31, 2021 or earlier and that involve a CRISPR plant application.

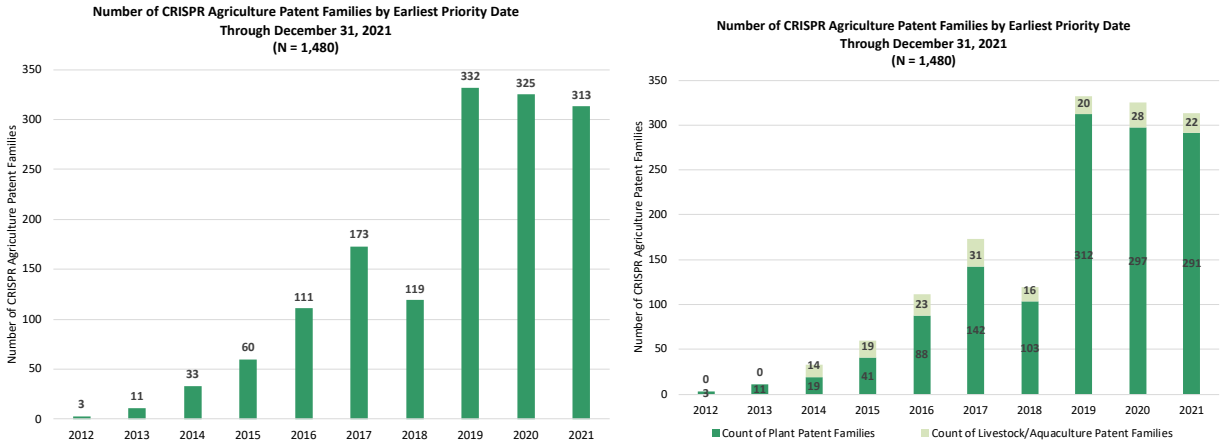

Figure 8 a-b: Count of CRISPR agriculture (a) and plant versus livestock/aquaculture (b) patent families worldwide by Earliest Priority Date

As with CRISPR plant articles, patent applicants in CRISPR plants are geographically biased as seen in **Figure 9**. Applicants only come from 27 countries and the vast majority of families have at least one applicant from either China (57.2% = 748/1,307) or the United States (27.1% = 354/1,307). Although the European Union as a whole still ranks highly in patenting, applicants from the United Kingdom and Germany do not seem to patent as often as their publication records might indicate. However, Germany's rank in patenting is a bit higher (2.3% = 30/1,307) than the United Kingdom (2.1% = 27/1,307).

As with papers, China's dominance may be due to China's 13th Five-Year Plan (2016-2020) which emphasized becoming a global leader in innovation and technology and encouraged applying for patents (Koleski 2017 and Central Committee of the Communist Party of China 2016). In the United States, some of the world's largest agricultural firms patent, including Pioneer/DuPont, Monsanto, Syngenta, and Dow. Given the strong incentives to get patents in China and the United States, it is not surprising that applicants from these two countries dominate the space.

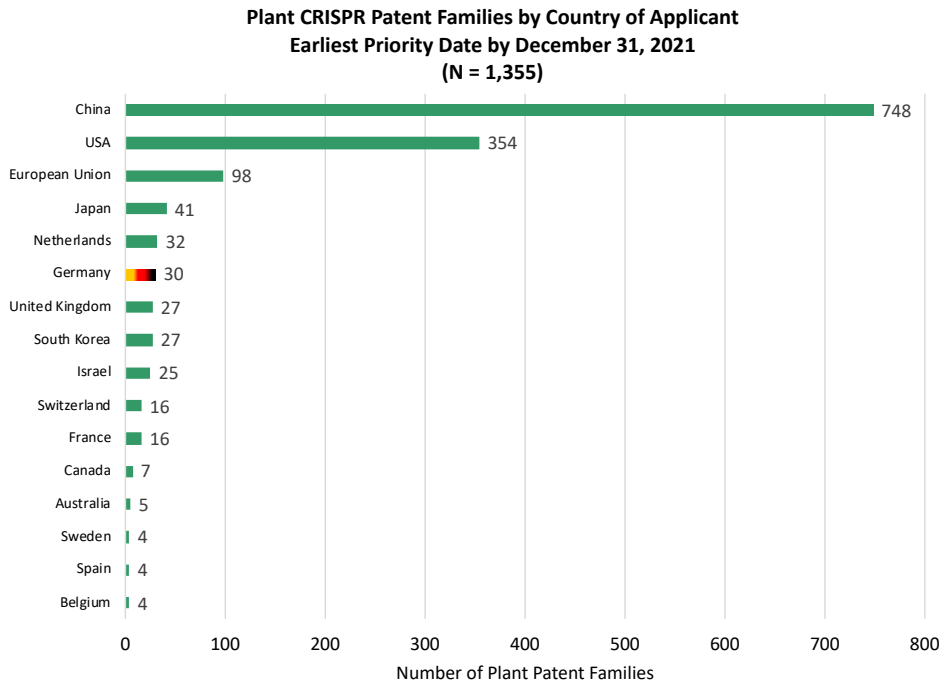

Figure 9: Count of CRISPR plant patent families worldwide

Note: Patent families can have applicants in more than one country, and the family is counted once for each country represented, so some families will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

ii. Patent Family Quality

Again, with the number of patents filed in such a short time frame, there are concerns about the quality of the patent applications in CRISPR plants. Because the majority of CRISPR plant patent families are new, standard measures of patent quality like forward citations are limited, but organizations that want to commercialize widely will have applications in a number of different countries, creating a large patent family. The number of countries in the patent family can be used as a proxy for expected use and quality of the idea. There are 228 CRISPR plant patent families with 3 or more applications or grants in different jurisdictions.

Of the 228 largest patent families, 114 (50.0%) are from applicants in the United States. No other country or groups of countries comes close. China only has 23.2% (53/228) of the largest patent families. This is because most Chinese patents are filed only in China by Chinese applicants with no connection to other countries. Germany does the best out of the European Union countries though (**Figure 10**).

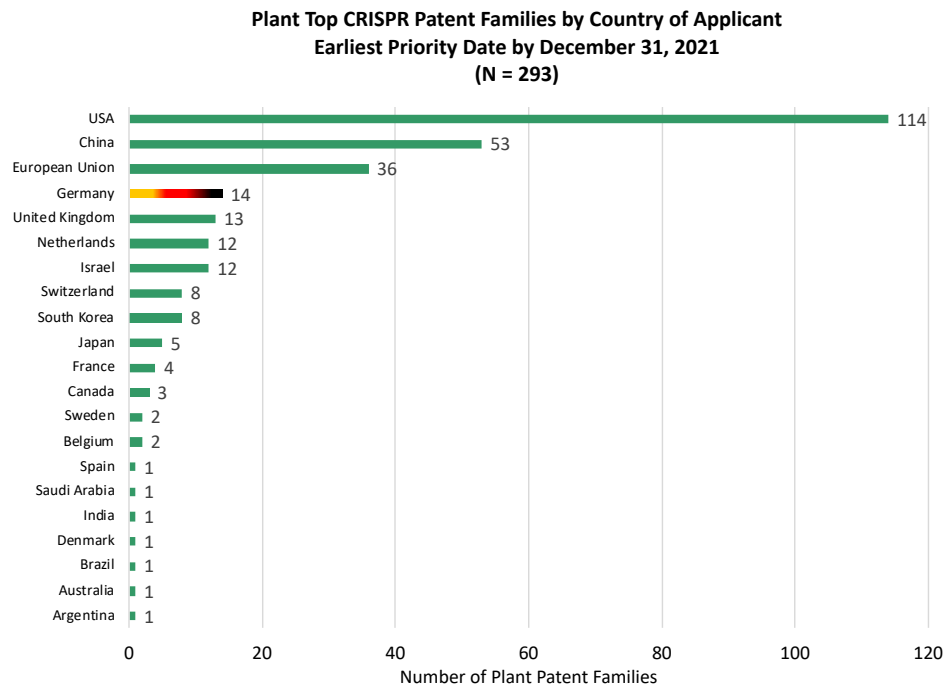

Figure 10: Count of largest CRISPR plant patent families worldwide by country of applicants

Note: The largest CRISPR patent families have contain 3 or more applications or grants. Patent families can have applicants in more than one country, and the family is counted once for each country represented, so some families will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

To highlight which countries may have a larger proportion of higher value patent families, **Figure 11** shows these largest CRISPR plant patent families as a percent of total CRISPR plant patent families for each country. To make sure there was enough activity, countries had to have at least 5 plant patent families to be included. As with papers, countries vary substantially in their proportion of large patent families For example, 50% of Switzerland's 16 CRISPR plant patent families included 3 or more application or grants.

The United Kingdom (13/27), Israel (12/25) and Germany (14/30) are also very successful at creating plant patent families in many jurisdictions. About half of their patent families are in multiple jurisdictions. Again, the major exception to is China. Only 7% of its 748 plant patent families are outside China. This finding continues to support the idea that Chinese scientists and corporations tend to remain local to China.

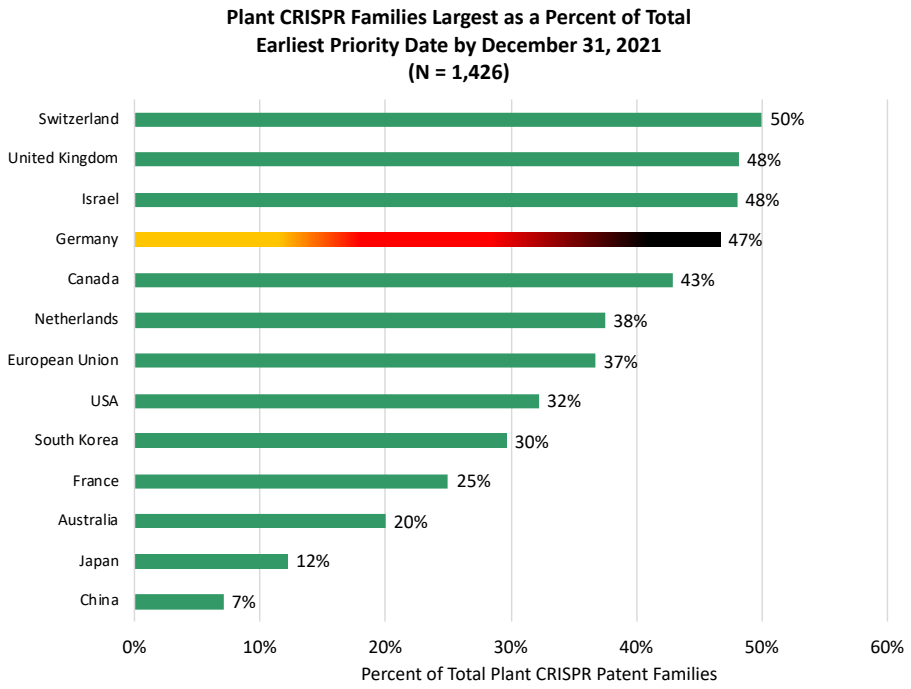

Figure 11: Largest CRISPR plant patent family applicants worldwide as a percent of all CRISPR plant patent families by country of applicant. Countries must have at least 5 plant patent families.

Note: The largest CRISPR plant patent families have contain 3 or more applications or grants. Patent families can have applicants in more than one country, and the family is counted once for each country represented, so some families will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

iii. Patent Families by Application Category

To put the number and growth of plant patent families in perspective, this section updates and expands the CRISPR Patent Database described in Zyontz and Pomeroy-Carter (2021). CRISPR patent families were now classified into five categories: Health/Medicine (including medical applications), Plants, Livestock/Aquaculture, Industrial Applications (including biofuels and food manufacturing), and Technical Improvements (improvements made to the CRISPR tool, including new delivery mechanisms). Patent families are in mutually exclusive categories as described in Section I.

Patent families in all categories rise rapidly over time, with Technical Improvement patents leading the way (**Figure 12**). Health/Medicine starts to increase more rapidly after 2014 but does not see the same rise as observed in papers. As a commercial matter, Health and Medicine applications are the most potentially lucrative, so an increase in such patents over time would be expected. Plant patent families are the next to see an increase since they are also highly commercialize in the form of more robust crops and longer lasting

produce. There is a dip in 2018 and another leveling off during the COVID years, possibly as companies shifted priorities. Agriculture/Livestock and Industrial Applications patent families also increase over time, but make up a much smaller portion of the patent families per year.

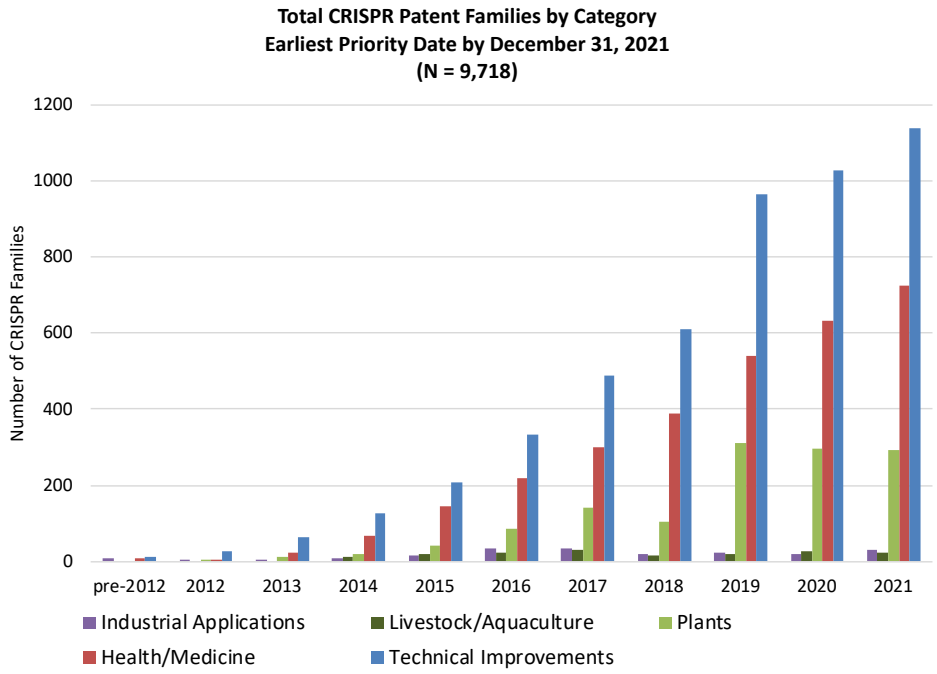

Figure 12: Count of CRISPR patent families worldwide by Earliest Priority Date and Application Category

iv. CRISPR Plant Patent Families in Germany

German plant patent family applicants have 30 CRISPR plant patent families, less than 10% of those from the United States or China. Although China's growth in plant patent families dominates every other county from 2015 on, plant patent families from Germany are increasing every year (**Figure 13**).

The increase in Chinese patent families over time is substantial. Although, as noted above, most of these are single patent applications or grants to the Chinese patent office. They generally do not leave China.

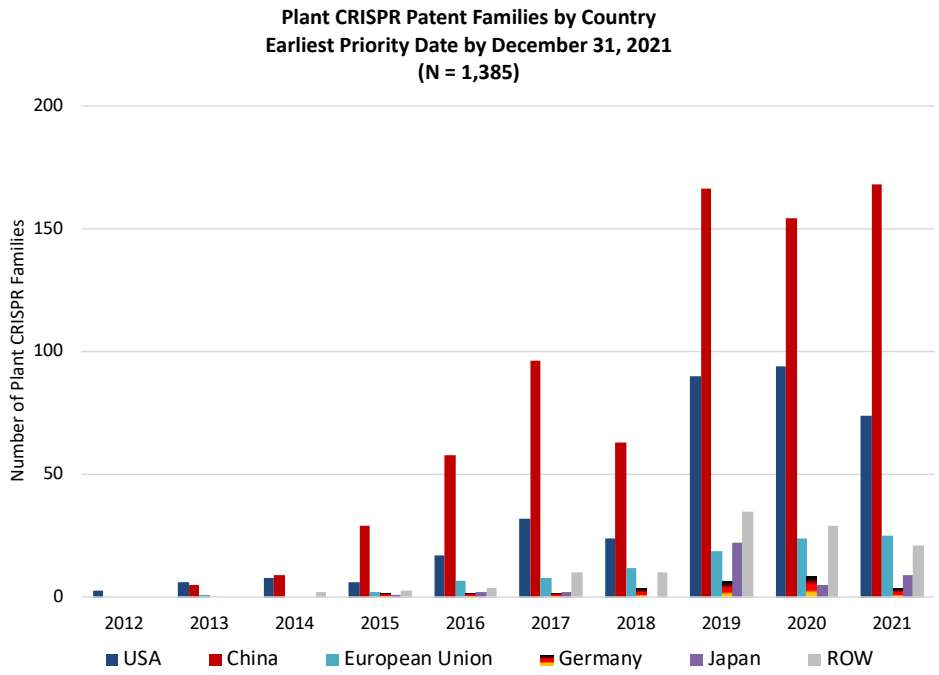

Figure 13: Count of CRISPR plant patent families by Earliest Priority Year and country of applicant
Note: Patent families can have applicants in more than one country, and the family is counted once for each country represented, so some families will be double counted. Attribution is not proportional. The European Union does not include the United Kingdom.

Patent plant family applicants from Germany are primarily two companies: KWS and Klemm & Sohm as shown in **Table 3**. There are almost no CRISPR plant patent families from German universities or research organizations.

German Patent Family Applicant - Plants	# Patent Families
KWS SAAT	21
KLEMM & SOHN GMBH & CO KG	5

Table 3: Top German CRISPR plant patent family applicants

This is in stark contrast to the United States, for example (**Table 4**). In addition to the global agricultural companies like Pioneer/Dupont, Monsanto, Syngenta, and Dow, United States CRISPR plant applicants represent a number of universities and research centers. Many of these universities are land grant institutions which emphasize, in part, education in agriculture and related fields. These universities are also encouraged to patent in the United States, which could account for the patenting activity seen here but not in Germany.

USA Patent Family Applicant - Plants	# Patent Families
BENSON HILL SEEDS INC	59
PIONEER HI BRED	45
HM CLAUSE INC	32
PAIRWISE PLANTS SERVICES INC	25
UNIV CALIFORNIA	22
MONSANTO	17
SAKATA SEED AMERICA INC	14
INARI AGRICULTURE INC	13
DONALD DANFORTH PLANT SCIENCE CENTER	7
SYNGENTA CROP PROTECTION LLC	7
UNIV MINNESOTA	6
COLD SPRING HARBOR LABORATORY	5
UT BATTELLE LLC	5
DOW AGROSCIENCES LLC	4
CIBUS US LLC	3
DU PONT	3
FLAGSHIP PIONEERING INC	3
PURDUE RESEARCH FOUNDATION	3
UNIV FLORIDA	3
UNIV ILLINOIS	3
UNIV MARYLAND	3
YIELD10 BIOSCIENCE INC	3

Table 4: Top United States CRISPR plant patent family applicants

C. CRISPR Companies Database for Agriculture Applications

As described in Section I, the companies included in the CRISPR Companies Database are those that are either observably active in the CRISPR or CRISPR-related product space or those that have filed relevant patents. Given the search criteria, the Database does not contain a random sample of companies working in CRISPR, but rather selects on visible players. Thus, the dataset provides insight on the firms that are vocal about using CRISPR or have applied for patents but cannot capture those that do not publicly reveal their CRISPR work in those ways. Because China does not report much information on its companies, they are excluded from this database as they were in Zyontz and Pomeroy-Carter (2021).

It is also difficult to tell if CRISPR companies are developing plant applications, livestock/aquaculture applications, or both in all cases. As such, the 57 companies in this section represent CRISPR agriculture, combining plants and livestock/aquaculture.

i. Worldwide Active CRISPR Agriculture Companies

The United States dominates the active CRISPR agriculture company landscape. Over 50% (29/57) of the active agriculture companies in the Database are based in the United States, while 17.5% (10/57) are based in the European Union (**Figure 14**). On an individual country basis, Germany is right behind Israel, though its proportion (5.3% = 3/57) is much less than the United States.

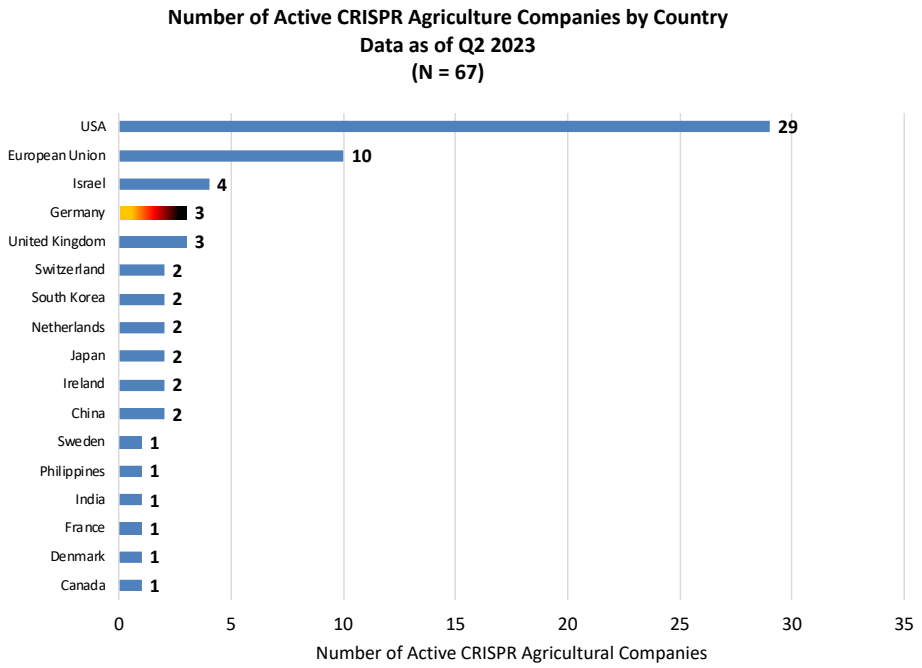

Figure 14: Active agriculture companies in the CRISPR Companies Database by country.
Note: Companies can be in more than one country, and is counted once for each country represented, so some companies will be double counted. The European Union does not include the United Kingdom.

Active CRISPR agriculture companies vary with founding date. About half of the companies are large and established with founding dates of 2009 or earlier. Surprisingly, the other half were all founded in the last 12 years. This is likely because start-ups can take advantage of the opportunities the new CRISPR technology offered (**Figure 15**).

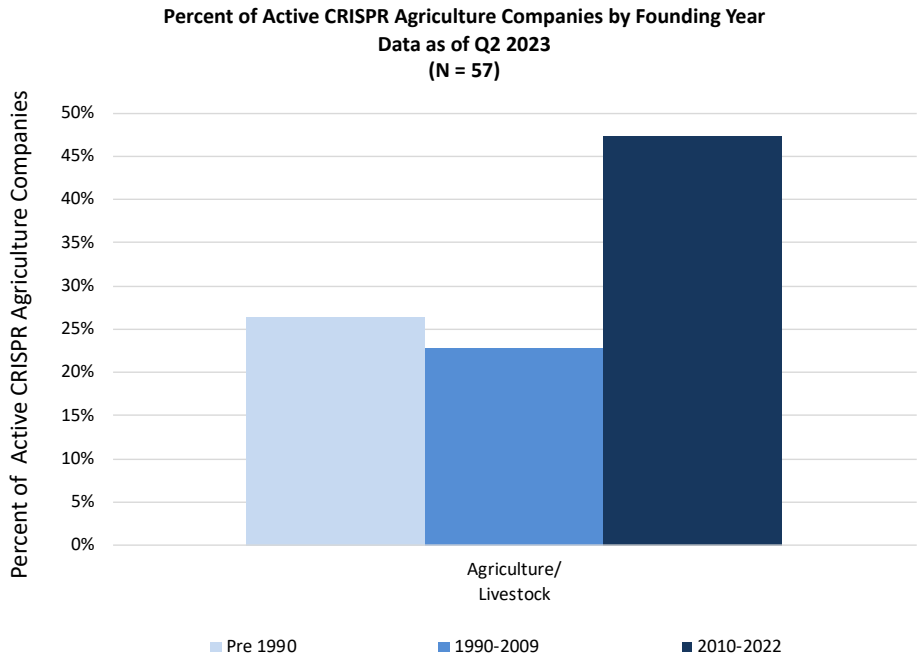

Figure 15: Active agriculture companies in the CRISPR Companies Database by founding year
Note: Two companies did not have a founding date that could be located.

Agriculture companies also vary somewhat by company size (**Figure 16**). Most have either 11-100 employees or over 501, which reflects the age of these companies as well.

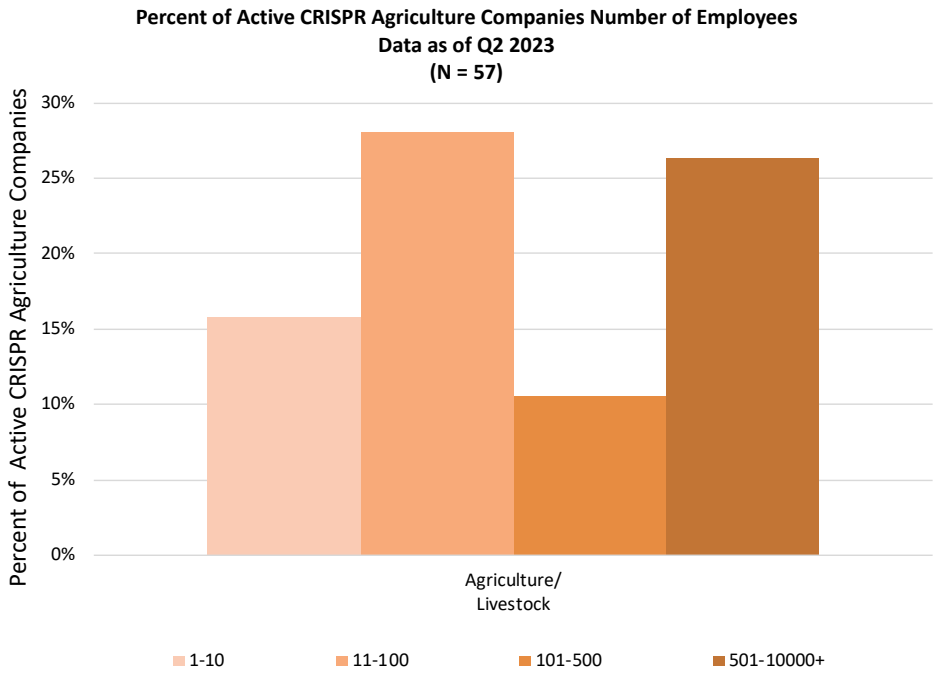

Figure 16: Active agriculture companies in the CRISPR Companies Database by number of employees, as a percentage of all agriculture companies

Note: There are eleven companies whose size could not be determined.

Finally, agriculture companies varies to some degree with location. The United States leads in part due to its propensity to nurture start-up ventures in this space (**Figure 17**). In contrast, Germany only has three very established companies actively working in agricultural CRISPR: BASF, KSW, and Bayer Cropscience.

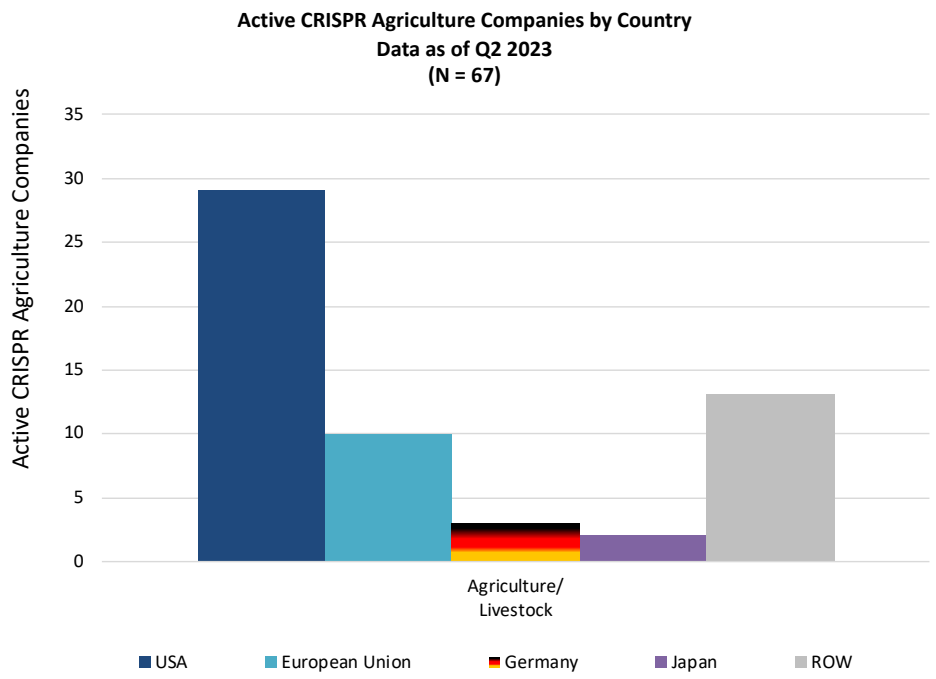

Figure 17: Active agriculture companies in the CRISPR Companies Database by country
Note: Companies can be in more than one country, and is counted once for each country represented, so some companies will be double counted. The European Union does not include the United Kingdom.

III. DISCUSSION

The results of the databases updated for this report reveal a number of important trends in the global CRISPR plant ecosystem. First, only a few countries still dominate in CRISPR plants, but there are many countries that innovate in this space. Second, innovation strategies in CRISPR plants are still influenced by the existing academic, business, and cultural environments at the time CRISPR was introduced. Third, Germany's strengths and weaknesses discussed in Zyontz and Pomeroy-Carter (2021) still hold for plant applications.

China is the undisputed leader in CRISPR plants. They have the largest number of papers and patents of any country and do not show an indication of slowing down. As in discussed in Zyontz and Pomeroy-Carter (2021), Chinese academics and organizations were fast followers in CRISPR as they were not involved in the initial development of the technology. They did take a great interest in CRISPR's potential for agriculture and plants, however. This can be seen in the government's 13th Five-Year Plan (2016-2020) (Koleski 2017 and Central Committee of the Communist Party of China 2016). The CRISPR plant work coming from China echoes their CRISPR work in general, which seems to be more about quantity than quality. In China, regulations are also more relaxed, which could incentivize more work, especially in

agriculture. For example, crops modified by CRISPR are not treated as GMOs. The combination of top-down encouragement and more relaxed regulations can lead to a substantial amount of production.

China may dominate, but the CRISPR plant space has many participants. There are also 38 countries publishing and 27 patenting in CRISPR plants, which expands the community of innovators. The United States and European Union have the next highest numbers of articles and patents. Their companies also contribute to the eventual worldwide commercialization of CRISPR crops and other plants. This will be critical as climates change and the world population continues to grow. Increasing crop yields with CRISPR can be an important tool in feeding future generations.

Much like with CRISPR in general, the United States took advantage of its position as the first mover in CRISPR to be an early participant in CRISPR plants. But it also was in a position to experiment with the new tool through its land-grant universities that have a mission to educate students in agriculture and related fields. United States land-grant universities are some of the most prolific article writers in CRISPR plants and, thanks to technology transfer offices (TTOs) in universities, are frequent patent applicants. TTOs proliferated after the Bayh-Dole Act of 1980, which encourages academics to patent their research findings and bring their products to a commercial market. The entrepreneurial ecosystem in the United States, discussed in Zyontz and Pomeroy-Carter (2021), has also led to about half of the United States CRISPR agricultural companies being founded in the last 12 years.

Germany's CRISPR plant innovation is different from either China or the United States. As with CRISPR in general, Germany is one of the leaders in CRISPR plant publishing but is less active in patenting. The research and innovation produced by Germany is of very high quality though. The concern is that the universities do the majority of the publishing and the companies primarily patent. There is not a lot of evidence of the university-company co-creation that is seen in the United States. This may be why Germany's dominant CRISPR plant companies are much older, well established entities and not new ventures. As before, the three counties' different paths in CRISPR plants still seem to be largely influenced by the existing academic, business, and cultural environments at the time CRISPR was introduced.

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