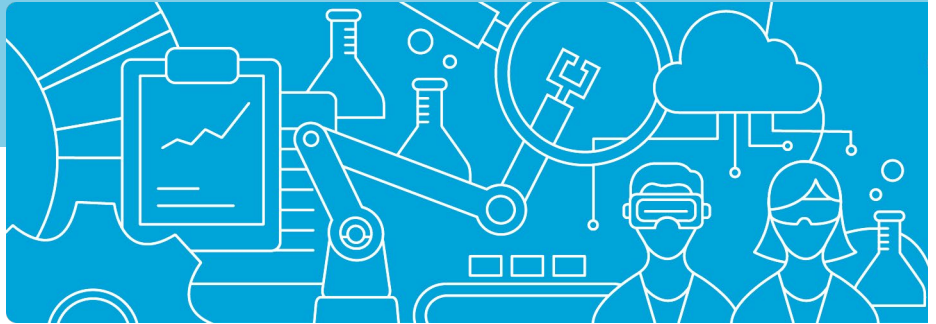


Study on the German innovation system | No. 12-2021



Samantha Zyontz, Cassidy Pomeroy-Carter

Mapping of the Research, Innovation and Diffusion Activity of CRISPR across Countries

Stanford
LawSchool

This study was conducted on behalf of the Commission of Experts for Research and Innovation (EFI). The findings and interpretations are the sole responsibility of the institute that conducted the study. The EFI has exerted no influence on the wording of the report.

Performing Institute

Stanford Law School
Crown Quadrangle, 559 Nathan Abbott Way,
Stanford CA 94305-8610, USA
www.law.stanford.edu

Studies on the German innovation system

No. 12-2021
ISSN 1613-4338

Deadline

February 2021

Publisher

Commission of Experts for Research and Innovation (EFI)

Office

Pariser Platz 6 | D-10117 Berlin
www.e-fi.de

All rights reserved, particularly the rights of reproduction, distribution and translation. No part of this work may be reproduced or stored, processed, duplicated or distributed using electronic systems in any form (by photocopy, microfilm or any other process) without the written approval of the EFI or the institute.

Contact and further information

Dr. Samantha Zyontz
Stanford Law School
Crown Quadrangle, 559 Nathan Abbott Way,
Stanford CA 94305-8610, USA
T + 001 (0) 65 07 23 24 65
M szyontz@law.stanford.edu

TABLE OF CONTENTS

EXECUTIVE SUMMARY	7
ACKNOWLEDGEMENTS	11
I. INTRODUCTION	12
II. A BRIEF HISTORY OF CRISPR INNOVATION.....	12
A. <i>EARLY DISCOVERY</i>	12
B. <i>WORLDWIDE DISTRIBUTION.....</i>	13
C. <i>CRISPR PATENT DISPUTES</i>	14
D. <i>CRISPR'S CONTRIBUTIONS AND FUTURE DIRECTIONS.....</i>	17
III. COLLECTING DATA ON THE RESEARCH, INNOVATION, AND DIFFUSION ACTIVITY OF CRISPR ACROSS COUNTRIES OVER TIME	18
A. <i>CRISPR PAPERS DATABASE</i>	19
B. <i>CRISPR PATENTS DATABASE.....</i>	20
C. <i>CRISPR COMPANIES DATABASE</i>	22
D. <i>CRISPR CLINICAL TRIALS DATABASE</i>	24
IV. RESULTS	25
A. <i>CRISPR PAPERS DATABASE</i>	25
i. <i>Worldwide Publications</i>	25
ii. <i>Publication Quality.....</i>	28
iii. <i>Papers by Application Category</i>	33
iv. <i>Germany.....</i>	37
B. <i>CRISPR PATENTS DATABASE.....</i>	41
i. <i>Worldwide Patent Families.....</i>	41
ii. <i>Patent Family Quality</i>	43
iii. <i>Patent Families by Application Category.....</i>	47
iv. <i>Germany.....</i>	52
C. <i>CRISPR COMPANIES DATABASE</i>	54
i. <i>Worldwide Active Companies</i>	56
ii. <i>Active Company Application Categories</i>	64
iii. <i>Notable Active Companies.....</i>	68
iv. <i>Germany.....</i>	69
D. <i>CRISPR CLINICAL TRIALS DATABASE</i>	70
i. <i>Clinical Trials: Time, Trial Type, and Disease Target.....</i>	71
ii. <i>Clinical Trials: Location</i>	77
V. DISCUSSION.....	84
VI. IMPLICATIONS FOR GERMANY'S CRISPR INNOVATION STRATEGIES.....	87
A. <i>IMPLICATIONS</i>	87
B. <i>SUGGESTED FUTURE STUDIES</i>	88
REFERENCES.....	90

LIST OF FIGURES

Figure 1: Timeline of the US CRISPR patent interferences.....	15
Figure 2: Count of CRISPR academic articles in Web of Science by publication year.....	26
Figure 3: Count of CRISPR academic articles in Web of Science by the top 25 countries or country groups	27
Figure 4: Comparison of a country's proportional contribution to total papers in CRISPR, Biological and Biomedical Sciences, and Health Sciences	28
Figure 5: Count of CRISPR academic articles in Web of Science by number of citations	29
Figure 6: Most common journals for CRISPR publications in Web of Science	30
Figure 7: Count of CRISPR academic articles in the top 10% of journals by impact factor in Web of Science by the top 25 countries	32
Figure 8: Top Papers as a percent of all CRISPR papers in the country	33
Figure 9: Percent of CRISPR academic articles in Web of Science by Application Category.....	34
Figure 10: Count of CRISPR academic articles in Web of Science by Application Category and year.....	35
Figures 11a-d: Total CRISPR academic articles by Application Category in countries with the most publications .	36
Figure 12: Percent of CRISPR academic articles by Application Category in selected countries.....	37
Figure 13: Count of CRISPR academic articles by publication year and country.....	38
Figure 14: Average number of counties represented in each CRISPR academic article in Web of Science by authors in a focal country.....	40
Figure 15: Common German co-authoring organizations as reported in Web of Science	40
Figure 16: Count of CRISPR patent families worldwide by Earliest Priority Date	41
Figure 17: Count of CRISPR patent families worldwide	42
Figure 18: Comparison of a country's proportional contribution to total patent families in CRISPR and total patent families reported in the WIPO IP Statistics Data Center.....	43
Figure 19: Count of largest CRISPR patent families worldwide by country of applicants.....	46
Figure 20: Largest CRISPR patent family applicants worldwide as a percent of all CRISPR patent families by country of applicant	47
Figure 21: Percent of CRISPR patent families by Application Category	48
Figure 22: Count of CRISPR patent families worldwide by Earliest Priority Date and Application Category	49
Figures 23a-d: Total CRISPR patent families by Application Category and county of applicant	50
Figure 24: Percent of CRISPR patent families by Application Category in selected countries	51
Figure 25: Count of CRISPR patent families by Earliest Priority Year and country of applicant.....	52
Figure 26: Count of CRISPR patent families for German applicants by Earliest Priority Date and Application Category	53
Figure 27: All CRISPR companies by country of headquarters.....	55
Figure 28: Active companies in the CRISPR Companies Database by founding year	57
Figure 29: Active companies in the CRISPR Companies Database by founding year, 2010-2019.....	58
Figure 30: Active companies in the CRISPR Companies Database by company type	59
Figure 31: Active companies in the CRISPR Companies Database by year and company type	60
Figure 32: Active companies in the CRISPR Companies Database by number of employees	61
Figure 33: Active companies in the CRISPR Companies Database by country.....	62
Figure 34: Active companies in the CRISPR Companies Database by company size, as a percentage of companies in each geographic region.....	63
Figure 35: Active companies in the CRISPR Companies Database by founding year, as a percentage of companies in each geographic region.....	64
Figure 36: Active companies in the CRISPR Companies Database by Application Category.....	65
Figure 37: Active companies in the CRISPR Companies Database by founding year as a percent of Application Category grouping	66

Figure 38: Active companies in the CRISPR Companies Database by number of employees, as a percentage of Application Category grouping	67
Figure 39: Active companies in the CRISPR Companies Database by country, as a percentage of Application Category grouping	68
Figure 40: Clinical trials in the CRISPR Clinical Trials Database by start year	71
Figure 41: Clinical trials in the CRISPR Clinical Trials Database by CRISPR use	72
Figure 42: Clinical trials in the CRISPR Clinical Trials Database by CRISPR use and year	73
Figure 43: Clinical trials in the CRISPR Clinical Trials Database by disease category	75
Figure 44: CRISPR-edited cell trials in the CRISPR Clinical Trials Database by disease category	75
Figure 45: Clinical trials in the CRISPR Clinical Trials Database by country of sponsor	78
Figure 46: Clinical trials in CRISPR Clinical Trials Database by CRISPR use and country	78
Figure 47: Percentage of CRISPR clinical trials by country compared to global clinical trial rates	79
Figure 48: Clinical trials in the CRISPR Clinical Trials Database by start year and country of sponsor	80
Figure 49: Clinical trials in the CRISPR Clinical Trials Database by disease category and country	81
Figure 50: Clinical trials in the CRISPR Clinical Trial Database by sponsor type	83
Figure 51: Clinical trials in the CRISPR Clinical Trial Database by sponsor country and type	83

LIST OF TABLES

<i>Table 1: Most prolific organizations publishing in the top 10% of journals for CRISPR worldwide.....</i>	<i>30</i>
<i>Table 2: 10 most common journals for CRISPR publications in Web of Science by year</i>	<i>31</i>
<i>Table 3: Most prolific German organizations publishing in the top 10% of journals for CRISPR worldwide</i>	<i>39</i>
<i>Table 4: Applicants that have CRISPR patent families with 3 or more applications or grants</i>	<i>45</i>
<i>Table 5: Top German CRISPR patent family applicants</i>	<i>54</i>
<i>Table 6: Notable companies in the Database founded by CRISPR pioneers</i>	<i>69</i>
<i>Table 7: Institutions sponsoring more than one trial in the CRISPR Clinical Trials Database.....</i>	<i>82</i>

EXECUTIVE SUMMARY

Between June 2012 and January 2013, separate research teams at Berkeley led by Jennifer Doudna (Jinek et al. 2012), MIT led by Feng Zhang (Cong et al. 2013), and Harvard led by George Church (Mali et al. 2013) were some of the first to introduce the CRISPR system (short for Clustered Regularly Interspaced Short Palindromic Repeats), a breakthrough technology that allows for the editing of DNA in almost any organism. CRISPR was an unexpected shock to scientists, but enthusiasm for the tool was almost immediate due to its flexibility, ease of use, and accuracy compared to alternative editing methods (Pennisi 2013). Since then, interest in CRISPR has shown no signs of slowing. For example, over 11,000 worldwide academic articles involving CRISPR were listed in Web of Science (WoS) by December 2019, and over 2,000 patent families on CRISPR technologies have priority dates before December 2017 (Martin-Laffon et al. 2019). The earliest biotech firms founded on CRISPR technology, Caribou Biosciences (Berkeley, CA), Editas Medicine (Cambridge, MA), CRISPR Therapeutics (Basel, Switzerland), and Intellia Therapeutics (Cambridge, MA) collectively raised initial funding of more than \$150 million. The last three all had IPOs in 2016, and each is currently valued at over \$1 billion.

CRISPR's effect on gene editing has been profound. As geneticist John Schimenti at Cornell University noted: "I've seen two huge developments since I've been in science: CRISPR and PCR ... CRISPR is impacting the life sciences in so many ways" (Ledford 2015). One of the CRISPR pioneers, Jennifer Doudna, stated that CRISPR "has triggered a veritable revolution as laboratories worldwide have begun to introduce or correct mutations in cells and organisms with a level of ease and efficiency not previously possible." (Doudna 2015). CRISPR has already been used to create blight resistant crops (Wang et al. 2014) and "malaria-proof" mosquitoes that are genetically unable to transmit malaria (Gantz et al. 2015). The introduction of CRISPR is especially useful in medical applications since it has the potential to correct disease-causing genetic mutations. Currently, CRISPR allows researchers to build mouse and human cell disease models quickly (e.g., Platt et al. 2014; Specter 2015), has been used to cure HIV in a mouse (Stockton 2017), and has even been used to edit human embryos (Ma et al. 2017; Cyranoski 2018). CRISPR has already proven to be an important medical discovery, winning the prestigious Kavli Prize in Neuroscience. The technology is often lauded as a likely Nobel Prize candidate.

Recognizing the importance of CRISPR, the Independent Commission of Experts for Research and Innovation (EFI) commissioned a project "to outline the potential of CRISPR as a gene-editing tool for innovation while also addressing its concerns." This report addresses Tender 2: Mapping of the Research,

Innovation and Diffusion Activity of CRISPR Across Countries. In this report, we provide novel data that tracks CRISPR activities geographically and temporally; we then analyze the data with a particular focus on Germany's role in the CRISPR innovation ecosystem. By doing so, the work contributes to the EFI's goal of "gathering insights into worldwide CRISPR research and innovation activities, its drivers and, in particular, Germany's position in it."

This report develops four databases that capture the population of publicly available information worldwide on CRISPR academic articles (CRISPR Paper Database), patent families (CRISPR Patent Database), companies (CRISPR Company Database), and clinical trials (CRISPR Clinical Trials Database). We then provide descriptive results for each Database in turn. We also highlight Germany's performance in each measure as compared to other highly ranked countries. The results of the four databases constructed for this report reveal a number of important trends in the global CRISPR innovation ecosystem for the EFI to consider.

First, the CRISPR innovation ecosystem is dominated by organizations and individuals in the United States and China by all measures. However, they have starkly different relationships with the technology. CRISPR's success in the United States is characterized by early discovery, entrepreneurial ecosystems for biotechnology, and Technology Transfer Offices (TTOs) at large research universities. Further, the CRISPR pioneers founded and are actively involved in their own CRISPR startup companies. These surrogate companies, were given rights by the CRISPR pioneers to not only develop CRISPR products but to license them to others. This involvement has strengthened the tie between the academic and corporate labs, making it easier to innovate with the new technology quickly. It has also likely contributed to the increase in additional CRISPR startups in the United States.

China followed a very different path to their CRISPR dominance. Chinese academics and organizations were fast followers in CRISPR having initially low rates of publishing and patenting and then explosive growth in both in later years. This extraordinary growth is likely related to the government's 13th Five-Year Plan (2016-2020) that emphasized becoming a dominant hub in innovation and technology. However, the CRISPR work coming from China seems to be more about quantity than quality. The combination of top-down encouragement and more relaxed regulations has led to a flurry of activity, but has also led to some serious ethical dilemmas in the use of CRISPR in the country.

Second, Germany seems to be following a different CRISPR innovation model. Although Germany has the academic and corporate infrastructure and experience in biotechnology and pharmaceuticals necessary

for CRISPR commercialization, Germany remains a dominant player in CRISPR academic research, especially in Technical Improvements, but is less active in patenting, clinical trials, and new CRISPR companies. The German CRISPR companies that do exist are larger, more established, and more likely to offer CRISPR research services or follow a partnership/acquisition strategy for CRISPR innovation. These organizations are comfortable working with foreign organizations and are able to identify exciting new technologies from others. However, there are only a small number of research and product relationships between academia and corporations in Germany, which may be why Germany has only a few startup companies making or selling CRISPR technology.

Third, countries focus on different niche areas within CRISPR consistent with the existing academic, business, and cultural environments at the time CRISPR was introduced. The chosen application areas of each country seem to hold over the four databases. Thus any future CRISPR innovation strategy should carefully consider whether the necessary environment to expand to other areas exists. For example, innovation strategies should consider current academic and corporate resources; regulations and government support; and culture and risk preferences.

Based on these results, there are a number of implications for a future CRISPR innovation strategy.

1. *The translation from academic ideas to commercial outcomes through academic and corporate partnerships may be an opportunity for Germany*, especially if considering entering Health and Medicine. There is little to no evidence of corporate and academic organizations co-authoring, patenting, or forming other alliances even outside Germany. Given the importance of the academic-corporate relationships to CRISPR development in the United States, it may be difficult to compete without building these relationships.
2. *Germany should carefully consider how to position itself in the CRISPR space*. Germany already has a strong base for technical improvements and services in CRISPR as well as established and experienced companies with capabilities in scientific tools and services related to health applications. Given Germany's current strengths, it could consider incentivizing a particular niche - creating quality solutions for the biggest challenges with CRISPR tools (e.g., delivery mechanisms or improving editing efficiency).
3. *As a longer term strategy, Germany may choose to consider incentivizing the creation of more German-headquartered CRISPR startups*. However, without a strong entrepreneurial support

structure like those in the United States, this strategy could be more difficult. Before encouraging the creation of new ventures it will be important to understand the current barriers to founding new firms. Alternatively, Germany may not need to directly encourage new ventures, but could help current established companies leverage their experience in finding and supporting new technologies from others or further developing these capabilities in-house. Established firms could also be encouraged to create more strategic alliances with existing CRISPR companies around the world.

4. *Germany has the experience and standing to go beyond just new CRISPR innovation and become a global thought leader.* Germany could take the lead in creating regulatory frameworks for the ethical development and use of the future tools. As the CRISPR technology matures, understanding the societal implications and ethics of this exciting technology will become increasingly important.

To develop a comprehensive innovation strategy, questions arising from the implications above suggest potential future studies that will help to better understand Germany's CRISPR environment, but that are not covered by the results in this report. Our report concludes with several options that could provide a richer understanding of the CRISPR ecosystem and identify opportunities and constraints for Germany's strategic initiatives moving forward.

ACKNOWLEDGEMENTS

We would like to thank Yvo Sandjideh for her extraordinary work on putting together the CRISPR companies database. The CRISPR companies analysis would not be possible without her help and efforts. We would also like to thank Orly Salik for all of her excellent research assistance throughout the project. Rebecca Grunberg provided excellent support in creating the natural language processing algorithm used for classifying papers and patents into application categories. Fabian Hans and his team also provided much needed advice on harmonizing the various German organizations under common names. Melissa Staha must also be thanked for taking the time to read drafts and provide comments.

We are grateful to Carolin Häussler, Christopher Stolz, Jano Costard, and the Expertenkommission Forschung und Innovation for their helpful comments on earlier drafts. We also thank EFI for inviting us to be a part of this project. All errors are our own.

I. INTRODUCTION

The DNA-editing system CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is proving to be one of the most important breakthroughs in modern genetics. The powerful tool has the potential to drive innovation in a number of industries, including health and medicine; agriculture and livestock; biofuels and other industrial applications; and CRISPR system improvements, among other uses. Recognizing the importance of CRISPR, the Independent Commission of Experts for Research and Innovation (EFI) commissioned a project “to outline the potential of CRISPR as a gene-editing tool for innovation while also addressing its concerns.” This report addresses Tender 2: Mapping of the Research, Innovation and Diffusion Activity of CRISPR Across Countries. In this tender, we provide novel data that tracks CRISPR activities geographically and temporally; we then analyze the data with a particular focus on Germany’s role in the CRISPR innovation ecosystem. By doing so, the work contributes to the EFI’s goal of “gathering insights into worldwide CRISPR research and innovation activities, its drivers and, in particular, Germany’s position in it.”

The report is organized around four databases built for this report that capture the population of publicly available information on CRISPR academic articles (CRISPR Paper Database), patent families (CRISPR Patent Database), companies (CRISPR Company Database), and clinical trials (CRISPR Clinical Trials Database). Unless otherwise noted, the databases cover the time period from the tool’s introduction in late June 2012 through December 2019. Section 2 of the report provides a brief history of CRISPR’s development and institutional background with an emphasis on factors that could affect diffusion and innovation. Section 3 details the methods used to collect the data for each of the four databases. Section 4 analyzes the data and outlines results. The results from all four datasets are interpreted and discussed in Section 5, with specific attention devoted to comparisons between Germany and other countries. Finally, Section 6 provides data-driven policy implications for Germany as well as recommendations for future studies.

II. A BRIEF HISTORY OF CRISPR INNOVATION

A. EARLY DISCOVERY

Although best-known as a gene editing tool, CRISPR is a natural phenomenon that plays a role in adaptive bacterial immunity. CRISPR helps bacteria identify viral DNA sequences and uses the protein Cas9 to cut the viral DNA to render invading phages harmless. CRISPR was first reported in the literature in 1987

(Ishino et al. 1987). Its significance remained unclear, however, until its role in bacterial immunity was confirmed experimentally in 2007 (Barrangou et al. 2007).

Researchers soon realized the power of this natural system and began looking to repurpose it for gene editing applications. In 2012, two teams published separate proof-of-concept papers demonstrating that CRISPR/Cas 9 could be engineered to target a DNA site of choice. Jennifer Doudna (University of California, Berkeley (UC Berkeley), United States), collaborating with Emmanuelle Charpentier (University of Vienna, Austria; Umeå University, Sweden), showed that CRISPR/Cas9 could be used to locate and edit non-viral DNA sequences *in vitro* (Jinek et al. 2012). Similarly, in a paper submitted before Doudna and Charpentier's work but published three months after, Virginijus Šikšnys (Vilnius University, Lithuania) characterized Cas9's mode of action and demonstrated that the system could be programmed to target specified DNA sequences (Gasiunas et al. 2012).

The earliest work on CRISPR/Cas9 focused on refining the technique for use in prokaryotic cells. But in January 2013, Feng Zhang (Massachusetts Institute of Technology (MIT), United States) and colleagues showed that the tool could edit eukaryotic (including mammalian and human) cells as well (Cong et al. 2013). Related research published contemporaneously by George Church (Harvard Medical School, United States) and collaborators reported similar findings (Mali et al. 2013).

B. WORLDWIDE DISTRIBUTION

The new tool quickly generated enthusiasm because it offered substantial improvements over existing gene editing tools, particularly for mammalian cells (Pennisi 2013). As a result, uptake of CRISPR/Cas9 was rapid. Academic research began emerging shortly after Doudna/ Charpentier's foundational paper:

With over 11,000 academic articles by December 2019. Over 4,000 patent families and funding for firms commercializing the technology followed, with CRISPR-focused biotech companies springing up in the United States and Europe. Collectively, initial funding for the major biotech firms focused on CRISPR commercialization—Caribou Biosciences (Berkeley, California, United States), Editas Medicine (Cambridge, Massachusetts, United States), CRISPR Therapeutics (Basel, Switzerland), and Intellia Therapeutics (Cambridge, Massachusetts, United States)—exceeded \$150 million. Today these companies are valued in the billions.

While the United States and Europe led the way in early CRISPR research and commercialization, CRISPR was quickly distributed worldwide with researchers all over the world adopting the tool and making new

contributions. The non-profit company Addgene, which provides plasmids for research purposes, has facilitated the spread of CRISPR to labs and industry researchers around the world. The organization maintains a repository of validated, ready-to-use viral vectors (Fan et al. 2005). Doudna, Charpentier, and Zhang donated plasmids for use with CRISPR following the publication of their seminal papers. Since then, Addgene has distributed more than 190,000 CRISPR plasmids to over 4,000 organizations around the globe (LaManna, Pyhtila, and Barrangou 2020).

Addgene made access to CRISPR easier for academic researchers worldwide, and key CRISPR patent holders like the Broad Institute made their licenses on the CRISPR technology royalty free for research purposes. CRISPR licenses for commercial purposes were not as easily acquired however. As the technology proliferated, inventors applied for new patents and created a patchwork of licensing rights needed to operate in the CRISPR space freely (Contreras and Sherkow 2017). Further complicating the situation is the uncertainty around ownership of the original CRISPR idea.

C. CRISPR PATENT DISPUTES

In the background of CRISPR/Cas9's global proliferation lies a patent dispute over the underlying intellectual property rights. The primary claimants are the Regents of the University of California (UC) for the University of California, Berkeley, and the Broad (Broad) Institute in collaboration with MIT and Harvard (**Figure 1**). When Jennifer Doudna and Emmanuelle Charpentier published their seminal CRISPR paper in 2012, Doudna's institution (UC) filed for a patent with the United States Patent and Trademark Office (USPTO) (priority application 61/652,086 filed May 25, 2012; application 13/842,859 filed March 15, 2013). Shortly after, in December 2012, Broad filed a patent based on Feng Zhang's early CRISPR work (priority application 61/736,527 filed December 12, 2012). Because Broad filed for accelerated examination, its patent was granted on April 15, 2014 (patent US 8,697,259), while UC's application remained under review. The initial Broad patent was followed by at least twelve additional patents.

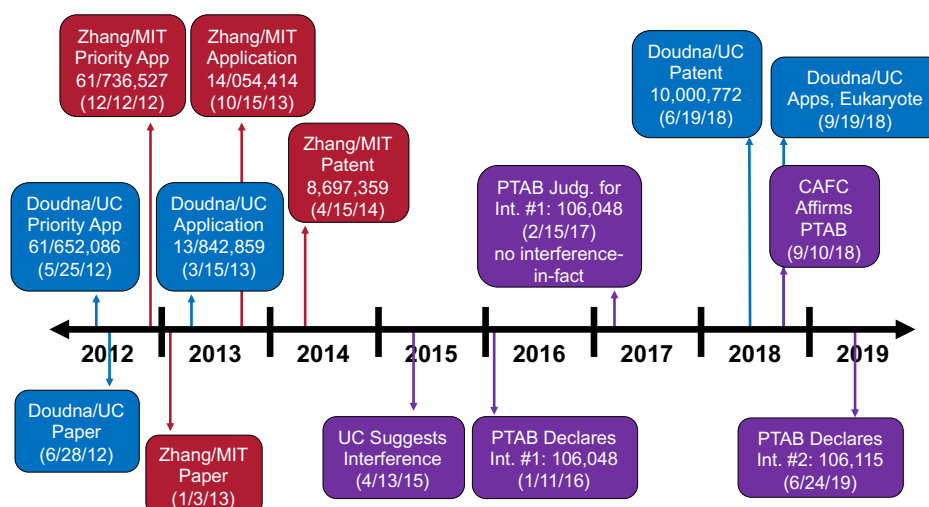


Figure 1: Timeline of the US CRISPR patent interferences

Notes: Red boxes are Broad/MIT events, blue boxes are UC events, and purple boxes are case events.

In April 2015, following the USPTO’s grant of the first Broad patent, UC requested an interference proceeding—a special adjudication that determines the right to a patent among claimants who have filed patent applications covering the same subject matter.¹ In January 2016, the USPTO Board of Patent Appeals and Interferences granted UC’s request, and in February 2017, the Patent Trials and Appeal Board (PTAB) ruled that there was no interference because “given the differences between eukaryotic and prokaryotic systems, a person of ordinary skill in the art would not have had a reasonable expectation of success in applying the CRISPR-Cas9 system in eukaryotes” (Regents of the University of California v. Broad Institute, 2018). The ruling declared the two sets of patents distinct. Thus, although Broad was able to maintain its patents, UC’s patent could also be granted. And in June 2018, it was. Shortly after, in September 2018, the PTAB’s no-interference decision was upheld by the U.S. Court of Appeals for the Federal Circuit (CAFC).

Nine days after CAFC’s affirmance, UC filed a series of CRISPR/Cas9 patents specific to eukaryotic cells (e.g., Patent Trial and Appeal Board 2019). This action eventually prompted the PTAB to initiate a new patent interference proceeding to adjudicate the issue with regard to eukaryotic systems specifically. Although it was requested by neither party, the proceeding was initiated in June 2019; as of July 2020, it has not yet been resolved. Further complicating the issue is the fact that other parties may have interfering

¹ The US has since switched to a form of “first-to-file” patent system that has made such interference proceedings obsolete. However, as the CRISPR applications at issue were filed prior to March 16, 2013 they are still subject to the prior “first-to-invent” system.

claims on CRISPR/Cas9 including Northwestern University (US Patent Application No. 61/099,317 in September 2008); Vilnius University (US Patent Application No. 61/613,373 in March 2012); ToolGen (US Patent Application No. 61/717,324 in October 2012); and Sigma-Aldrich (US Patent Application No. 61/734,256 in December 2012) (Broad Communications 2020).

The UC-Broad patent dispute has not been confined to the United States. In a 2018 decision, the European Patent Office (EPO) revoked the Broad Institute's previously granted patent for lack of novelty; in January 2020, the ruling was affirmed by the EPO Board of Appeal (European Patent Office Board of Appeal 2020). The denial was decided on a technical (rather than scientific) basis.² UC, for its part, has fared far better outside of the United States—it has secured a number of patent rights to CRISPR technologies in Europe.

The uncertainty regarding the patenting landscape has resulted in a patchwork of rights across the field, both topically and geographically. There are costs associated with that ambiguity—uncertainty surrounding licensing can stifle innovation and entrepreneurship (e.g., Gans, Hsu, and Stern 2008). Commercial firms looking to use CRISPR do not always know where they have freedom to operate as which licenses they need may vary by application. A European patent attorney commenting on the situation noted that “[t]he situation is paralyzing small companies. They are afraid of being held liable for patent infringement so they’d rather not use the technology” (Fernandez 2020). To help alleviate some of the challenges stemming from that ambiguity, the U.S. patent firm MPEG LA is attempting to create a CRISPR patent pool (MPEG LA 2020). This would allow stakeholders interested in using the technology to apply for a single license covering the entire system. The firm's efforts, however, have been unsuccessful thus far.

Despite the multiyear dispute from the earliest days of CRISPR's introduction, the importance of the patents at issue may be limited in some areas. Notably, the contested patent rights pertain to CRISPR/Cas9 systems. While early CRISPR work focused on Cas9, it has since become clear that other enzymes (e.g., Cas12) are also effective tools for gene editing and screening. Cas9 remains a leading CRISPR-associated protein, but applications have increasingly focused on others, many of which are covered by patents that likely fall outside the UC-Broad conflict.

² Europe assesses novelty at the time of application. Because a scientist on the provisional U.S. application was affiliated with a university that was not listed on the official application later filed at the EPO, the filing date was determined to be that of the official, rather than the earlier provisional, application. Critically, in the timespan between the provisional and official applications, several publications came out that destroyed the novelty of the patent.

D. CRISPR'S CONTRIBUTIONS AND FUTURE DIRECTIONS

The ongoing patent dispute has not stalled developments in the field entirely. To date, CRISPR has resulted in major contributions across a range of applications and its effect on gene editing has been profound. As geneticist John Schimenti at Cornell University noted: “I’ve seen two huge developments since I’ve been in science: CRISPR and PCR ... CRISPR is impacting the life sciences in so many ways” (Ledford 2015). One of the CRISPR pioneers, Jennifer Doudna, stated that CRISPR “has triggered a veritable revolution as laboratories worldwide have begun to introduce or correct mutations in cells and organisms with a level of ease and efficiency not previously possible.” (Doudna 2015). CRISPR has already been used to create blight resistant crops (Wang et al. 2014) and “malaria-proof” mosquitoes that are genetically unable to transmit malaria (Gantz et al. 2015). The introduction of CRISPR is especially useful in medical applications since it has the potential to correct disease-causing genetic mutations. CRISPR allows researchers to build mouse and human cell disease models quickly (e.g., Platt et al. 2014; Specter 2015), has been used to cure HIV in a mouse (Stockton 2017), and has even been used to edit human embryos (Ma et al. 2017; Cyranoski 2018).

Most recently, a related CRISPR technology allows for base editing that corrects point mutations in DNA (Davies 2019a, Komor 2016, Gaudelli 2017). Further, new iterations of CRISPR employ enzymes other than Cas9 to advance diagnostics such as Zhang’s SHERLOCK tool (Gootenberg et al. 2017) and Doudna’s DETECTR (Chen et al. 2018). Both of these tools are currently being used to develop rapid diagnostic tests for COVID-19 (Sherlock Biosciences 2020 and Alvarez 2020).

CRISPR advances continue to come at an impressive rate (Begley 2020).³ Although, the goal of CRISPR research is not necessarily to provide a CRISPR-based solution to every problem. Ideally, alternative tools that can provide analogous functions (e.g., TALENs or ZFNs for gene editing) will continue to evolve contemporaneously, while CRISPR will be used to address problems to which it is especially well-suited. Thus, as CRISPR technology matures, additional applications that capitalize on the system’s strengths will emerge. CRISPR has shown particular promise as a therapeutic tool. To date, most work in medical applications has focused on using CRISPR’s editing capabilities outside of a patient’s body (*i.e., ex vivo*), but as research on *in vivo* delivery methods progresses, addressing pathologies in other targets (e.g., diseased organs) will become increasingly feasible. In the realm of public health, CRISPR-based gene drives might help control disease transmission via pests, such as mosquitoes or rodents. In agriculture,

³ STAT News has been compiling a list of most published CRISPR advances at the CRISPR Tracker at <https://www.statnews.com/feature/crispr/tracker/>.

CRISPR can be used to develop crops and fruits with high yields and better adaptability to changes in the environment in order to feed a growing population.

For all CRISPR's advances, the technology must still overcome some key hurdles (e.g., Moon et al. 2019). Thus, work on improving the CRISPR system itself is also particularly desirable in the future. One of the most important problems to solve is how to effectively deliver the tool into the desired target cells inside a living organism. As Jennifer Doudna, notes in her book, "That's not to say that it'll be easy to get CRISPR inside the cells themselves. This delivery problem is one of the greatest challenges" (Doudna and Sternberg 2017). CRISPR also can create off-target cuts with unknown consequences, which is especially concerning for gene therapies. Further, some Cas enzymes can provoke unexpected immune responses, so a search for alternative enzymes may be necessary. Generally, improvements to CRISPR efficiency and safety are still needed. These challenges are application specific, so solutions must also consider how the CRISPR tool is intended to be used.

III. COLLECTING DATA ON THE RESEARCH, INNOVATION, AND DIFFUSION ACTIVITY OF CRISPR ACROSS COUNTRIES OVER TIME

To identify the research, innovation, and diffusion activity of CRISPR, we constructed four datasets of key measures: (1) CRISPR publications; (2) CRISPR patents; (3) CRISPR companies; and (4) CRISPR clinical studies. 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. Papers are often followed by patents in the commercialization timeline. 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; these are often the same companies filing for patents. Finally, the CRISPR Clinical Trials Database shows efforts to develop CRISPR products that improve medical outcomes in humans. We discuss the development of each dataset below.

A. CRISPR PAPERS DATABASE

To collect CRISPR publications, we extracted data from one of the most commonly used bibliographic databases, Web of Science (WoS).⁴ The WoS Core Collection includes over 21,000 academic journals worldwide in over 250 areas in the sciences, social sciences, humanities, and arts.

We conducted a topic search for the term “CRISPR” in the WoS Core Collection from 2012 through 2019. 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, Zhang, and Church papers. Almost every subsequent CRISPR article cites to at least one of those three fundamental papers (Zyontz 2016).

To find new published ideas on CRISPR tools and applications, we restricted the CRISPR Paper Database to academic articles only, excluding other publication types.⁵ We also restricted the data to articles published after July 2012 but before January 2020. This allows capture of articles published after Doudna and Charpentier (2012) (generally considered the first CRISPR paper) while mitigating problems with reporting truncation.

For each article, we collected the following information:

- 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

⁴ Web of Science, Clarivate Analytics, www.webofknowledge.com.

⁵ WoS creates consistent categories of document types. To restrict our data to academic articles only, we dropped documents categorized as Meeting Abstract, Review, Editorial Material, Book Chapter, Book, Book Review, News Item, Letter, Proceedings Paper, Bibliography, and Reprint.

To allow aggregation for German organizations, we grouped institutions and harmonized names across articles manually. For example, some German organizations go by different names or are research consortia comprised of other organizations.

Each article was also classified by application category. 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, we simplified these to four: Agriculture/Livestock (combining Plants, Farm animals/aquaculture), 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).

We then used these categories along with the titles and abstracts of the patent families identified by Martin-Laffon et al. to create a training set for a support vector machine (SVM) algorithm. The 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 category. The accuracy of the categorization was verified with manual checks.

Finally, we used data from WoS InCites Journal Citation Reports 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, we used the five-year average impact factor from 2019. Journals that had no reported impact factor were omitted from quality analyses.

The dataset contains 11,552 academic articles published globally from Q3 2012 – Q4 2019 that include data on the year of publication, country of authors, and abstract or keywords.

B. CRISPR PATENTS DATABASE

Because we are interested in the number of independent inventions created with CRISPR, we focus mostly on patent families in this report. To build a database of worldwide patent families that describe CRISPR inventions, we began by following 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. We then extended the CRISPR patent families database using their methodology for patent families with the earliest priority date by December 31, 2019.

We collected worldwide CRISPR patent families from the Lens.org.⁶ Lens.org is an extensive source of patent metadata that is open to the public and linked to academic articles; as of June 2020, it included 67.5 million patent families with 123.5 million patent records (both applications and grants) in 105 jurisdictions. The jurisdictions include the USPTO, EPO, WIPO, and the Chinese Patent office (CNIPA), among others.⁷ We also searched the private Dimensions Plus⁸ dataset to verify the Lens.org data.

We used the same initial search strategy as Martin-Laffon et al. (2019), 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 with a priority date of December 31, 2019 or earlier.⁹ Once we identified all possible CRISPR patent families, we manually reviewed every record, checking for duplicates and removing patent families that were not directly related to the CRISPR system. We also verified the CRISPR patent families identified in Martin-Laffon et al. (2019) in the Lens.org database.

For each patent family, we collected the following information:

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

Each new article was also classified by application category. 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, we simplified these to four: Agriculture/Livestock (combining Plants, Farm animals/aquaculture), Health/Medicine (combining Medical and the

⁶ <https://www.lens.org/>

⁷ <https://www.lens.org/lens/search/patent/structured>

⁸ <https://www.dimensions.ai/>

⁹ 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.

pharmaceutical applications in Industrial applications), Industrial Applications (the remaining Industrial applications), and Technical Improvements (combining Technical improvements and Other in vitro uses). We then used these categories along with the titles and abstracts of the patent families identified by Martin-Laffon et al. to create a training set for a support vector machine (SVM) algorithm. The algorithm was applied to the titles and abstracts, of the new 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.

The dataset contains 4,041 CRISPR patent families with published applications and grants around the world with earliest priority dates by December 31, 2019 or earlier.¹⁰ Because different patent jurisdictions delay the publication of new applications longer than others, our analysis focuses on the 3,652 patent families with earliest priority date by December 31, 2018 for comparative purposes.

C. CRISPR COMPANIES DATABASE

Sources of firms and their activities vary widely in their coverage and content, so we used a number of methods to compile a list of the most publicly active commercial firms in CRISPR. We 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, we ran a Google search on each company and added to the list any additional licensees, parent companies, strategic partners, and other companies associated with the CRISPR work.

Next, we broadened the search by using the search strings “CRISPR companies” and “(CRISPR and (firm or company)) or agreement or license or venture or acquire” in Google. This search was designed to capture companies that 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,¹¹ Crunchbase,¹²

¹⁰ Worldwide patent families are often identified by the collection of patent applications they claim priority to, so we choose 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.

¹¹ <https://www.sec.gov/edgar.shtml>

¹² <https://www.crunchbase.com/>

and AngelList.¹³ We also searched for the term “CRISPR” in Crunchbase to find new biosciences and biotech companies claiming to use CRISPR. We also searched for the companies on the Germany-Biotech Company List¹⁴ to ensure we captured all possible German CRISPR companies.

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

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 we can only rely on publicly observable information, such firms will not be included in the database. As such, the database may not be comprehensive; instead, it contains publicly active, known firms.

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

- 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 2020, when the database was 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 four 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.

¹³ <https://angel.co/>

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.

We also added two additional categories for corporate activities that are not found in patents or papers. 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.

The Dataset contains 724 CRISPR companies that are active or could only be identified using patent information. Because many companies are missing information, database focuses mainly on the 311 active CRISPR companies (those that provide more information on their CRISPR activities than just a patent) worldwide as of Q2 2020.

D. CRISPR CLINICAL TRIALS DATABASE

Because CRISPR is a relatively new technology, clinical trials based on CRISPR are rare events. However, those that do exist are being heavily observed due to the possible advances (and pitfalls) in human disease treatment, so it is likely that most CRISPR-based clinical trials appear in public databases.

To gather publicly announced CRISPR clinical trials, we used the search string [CRISPR OR Cas9 OR Cpf1 OR gRNA* OR sgRNA* OR “RNA* guide*” OR “guide* RNA*”] in worldwide databases of clinical trials, including ClinicalTrials.gov,¹⁵ Global Clinical Trials Data,¹⁶ and the WHO International Clinical Trials Registry Platform.¹⁷ We included results where the search terms appeared anywhere in the text, and restricted to trials that had been announced as of Q2 2020. We further supplemented the data with the private Dimensions database,¹⁸ which provides access to clinical trials in the United States, Japan, the European Union, India, Australia, China, Germany, Netherlands, and South Korea. A manual review removed duplicates and trials that did not use CRISPR or directly reference the CRISPR system.

For each clinical trial, we collected the following information:

- Study Title
- Study Abstract
- Name of the Sponsor Organization(s)
- Anticipated Start Date of the Trial

¹⁵ <https://clinicaltrials.gov/>

¹⁶ <https://www.globalclinicaltrialsdata.com/>

¹⁷ <http://apps.who.int/trialsearch/>

¹⁸ <https://www.dimensions.ai/>

- Trial Phase (if available)
- Condition to be Treated
- Intervention Used
- Location(s) of the Sponsor Organization
- Location(s) of the Study

Since the clinical trials fit into the Health application area, we further classified the trials by subcategories, including the target disease type of the study, how CRISPR was used in the study (CRISPR-edited cells, CRISPR cell line creation/modeling, CRISPR genome sequencing/tests, surveys), type of sponsoring organization (industry, non-industry), and whether CRISPR delivery was *ex vivo* or *in vivo*. Most of the categorizations were completed manually with guidance from Hirakawa et al. (2020) and Li et al. (2020).

As of Q2 2020, the database contains 49 clinical trials worldwide involving CRISPR.

IV. RESULTS

A. CRISPR PAPERS DATABASE

i. Worldwide Publications

Over the past seven years, CRISPR has transitioned from a technology known by only a handful of people, to a one that has graced the front page of popular newspapers, been featured on late night television, and captured the public’s imagination in science fiction movies starting Dwayne (“The Rock”) Johnson. As discussed in Section II, CRISPR was initially a curiosity and is now a powerful tool that has allowed for substantial advances in agriculture, medicine, and several other industries. This rapidly increasing interest in CRISPR, especially by academic scientists, can be seen in **Figure 2**, where the number of CRISPR papers published in 2019 is 17.5 times greater than the number published in 2012. This trend is not due to general increases in biological or biomedical publications (National Science Foundation 2019), but rather reflects the explosion of work in CRISPR in a very short timeframe.

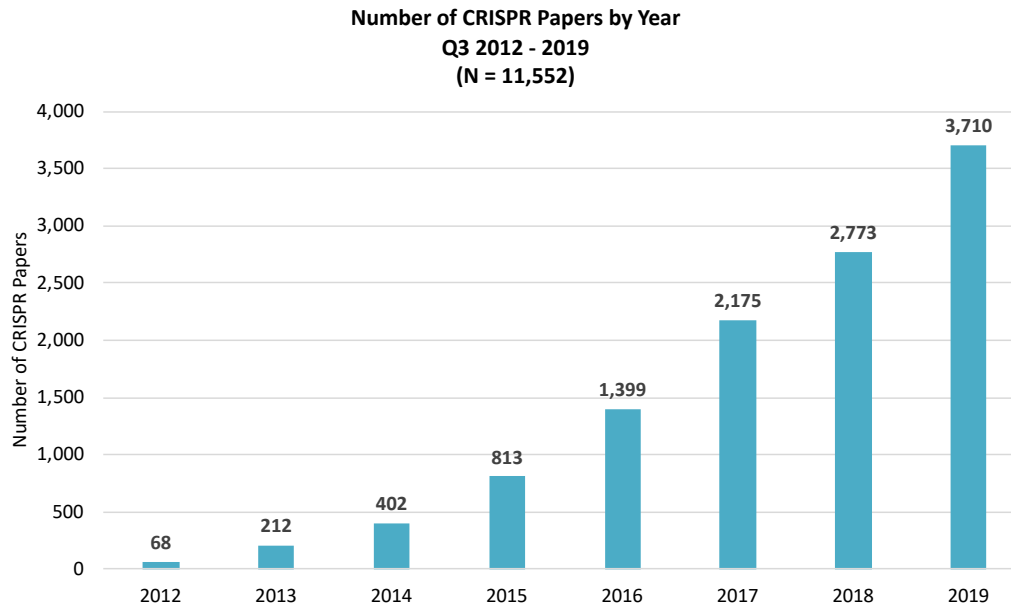


Figure 2: Count of CRISPR academic articles in Web of Science by publication year

Novel ideas involving CRISPR, as measured by academic publications, have some geographical bias, though they are not completely limited to a handful of locations (**Figure 3**). Academic teams from all over the world contribute to the advancement of CRISPR research, but countries like the United States, China, Germany, Japan, and the United Kingdom tend to dominate. Since CRISPR was originally discovered in the United States, it is not surprising that there is at least one U.S. co-author on 47.8% (5,517/11,552) of papers, more than any other country. Close behind are European co-authors at 28.7% (3,320/11,552) and Chinese co-authors at 25.6% (2,960/11,552). German scientists are especially prolific in CRISPR research for the relative size of the country, appearing in 9.0% (1,043/11,552) of all papers. Rounding out the top publishing locations are Japan at 8.5% (980/11,552) of papers and the United Kingdom at 8.4% (971/11,552) of papers. The rank ordering of countries changes only slightly if looking solely at the authors important enough to be listed as corresponding authors in the article. For example, Japan and Germany switch places and South Korea moves ahead of France and the Netherlands.

The dominant locations of publications are likely determined by a number of factors including the original locations of CRISPR discovery, access to tacit information on using CRISPR, resources (funding, personnel, appropriate lab equipment), and the regulatory and cultural environment (Zyontz and Thompson 2020). For example, China's 13th Five-Year Plan (2016-2020) 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. Nevertheless, CRISPR publications are

not limited to only a few locations; this may be due, in part, to the ease of access to the tool through organizations such as Addgene (discussed in greater detail in Section II).

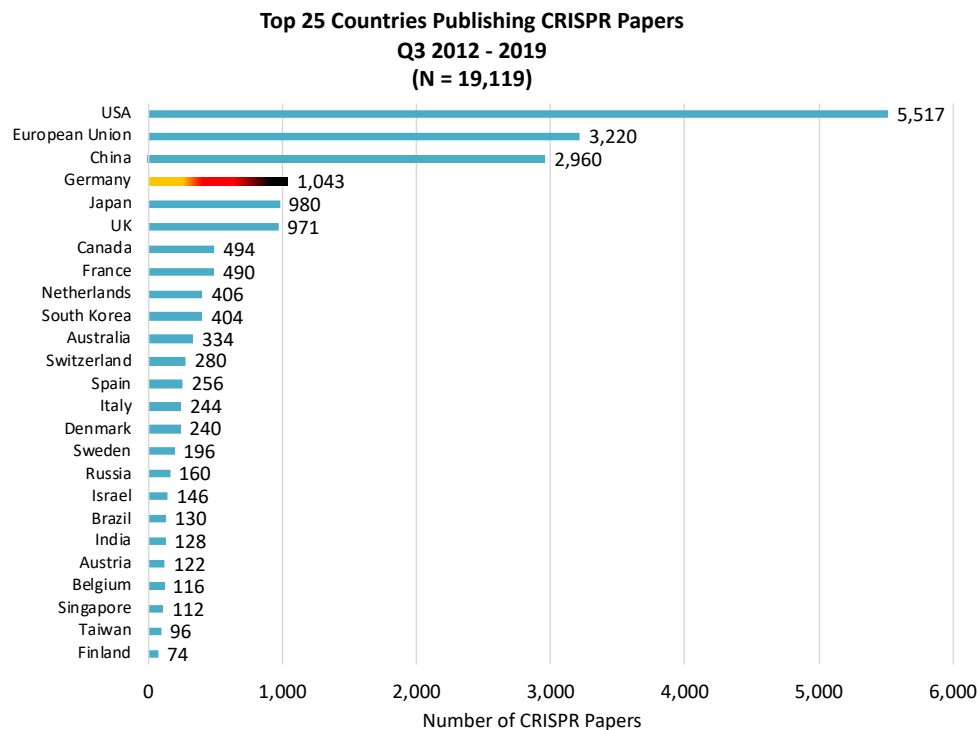


Figure 3: Count of CRISPR academic articles in Web of Science by the top 25 countries or country groups
Notes: Papers can have authors in more than one country, and the paper is counted once for each country represented, so some papers will be double counted. Attribution is not proportional. The European Union includes the United Kingdom.

To put the top CRISPR publishing countries in context, we compare each country's CRISPR publications to their overall publications in Biological and Biomedical topics and in Health topics as reported by the National Science Foundation (2019). The NSF report has data on publications by scientific fields by country going back to 2000. The data suggests that in Biological and Biomedical sciences and Health, Germany has a prominent position in such publishing, but tend to produce relatively more papers in CRISPR. This is in contrast to the EU in general, which produces relatively fewer CRISPR papers. The countries with the largest differences between CRISPR publications and Biological and Biomedical topics and in Health topics are the United States and China. These countries produce far more CRISPR papers than might be expected (**Figure 4**).

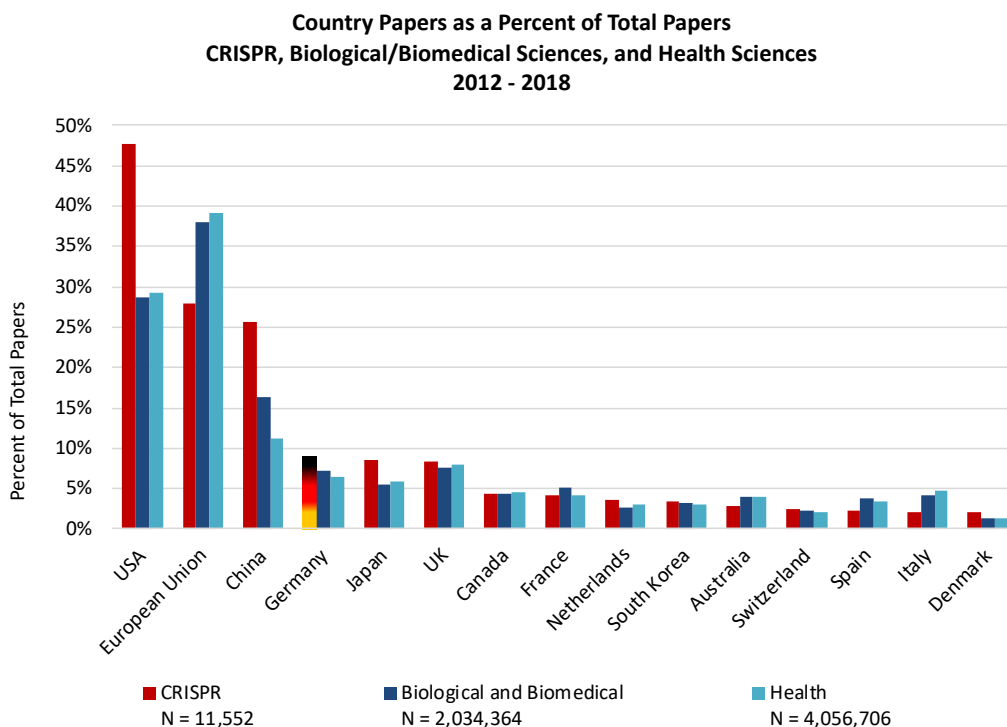


Figure 4: Comparison of a country's proportional contribution to total papers in CRISPR, Biological and Biomedical Sciences, and Health Sciences

Notes: Sources are Web of Science and NSF 2019. 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 includes the United Kingdom.

ii. Publication Quality

The rapid and worldwide proliferation of CRISPR publications could raise concerns about the overall quality of the research, as the race to be first could compromise the quality of the papers. CRISPR papers do follow a standard citation trend (**Figure 5**), where the majority have fewer than 10 citations. However, many articles are recent, and the top 10% of cited papers still have 60 or more citations. Controlling for the number of quarters since publication, 125 CRISPR papers received more than 100 cites per quarter on average. Further, the first three papers by Doudna, Zhang, and Church have over 4,000 citations each.

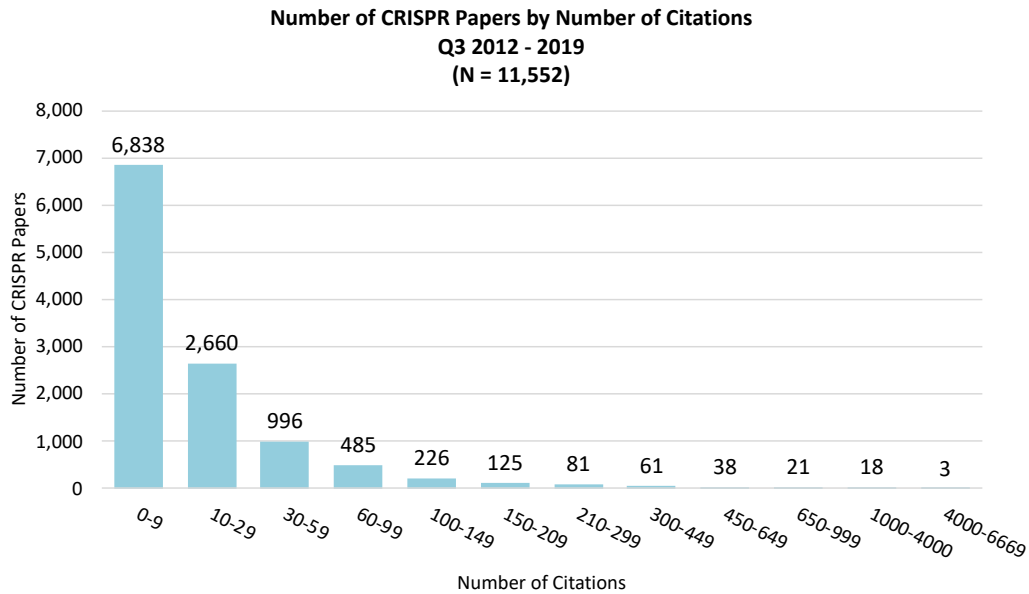


Figure 5: Count of CRISPR academic articles in Web of Science by number of citations

As expected for publications, the most prolific organizations working in CRISPR are academic institutions and their associated research centers and hospitals (Merton 1973, Sauermann and Stephan 2013), and they happen to be some of the highest quality institutions globally. Some of the most dominant organizations are part of the original CRISPR discovery in the United States, including UC Berkeley, MIT, the Broad Institute, and Harvard University. Other top publishing organizations throughout the world are internationally recognized such as the Chinese Academy of Sciences, China's globally recognized national research institution, (Chinese Academy of Sciences 2020); Stanford University; University of California San Francisco; the University of Tokyo; the University of Pennsylvania; Shanghai Jiao Tong University; Sun Yat Sen University; University of Toronto; Seoul National University; Kyoto University; and the University of Cambridge. The number of papers by the most prolific organizations publishing in the top 10% of journals is shown in **Table 1** below.

Publishing Organization	# Papers in the Top 10% of Journals
Harvard College	1028
University of California	863
Chinese Academy of Sciences	820
Massachusetts Institute of Technology	519
Broad Institute	277
Stanford University	274
University of Pennsylvania	158
Duke University	156
University of Toronto	134
Dana Farber Cancer Institute	116

Table 1: Most prolific organizations publishing in the top 10% of journals for CRISPR worldwide

CRISPR articles are also published in a number of high-impact journals including *Science*, *Nature*, *Nature Communications*, *PLOS One*, *PNAS*, and *Cell Reports*. The majority are published in *Scientific Reports*, which is a peer-reviewed, open-access journal in the natural and clinical sciences that is part of the Nature Research journals collection (**Figure 6**).

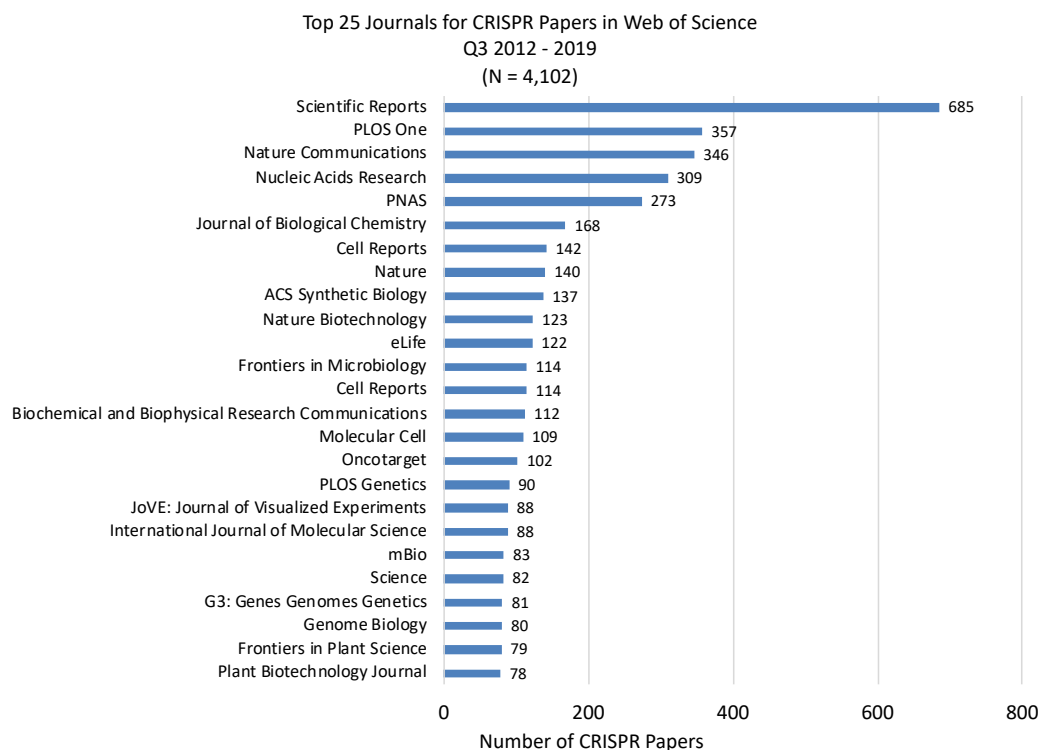


Figure 6: Most common journals for CRISPR publications in Web of Science

The set of most popular journals to publish CRISPR research has changed over time (**Table 2**). In the earliest years, CRISPR papers appeared mostly in biology and microbiology field journals, as that is where the initial discovery was made. Then, as the importance of the tool became more obvious to the academic community, the most popular journals in which to publish were highly-ranked general science journals like *Cell*, *PNAS*, *Nature Methods*, *Nature*, and *Scientific Reports*. Later, as CRISPR found uses in more applications, the popular journals shifted towards specific field journals such as *Oncotarget*, *ACS Synthetic Biology*, and the *Plant Biotechnology* journals.

Journal Name	2012 Rank	2013 Rank	2014 Rank	2015 Rank	2016 Rank	2017 Rank	2018 Rank	2019 Rank
PLOS One	1	5	1	1	2	3	4	7
Journal of Bacteriology	2							
Journal of Clinical Microbiology	3							
mBio	4							
Molecular Microbiology	5							
Nucleic Acids Research	6	3	2	3	3	6	5	3
Biology Direct	7							
BMC Genomics	8		7					
Frontiers in Microbiology	9					8	9	
Journal of Biological Chemistry	10				8		6	4
RNA Biology		1						
Biochemical Society Transactions		2						
Genetics		4		10				
Cell		6	10	6				
Nature Biotechnology		7	5	7				
PNAS		8	6	4	5	4	3	5
PLOS Genetics		9						
Nature Methods		10	8					
Scientific Reports			3	2	1	1	1	1
Nature Communications			4	8	6	2	2	2
Nature				5	7	10		
Genome Research			9					
Cell Reports				9	9		8	
Oncotarget					4	5		
ACS Synthetic Biology					10	9	7	10
Bio-protocol						7		
Biochemical and Biophysical Research Communications							10	
eLife								6
International Journal of Molecular Science								8
Plant Biotechnology Journal								9

Table 2: 10 most common journals for CRISPR publications in Web of Science by year

Restricting attention to CRISPR articles published in the highest ranked journals helps clarify where some of the highest quality papers appear. Only considering papers in the top 10% of journals by impact factor from the set of journals where CRISPR articles are published, results in 3,646 papers, or 31.6% of the 11,552 total CRISPR papers. We refer to this subset of 3,646 papers as “Top Papers.” In the Top Papers,

the same countries appear as the most prolific publishers, but Germany loses a position to the United Kingdom, suggesting that fewer of its total papers are published in the highest ranked journals (**Figure 7**).

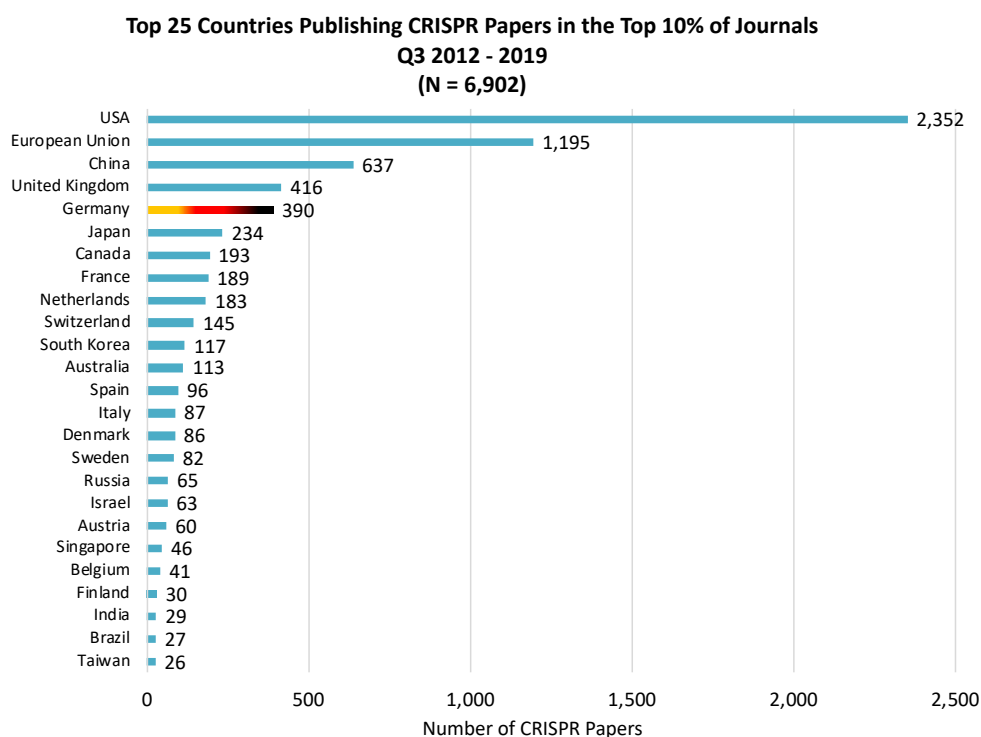


Figure 7: Count of CRISPR academic articles in the top 10% of journals by impact factor in Web of Science by the top 25 countries

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 includes the United Kingdom.

To explore the relationship between total CRISPR papers and Top Papers, **Figure 8** highlights Top Papers as a percent of total CRISPR papers for each country. Countries vary substantially in the proportion of total papers that are published in top journals. For example, 52% of Switzerland's 280 CRISPR papers were published in a top 10% ranked journal. Part of this could be due to the fact that Emmanuelle Charpentier has a Swiss affiliation. Brazil, by contrast, placed only 21% of its 130 CRISPR papers in higher ranked journals.

As might be expected given the location of the CRISPR pioneers and the prevalence of U.S. academics publishing in top journals, the United States has been able to place 43% of its 5,517 papers in the highest ranked journals. Other countries, including Israel, the United Kingdom, and Sweden, are on par with the United States. Germany ranks slightly lower: 37% of its 1,043 CRISPR papers appear in top journals,

placing it right in line with the European Union average. Asian countries in general seem to fare much more poorly. South Korea, Japan, Taiwan, China, and India all have less than 29% of their CRISPR papers in top journals. China does the worst: only 22% of its 2,960 papers appear in top journals. This may be because Chinese scientists tend to publish in local journals that are not highly ranked worldwide. It may also be due to the fact that certain application areas (discussed below) like Agriculture/Livestock are in slightly lower ranked journals on average than Health/Medicine and CRISPR Technical Improvements. A shift in proportion towards lower ranked topic areas can lead to a lower journal ranking overall.

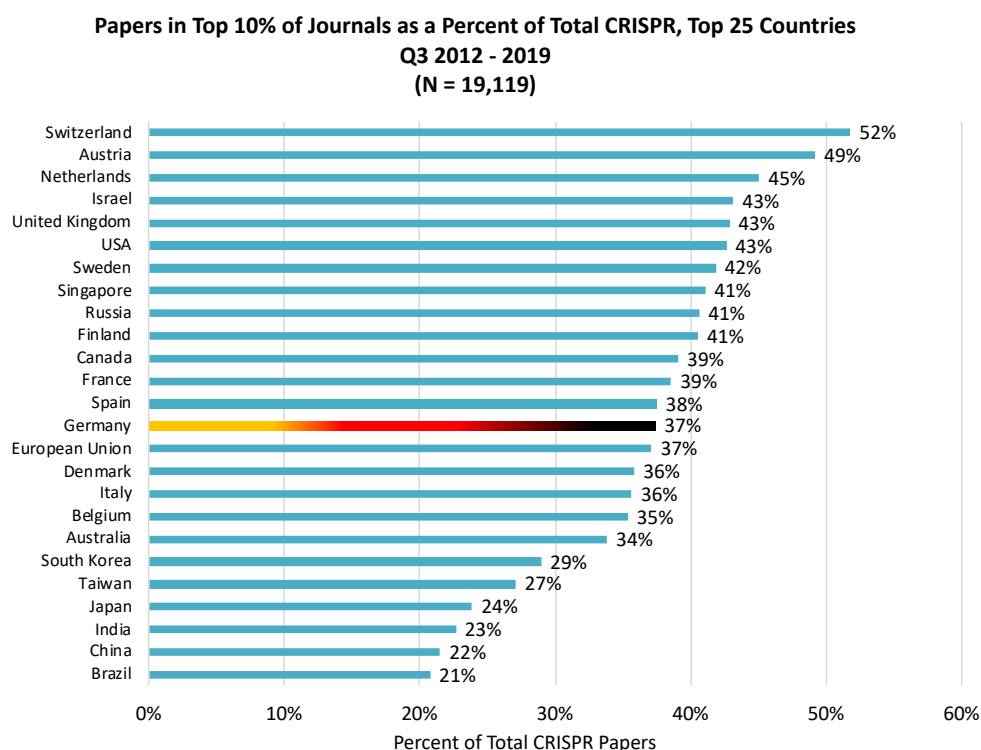


Figure 8: Top Papers as a percent of all CRISPR papers in the country

Notes: Top Papers are those CRISPR papers in the top 10% of journals 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 includes the United Kingdom.

iii. Papers by Application Category

To consistently compare application areas between CRISPR papers, patents, and companies, we classified CRISPR papers into four categories: Health/Medicine (including medical applications), Agriculture/Livestock (including plants and livestock), Industrial Applications (including biofuels and food

manufacturing), and Technical Improvements (improvements made to the CRISPR tool, including new delivery mechanisms). Papers are classified into mutually exclusive categories as described in Section III.

Figure 9 shows the proportional breakdown of the categories for all CRISPR publications. 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 48% of papers primarily address Health/Medicine. These capture research on new model organisms, treatments, genetic therapies, drugs, and similar uses,. Agricultural/Livestock applications, like creating new and better crops or hornless cattle, account for 8% of papers. The remaining 3% of papers focus on Industrial Applications, such as biofuels. As we will show in Section IVb, this breakdown is not substantially different for CRISPR patents, although there are some notable differences. For example, since papers are mostly published by academic scientists, while corporations (who are less likely to publish) do much of the work in Agriculture/Livestock, one might expect to see a lower proportion of papers, as compared to patents.

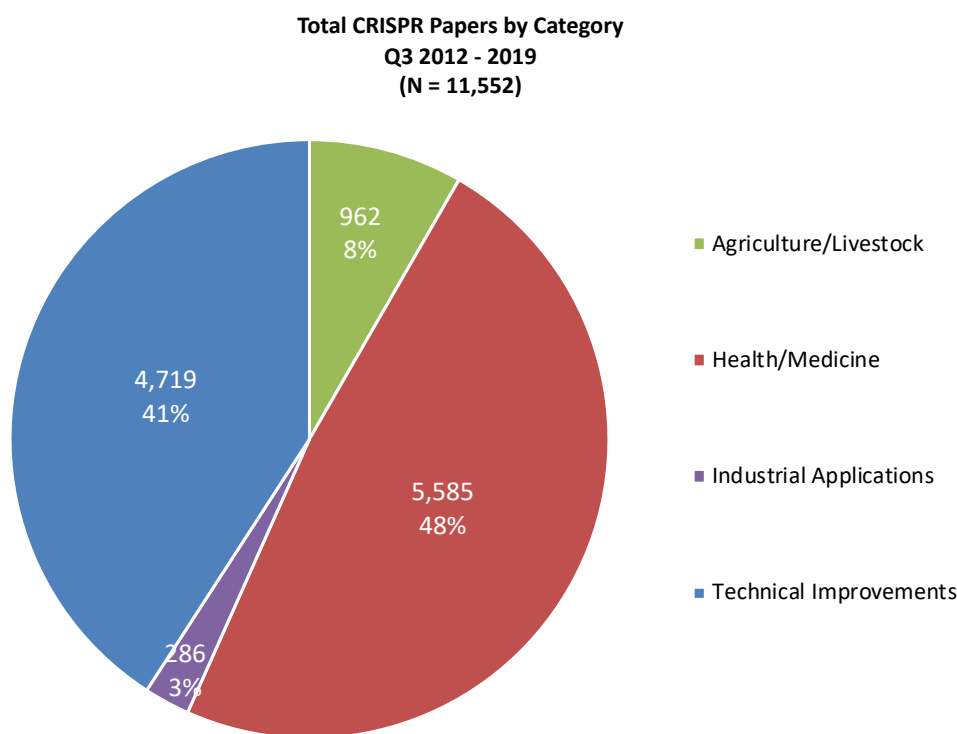


Figure 9: Percent of CRISPR academic articles in Web of Science by Application Category

Over time, publications in certain application areas have increased quickly (**Figure 10**). Since CRISPR's proof-of-concept was demonstrated first in bacteria, it is of little surprise that Technical Improvements

papers appear first. CRISPR was shown to work in mammals in early 2013, and a little later that year, the technology was shown to be superior to earlier editing technologies such as TALENs (Ding et al. 2013; Cohen 2017). After these discoveries, papers in Health began to explode. Health remains one of the most promising areas for CRISPR research as the CRISPR tool made certain experiments on mammalian cells possible where they were not before. Agriculture has a smaller growth trajectory, but there were still almost 400 papers published in 2019.

Technical Improvements to CRISPR will continue to emerge as researchers adapt CRISPR for use in new organisms and discover new CRISPR functions that can do more than cut DNA. Over the last seven years, CRISPR has been found to work in a large number of organisms including more commonly used model organisms such as mice, yeast, zebrafish, plants, and fruit flies. It also has been shown to work in model organisms that are less common and more complex such as rove beetles, cuttlefish, honey bees, butterflies, pea aphids, and reptiles. (Synthego Blog 2019). Currently, CRISPR tools can be used for a host of functions including creating knockouts, base editing, activating or repressing of genes, genome-wide screening, and imaging (Addgene 2020).

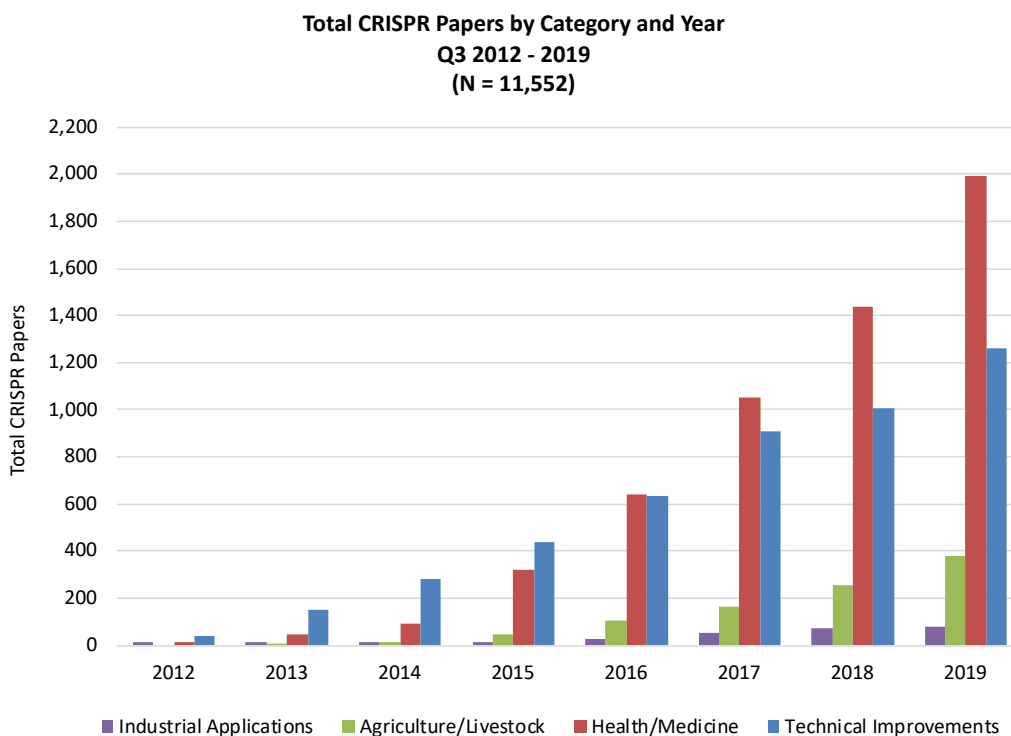
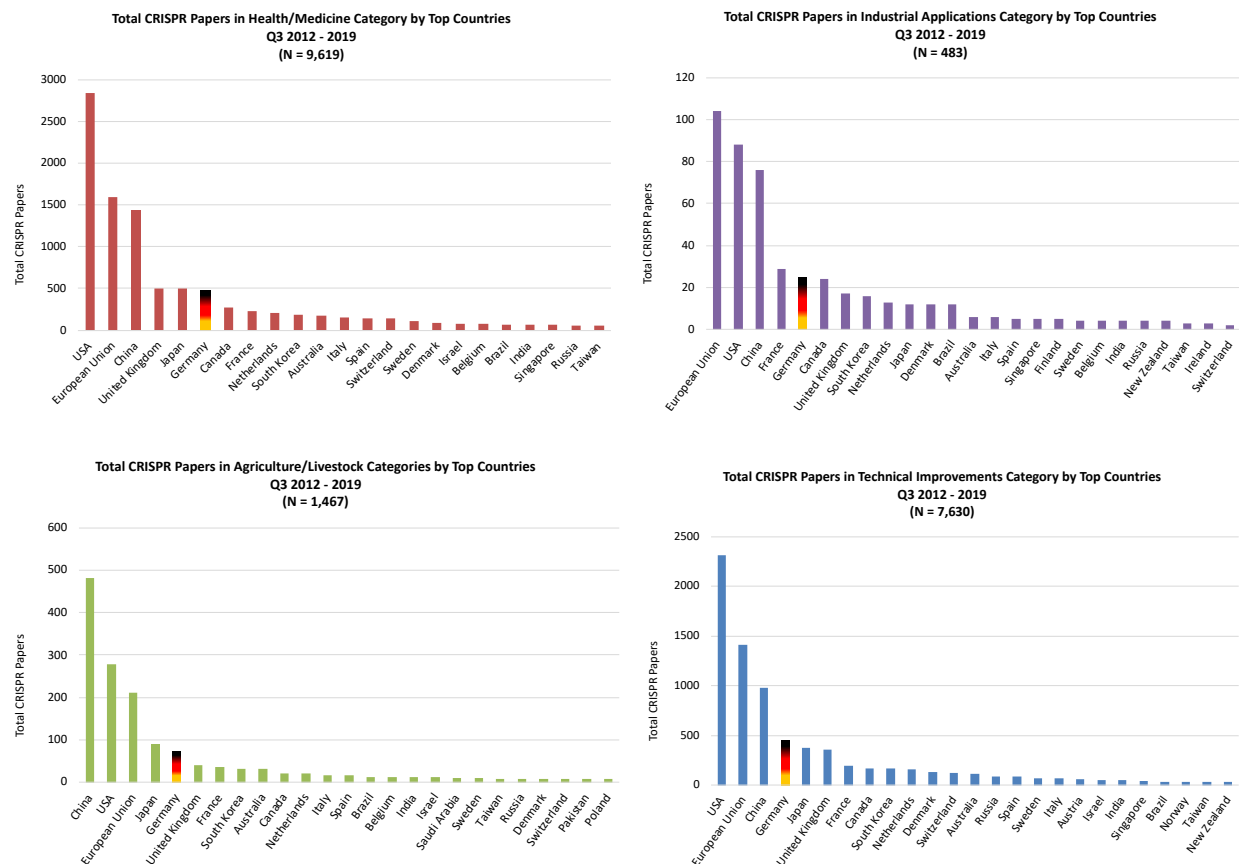


Figure 10: Count of CRISPR academic articles in Web of Science by Application Category and year

The top countries publishing CRISPR papers overall tend to also be the top publishers in specific application areas. However, the country with the most publications in each area does differ (**Figures 11a-**

11d). For example, the United States is the top publisher in Health/Medicine and Technical Improvements, while the European Union countries are the top publishers in Industrial Applications. Further, China has nearly twice as many Agriculture publications than any other country. These patterns are consistent with the United States' discovery of the CRISPR tool and China's focus on innovation and technology, with particular attention paid to agricultural advances.

Germany is a top overall publisher and ranks within the first 4-6 places in each application area. It ranks best in Technical Improvements and Agriculture/Livestock, but lags a bit behind in Health/Medicine. Most papers in Germany fall within the Technical Improvements (43.6% = 455/1,043) and Health/Medicine categories (46.9% = 489/1,043). Papers in Agriculture/Livestock represent 7.1% (74/1,043), and Industrial Applications 2.4% (25/1,043). This closely tracks the overall application breakdowns discussed above.



Figures 11a-d: Total CRISPR academic articles by Application Category in countries with the most publications

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 includes the United Kingdom.

The country trends are even starker when comparing each country's percent contribution to the total publications in each application area (**Figure 12**). For example, 50% of all Agriculture/Livestock publications has at least one author from China whereas less than a third of papers include a U.S. author. The complete opposite is true for Health/Medicine and Technical Improvement publications. Over 50% of all Health/Medicine publications include a U.S. author, but no other country (or set of countries) appears on more than 30% of papers. The same is true for Technical Improvement papers, although Chinese authors are proportionally less involved in this area. German and Japan remain rather consistent across categories, appearing on 8-10% of publications.

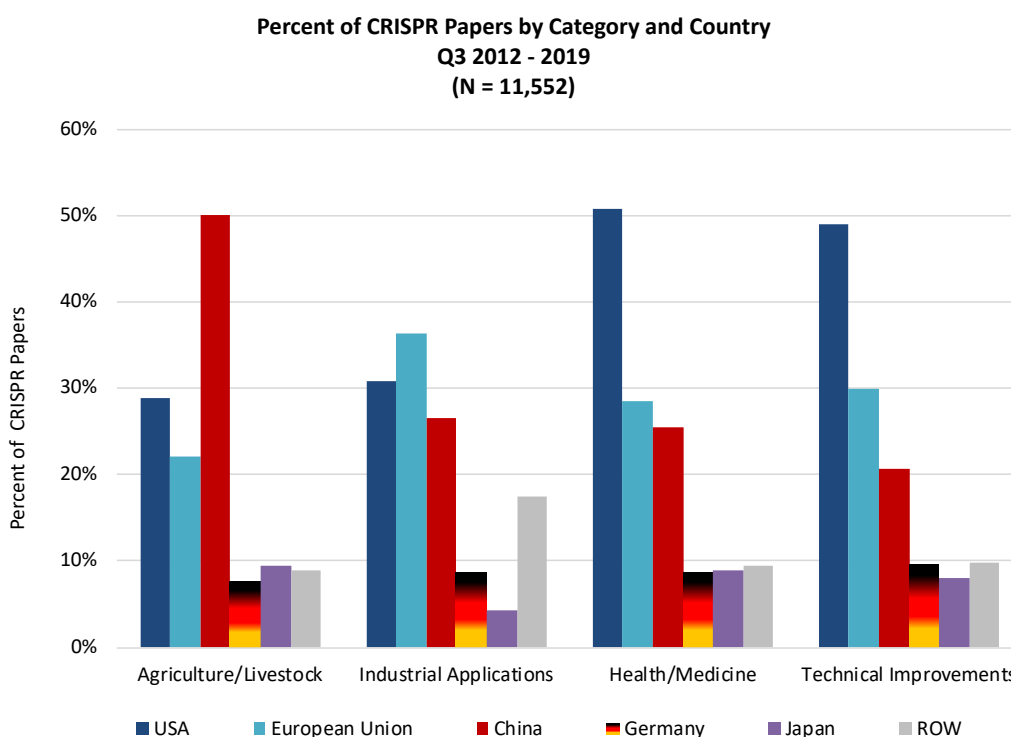


Figure 12: Percent of CRISPR academic articles by Application Category in selected countries
Note: Papers can have authors in more than one country, and the paper is counted once for each country represented, so some papers will be double counted. Attribution is not proportional. The European Union includes the United Kingdom.

iv. Germany

With 1,043 papers in CRISPR, Germany is one of the top contributors to new ideas in the field. Still, its rate of publications is slower than its larger counterparts (**Figure 13**). Germany's compound annual growth rate for publications is 55.2%, which is in line with Europe in general (at 54.8% growth), but is slower than

the U.S. rate at 64.9%. Over the period examined, publications in China grew an astronomical 96.1%. This clearly documents its delayed start but quick catch-up to the United States.

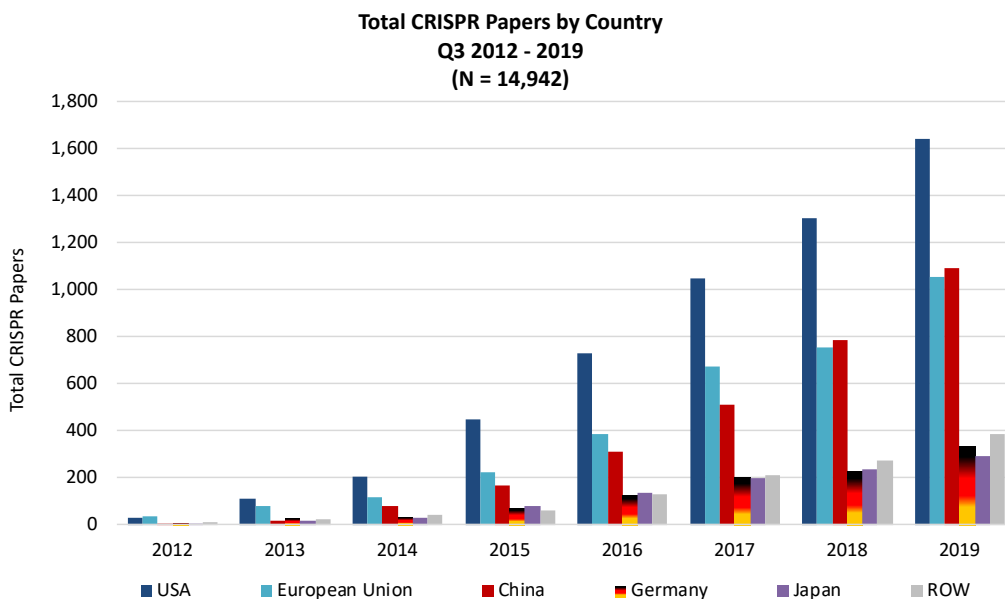


Figure 13: Count of CRISPR academic articles by publication year and country

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 includes the United Kingdom.

The German organizations publishing most frequently in the top 10% of journals are shown in **Table 3**. They primarily include universities and research centers.

Publishing Organization	# Papers in the Top 10% of Journals
Ludwigs Maximilians Universtaet Munich	76
Deutsches Krebsforschungszentrum	73
Heidelberg University	72
Albert Ludwigs University of Freiburg	65
Hannover Medical School	52
Technical University Munich	47
Heidelberg University Hospital	44
Charite	42
Helmholtz Zentrum Muenchen	42
Technische Universitaet Dresden	39

Table 3: Most prolific German organizations publishing in the top 10% of journals for CRISPR worldwide

German authors are not only prolific, but they are also inclined to be more collaborative with co-authors from other countries, especially in the United States. For example, German authors are on average co-authoring with authors from at least one other country. This is in contrast to Chinese authors who are more likely to only co-author with others in China (**Figure 14**).

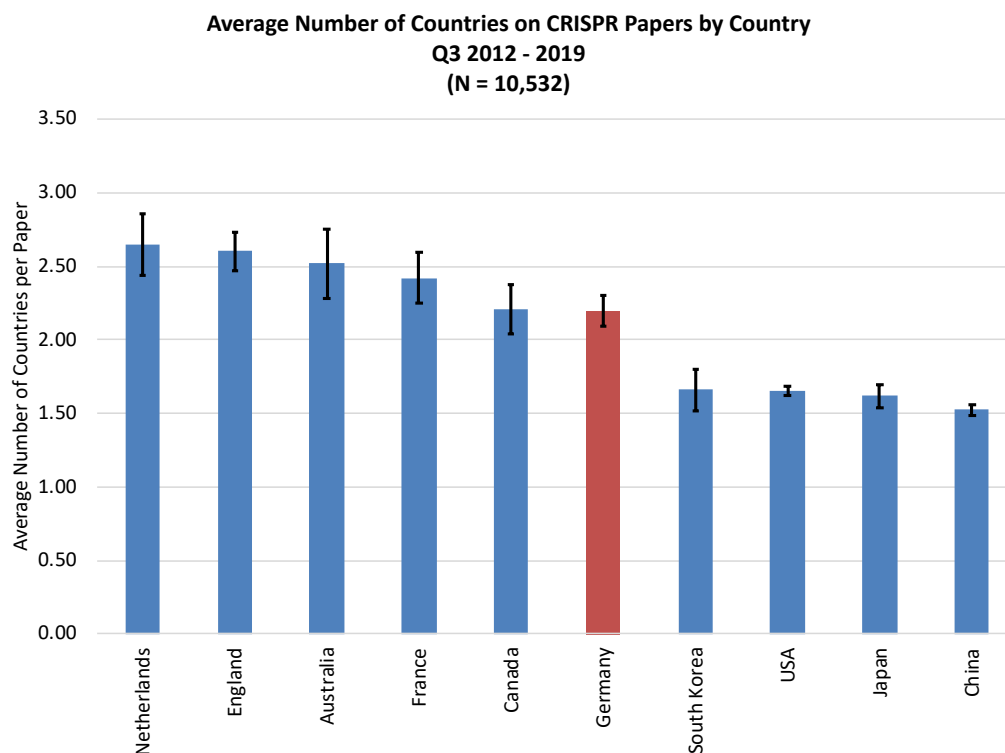


Figure 14: Average number of counties represented in each CRISPR academic article in Web of Science by authors in a focal country

Although German authors are willing to collaborate across countries and organizations, it is usually among academic scientists. It is very rare to see German universities publishing with industry. The most common German co-author groups are illustrated in **Figure 15**.



Figure 15: Common German co-authoring organizations as reported in Web of Science

B. CRISPR PATENTS DATABASE

i. Worldwide Patent Families

The rapidly increasing interest in CRISPR, also translates to more patent applications that use CRISPR or improve the tool itself. The increase in CRISPR patent families is even faster than observed in papers as seen in **Figure 16**. The number of CRISPR patent families that can be traced to the earliest application (earliest priority date) in 2018 is 33 times greater than those that rely on an application from 2012. We focus on patent families here as they are a more appropriate measure of distinct ideas, but families can have more than one associated application across several patent jurisdictions. Because jurisdictions have different publishing delays for applications, 2019 is incomplete for countries that have longer delays. To avoid this truncation problem, we focus the remaining analyses on families with an earliest priority date of December 31, 2018 or earlier.

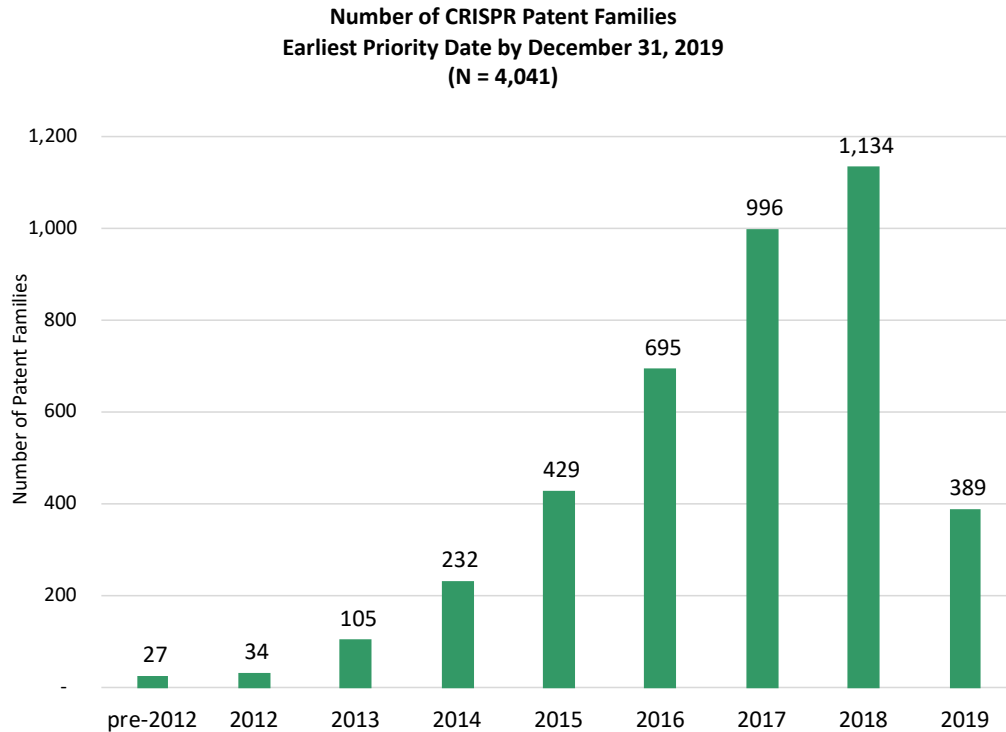


Figure 16: Count of CRISPR patent families worldwide by Earliest Priority Date

Protecting an idea involving CRISPR with a patent could be for eventual commercialization or could serve as an intellectual asset, for example for purposes of getting venture capital funding (e.g., Conti Thursby, and Thursby 2014; Haeussler, Harhoff and Mueller 2014) or to make transactions for the technology easier (e.g., Gans and Stern 2003; Gan, Hsu, and Stern 2008). Not all CRISPR ideas are patented, however, patent applicants in CRISPR are geographically biased as seen in **Figure 17**. Applicants only come from 34

countries and the vast majority of families have at least one applicant from either the United States 45.6% (1,667/3,652) or China 37.6% (1,372/3,652). 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. In fact, Germany's rank in patenting is lower (1.7% = 63/3,652) than both South Korea (3.5% = 126/3,652) and Switzerland (2.4% = 89/3,652), who have moved up in the ranks.

As with papers, the dominant locations of patent applicants are likely determined by a number of factors including the original locations of CRISPR discovery or the emphasis placed on getting patents by the government or other institutions. China's 13th Five-Year Plan (2016-2020) in emphasizing becoming a global leader in innovation and technology also encourages applying for patents (Koleski 2017 and Central Committee of the Communist Party of China 2016). Alternatively, in the United States, academic scientists are encouraged to get patents on their ideas and are often aided in doing so by university Technology Transfer Offices (TTOs). Venture capital firms also encourage startup firms to get patents as a signal of quality and as possible collateral if the startup should fail in the future. 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.

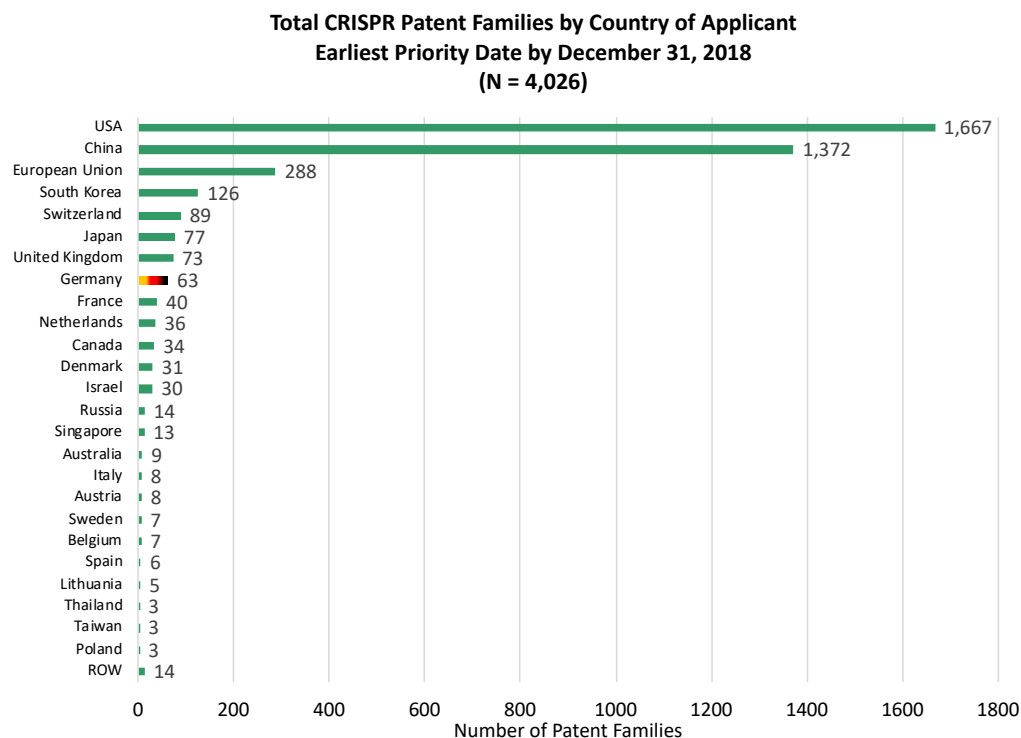


Figure 17: Count of CRISPR patent families worldwide

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 includes the United Kingdom.

To put the top CRISPR patent family applicant countries in context, we compare each country's CRISPR patent families to their overall patent families as reported to the World Intellectual Property Organization (WIPO). WIPO provides member countries with intellectual property information, services, and policy assistance. As part of their work, WIPO maintains the WIPO IP Statistics Data Center (WIPO 2020) to track patent applications filed under the international Patent Cooperation Treaty (PCT) and their related patent families. For the comparison below, we used all patent families by origin of applicant from 2012-2018. The data suggests that overall, Germany tends not to patent as much as other countries, but it does patent more in general than it does in CRISPR. China applicants tend to be very active and account for over 50% of all patent families overall. The United States is one of the top patentors overall, but it produces far more CRISPR patent families than might be expected (**Figure 18**).

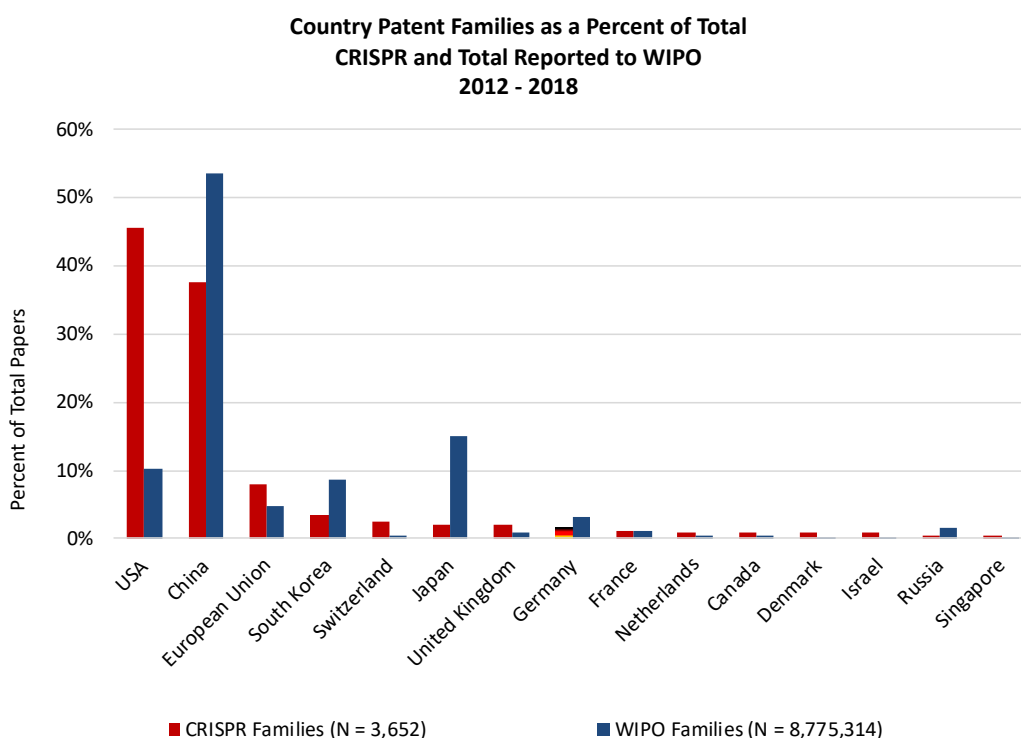


Figure 18: Comparison of a country's proportional contribution to total patent families in CRISPR and total patent families reported in the WIPO IP Statistics Data Center

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 includes the United Kingdom.

ii. Patent Family Quality

The rapid increase in patent applications, could again raise concerns about the quality of the patent applications. Because the majority of patent families are so new, standard measures of patent quality like

forward citations are limited. However, patent applicants who plan to use or sell their idea widely will often expend the effort to submit applications to a large number of patent jurisdictions in different countries, creating a large patent family. This can be used as a proxy for expected use and quality of the idea. As such, we restrict attention to the 1,086 patent families with 3 or more applications or grants in different jurisdictions.

The most active patent applicants are some of the same institutions who were also prolific publishers, including the University of California, MIT, the Broad Institute, and Harvard University. This time, the organizations also include the startup companies founded by the original inventors of CRISPR (e.g., Editas Medicine, CRISPR Therapeutics, Intellia Therapeutics, and Caribou Biosciences). As expected, more established companies appear in the patent families list including: Pioneer, Regeneron, Danisco, Toolgen, and Agilent. The number of patent families with more than 3 applications or grants by applicant is shown in **Table 4** below.

Patent Family Applicant	# Patent Families w/ 3+ Applications or Grants
Harvard College	78
Massachusetts Institute of Technology	78
Broad Institute	60
University of California	55
Editas Medicine	46
CRISPR Therapeutics	35
Chinese Academy of Sciences	23
Pioneer Hi-Bred	19
Regeneron Pharmaceuticals	17
Massachusetts General Hospital	15
Temple University	15
Duke University	14
Intellia Therapeutics	13
Danisco	12
Caribou Biosciences	11
Institute for Basic Science (S. Korea)	11
Toolgen	11
Dana Farber Cancer Institute	11
Agenovir	10
Agilent Technologies	10
DSM IP Assets (Royal DSM)	9
University of Pennsylvania	9
Cellectis	8
Stanford University	8
University of Massachusetts	8

Table 4: Applicants that have CRISPR patent families with 3 or more applications or grants

Focusing on the largest CRISPR patent families clarifies where some of the most active and higher quality patent applicants are located. Of the 1,086 largest patent families, 716 (65.9%) are from applicants in the United States. No other country or groups of countries comes close. The same countries do appear in the largest patent families, and Germany retains its position just looking at this subset of the data (**Figure 19**).

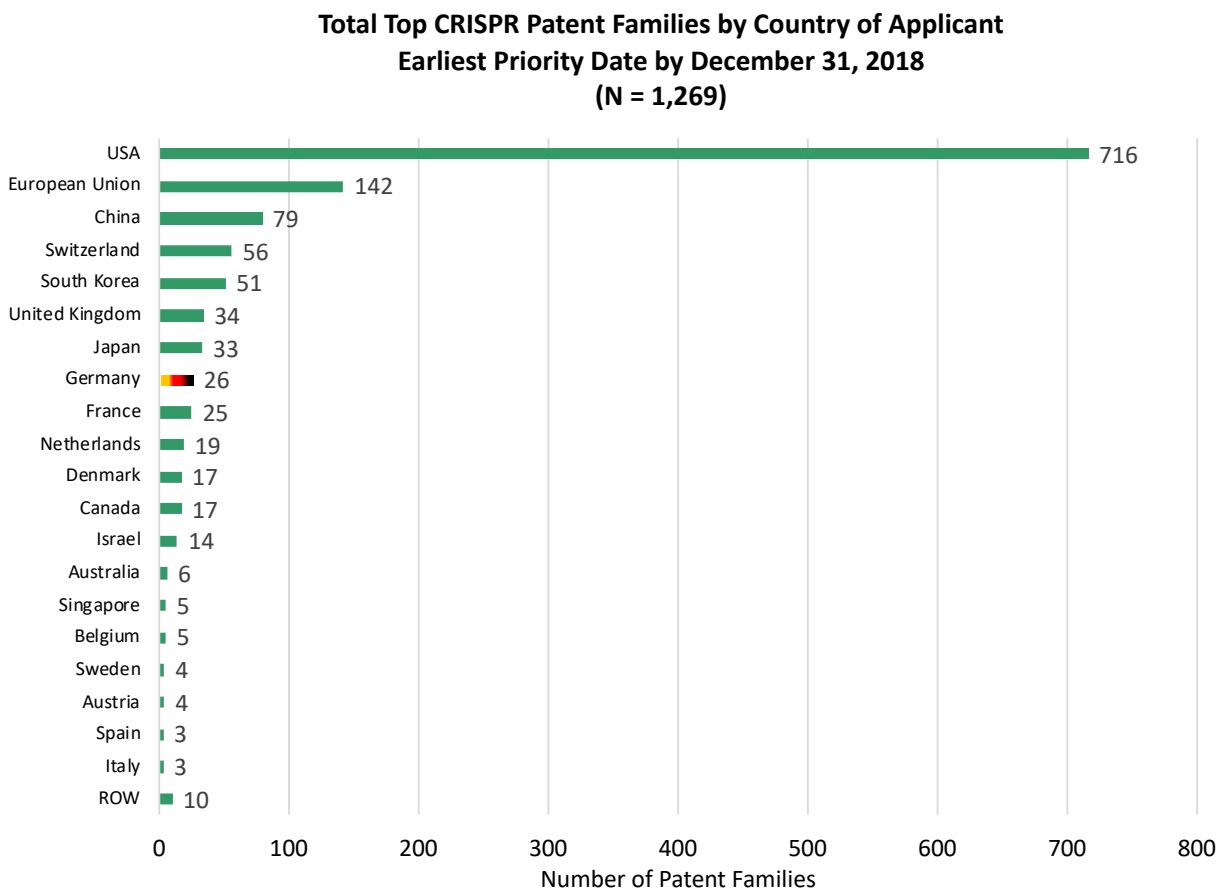


Figure 19: Count of largest CRISPR patent families worldwide by country of applicants

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 includes the United Kingdom.

To highlight which countries may have a larger proportion of higher value patent families, **Figure 20** shows these largest CRISPR patent families as a percent of total CRISPR patent families for each country. As with papers, countries vary substantially in their proportion of large patent families. For example, 63% of Switzerland's 89 CRISPR patent families included 3 or more application or grants. Part of this could be due to the fact that Emmanuelle Charpentier has a Swiss affiliation.

Given the location of the CRISPR pioneers and the emphasis on getting patents in the United States, 43% of its 1,667 patent families are in multiple jurisdictions. Other countries, including Japan, the United Kingdom, and Israel, are on par with the United States. Germany ranks slightly lower: 41% of its 63 CRISPR patent families are large. Asian countries in general seem to do much better in getting large families than in publishing in high quality journals. The major exception to this is China. Only 6% of its

1,372 patent families are outside China. This finding continues to support the idea that Chinese scientists and corporations tend to remain local to China.

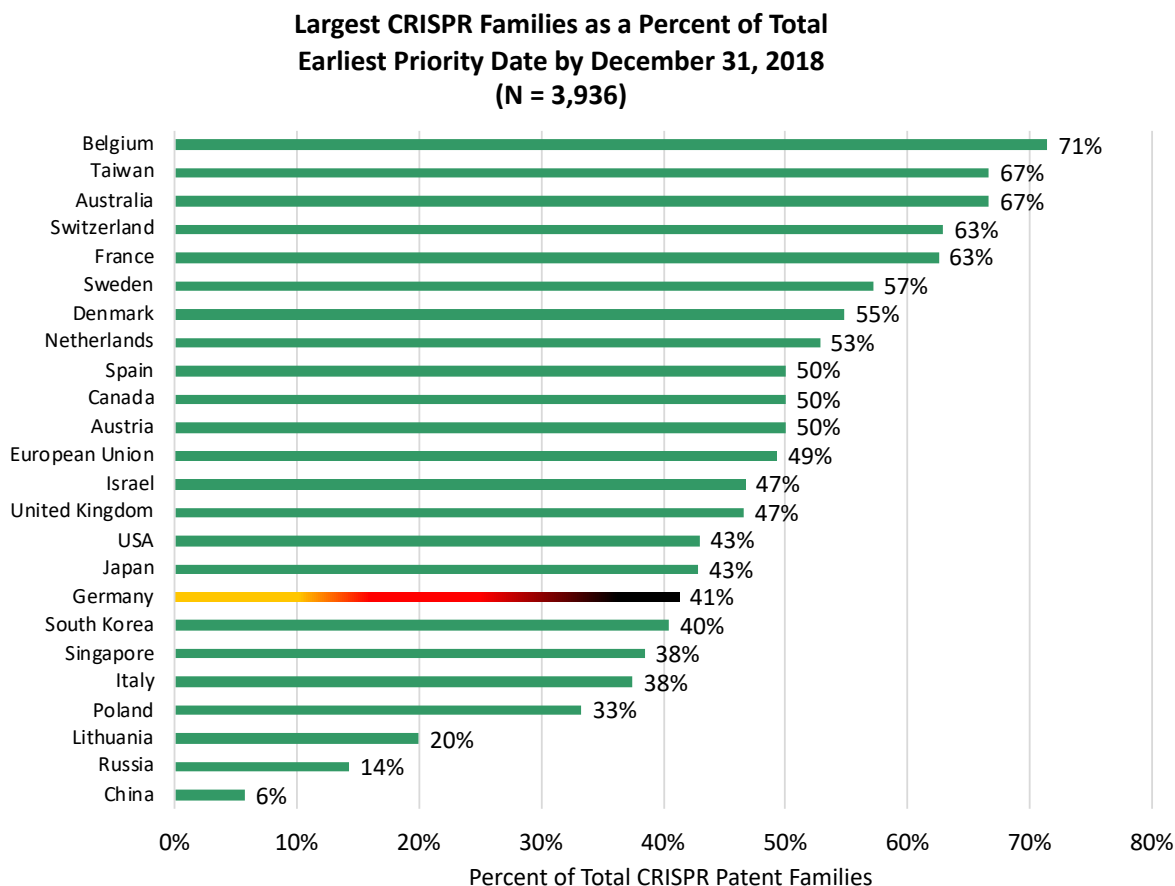


Figure 20: Largest CRISPR patent family applicants worldwide as a percent of all CRISPR patent families by country of applicant

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 includes the United Kingdom.

iii. Patent Families by Application Category

We use the same application categories for CRISPR papers to classify the patent families: Health/Medicine (including medical applications), Agriculture/Livestock (including plants and livestock), Industrial Applications (including biofuels and food manufacturing), and Technical Improvements (improvements made to the CRISPR tool, including new delivery mechanisms). As patents represent distinct novel ideas, each generally fits into one category. As such, patent families are placed into mutually exclusive categories as described in Section III.

Figure 21 shows the proportional breakdown of the categories for all CRISPR patent families. The patent families are in slightly different proportions to the CRISPR papers. Specifically, half of the patent families are in Technical Improvements to the CRISPR tool including new uses of CRISPR, improvements to delivery mechanisms, or improvements to editing efficiency. A third of patent families offer inventions in Health/Medicine including new model organisms, genetic therapies, or drugs. Agricultural/Livestock inventions account for a larger percentage of patent families than papers. Here, crop improvements and modifications to livestock are 15% of the total. The remaining 3% of patent families focus on Industrial Applications, such as biofuels, food manufacturing, and data storage. The shares do shift if we only consider the largest patent families. As shown above, the largest patent families exclude the majority of Chinese applicants since they tend to only file in China. The largest families also exclude some of the most recent as there has been less time to file and have published applications in multiple jurisdictions. Because China is dominant in Agriculture/Livestock, the largest patent families have a higher proportion of Technical Improvements (56% versus 49%) and a lower proportion of Agricultural/Livestock inventions (9% versus 15%). Health/Medicine and Industrial Applications change only slightly (31% versus 33% and 4% versus 3% respectively).

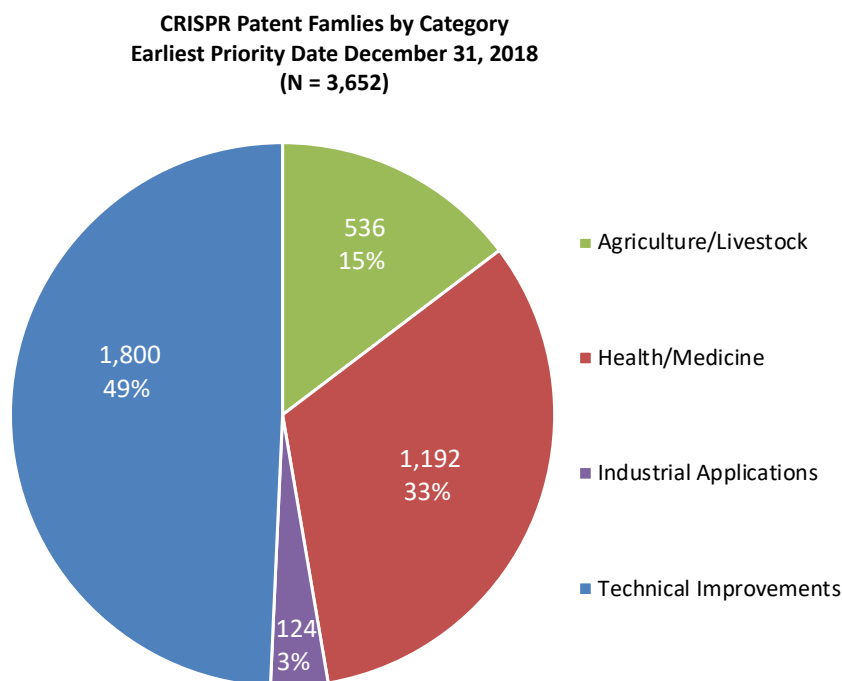


Figure 21: Percent of CRISPR patent families by Application Category

Patent families in all categories rise rapidly over time, with Technical Improvement patents leading the way (**Figure 22**). 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. CRISPR is expected to help treat myriad diseases for which there are few or no treatments. The patent families reflect treatments for many diseases including blood diseases, muscular dystrophy, cancers, and other inheritable diseases. Agriculture/Livestock and Industrial Applications patent families also increase over time, but make up a much smaller portion of the patent families per year. They also both experience a slight decrease in patent families with the earliest priority date in 2018. These trends hold for the largest patent families as well except that truncation removes most families with the earliest priority date in 2018.

Attention in patenting does appear to be focusing more on Technical Improvements to CRISPR again in later years. Although CRISPR has demonstrated its ability to provide solutions for previously unsolved problems, it is not perfect. Later Technical Improvements focus on making CRISPR easier to deliver to desired target cells, improving its efficiency, or improving its safety for use in gene therapies for humans. As of this report, there are no approved therapies using the CRISPR technology.

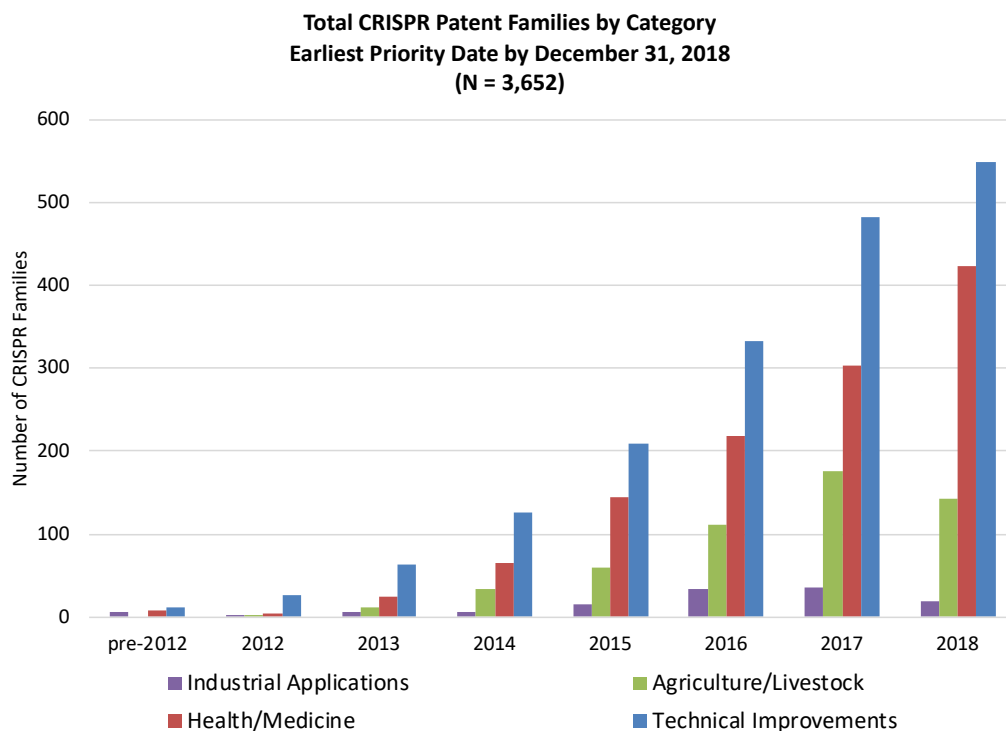
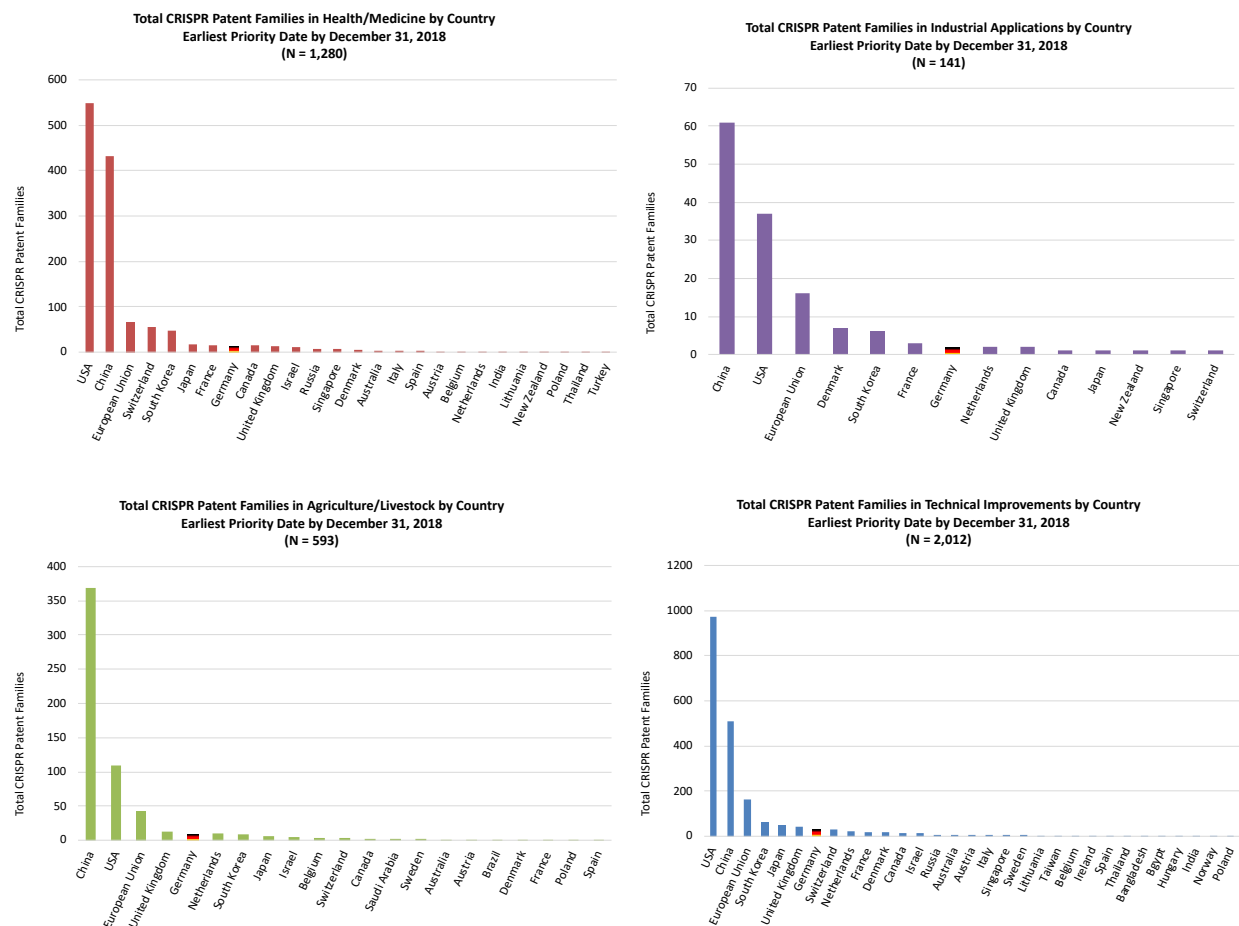


Figure 22: Count of CRISPR patent families worldwide by Earliest Priority Date and Application Category

Applicants who publish most also tend to choose particular categories on which to focus by their country of origin (**Figures 23a-23d**). For example, applicants in China have more than 3 times the patent families in Agriculture/Livestock than applicants in the next nearest country (the United States). China also dominates the much smaller Industrial Applications patent space, which is in contrast to CRISPR papers, where members of the European Union tend to lead. In contrast, Switzerland is one of the leaders in Health/Medicine but no other category and South Korea and Japan are leaders in the Health/Medicine and Technical Improvements categories. The United States is also highly ranked in all categories, but it dominates the Health/Medicine and Technical Improvement spaces. These patterns are consistent with the United States' discovery of the CRISPR tool, China's focus on innovation and technology in agriculture, and Emmanuel Charpentier's affiliation with a Swiss CRISPR startup company.



Figures 23a-d: Total CRISPR patent families by Application Category and county of applicant

Note: Papers can be assigned to more than one category. 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 includes the United Kingdom.

Germany, with only 63 patent families, is not as dominant a presence in the patenting space as in academic publications. Germany patent applicants only break into the top five ranking in Agriculture/Livestock, mostly due to KSW Saat's propensity to patent.

The country trends are even starker when comparing each country's percent contribution to the total patent families in each application area (**Figure 24**). For example, almost 70% of all Agriculture /Livestock patent families has at least one applicant from China whereas anyone else accounts for 20% or less. China also has about 50% of all Industrial Applications patent families.

The opposite is true for Technical Improvement patents. Over 50% of all Technical Improvement families include a United States applicant, but no other country (or set of countries) appears on more than 30% of families. The United States also is dominant in Health/Medicine, although Chinese applicants are proportionally more involved. Germany and Japan are similar and consistent across categories, although they only appear in 1-3% of patent families.

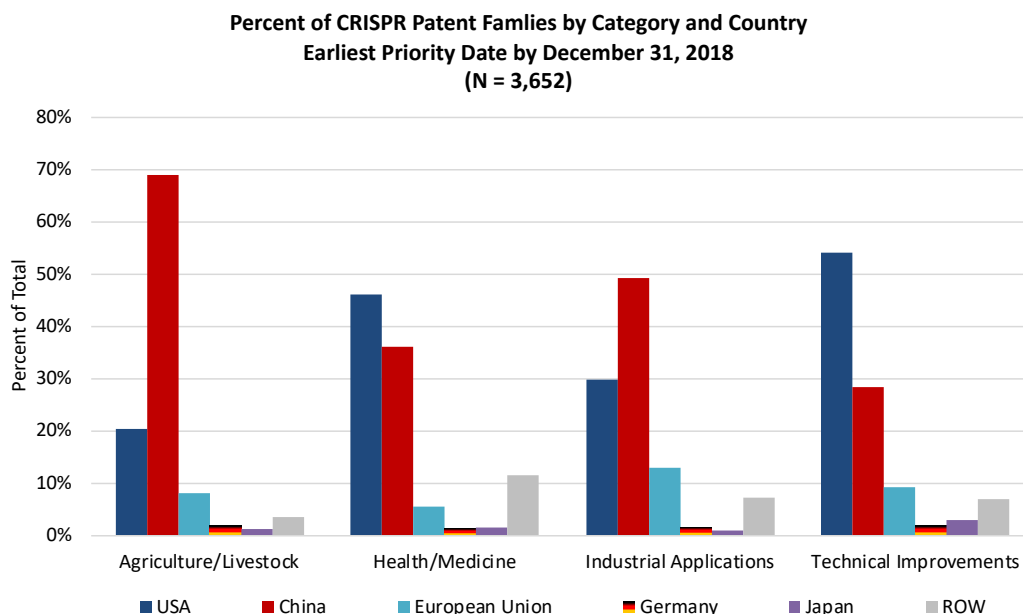


Figure 24: Percent of CRISPR patent families by Application Category in selected countries

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 includes the United Kingdom.

iv. Germany

German patent family applicants have 63 CRISPR patent families, less than 5% of those from the United States or China. As shown in Section IV.b.i, German applicants have proportionately fewer patent families overall, but one might still expect to see more CRISPR patent families from German applicants. Patent families from Germany are increasing every year, however (**Figure 25**).

The increase in Chinese patent families is truly astonishing. In later years, the number of Chinese patent families begins to overtake those from the United States. Although, as noted in Section IV.b.ii, most of these are single patent applications or grants to the Chinese patent office. They generally do not leave China.

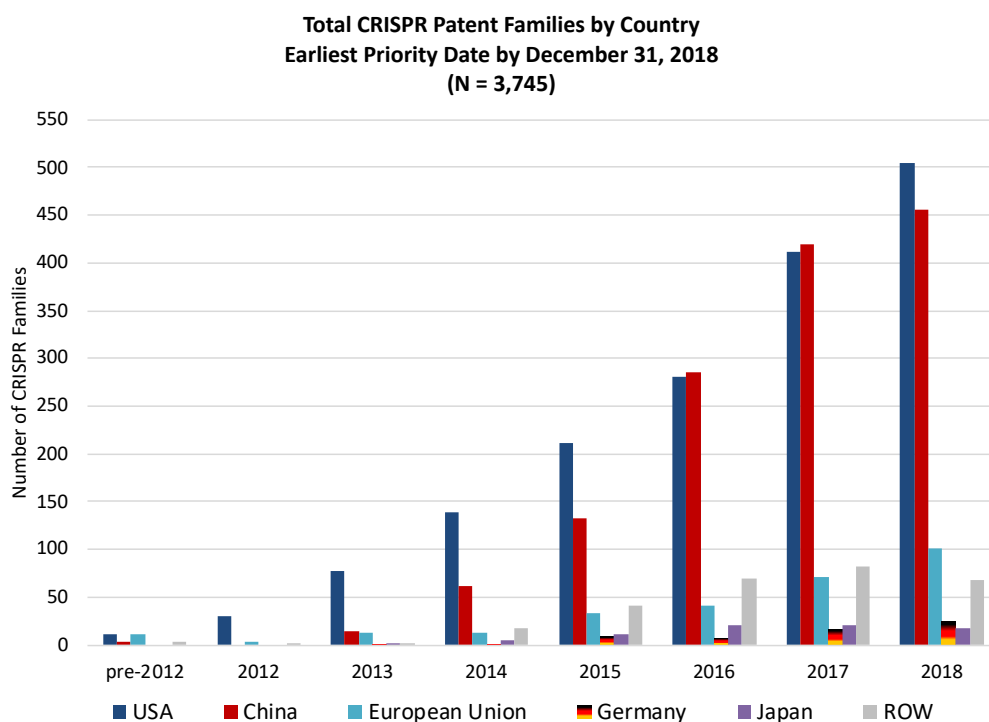


Figure 25: Count of CRISPR patent families by Earliest Priority Year and country of applicant

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 includes the United Kingdom.

The increase in CRISPR patent families by German applicants can be seen more readily in **Figure 26**. Generally, German applicants do not attribute priority to any applications earlier than 2015, so they may have gotten a slower start than other countries. However, almost 40% (25/63) of Germany's total patent families have an earliest priority date in 2018. The majority of Germany's focus is on Technical

Improvements followed by Health/Medicine, which follows from the types of organizations doing the patenting.

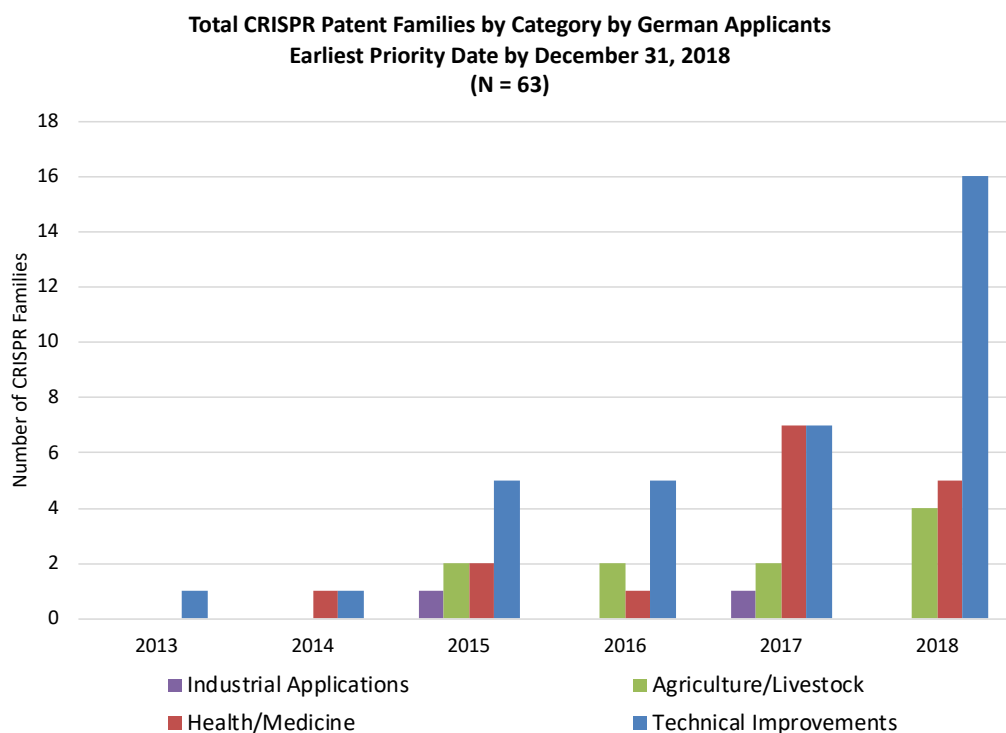


Figure 26: Count of CRISPR patent families for German applicants by Earliest Priority Date and Application Category

Patent family applicants from Germany generally have one or two patent families with priority dates between 2013 and 2018 as shown in **Table 5**. Although many of the top German applicants are large companies like KWS, Siemens, BASF, or Thermo Fisher there are a number of leading German universities and research societies patenting as well. Newer German companies are starting to join in the patent space as well including B R A I N, CureVac, ETHRIS, GeneBridges, or Rodos Biotarget.

German companies may be encouraging patenting in CRISPR in other ways, however. For example, the German headquarters of Bayer AG does not appear on any CRISPR patent family, but it has been supporting research done by CRISPR Therapeutics in Switzerland and the United States. The two organizations have created a joint venture called Casebia Therapeutics, managed by CRISPR Therapeutics in the United States where Bayer has opt-in rights (CRISPR Therapeutics 2019). The joint venture has 15 CRISPR patent families to date, but they are listed as having a United States applicant.

Despite the Casebia joint venture, German patent applicants are not as collaborative with organizations from other countries as German academic authors. Only five patent families involved a German organization with a non-German organization. One of these patent families exists because Emmanuelle Charpentier is affiliated with both CRISPR Therapeutics in Switzerland and the Max Planck Institute for Infection Biology in Germany. Further, this is the only patent family that has a collaboration between a corporation and a research organization. The few other collaborations that exist are between corporations or separately between universities or other research centers.

German Patent Family Applicant	# Patent Families
KWS SAAT	15
B R A I N	7
Heidelberg University	4
Max Planck Society	4
Siemens Healthcare	4
DKFZ	3
Helmholtz Society	3
BASF Plant Science	2
University of Freiburg	2
University of Göttingen	2
AMGEN	1
Bielefeld University	1
Charité – Universitätsmedizin Berlin	1
CureVac	1
ETHRIS	1
European Molecular Biology Laboratory	1
Fraunhofer-Gesellschaft	1
GeneBridges	1
Glycotope	1
Goethe University	1
Leibniz-Institut für Pflanzengenetik und Kulturpflanzenforschung	1
RIKEN	1
Rodos Biotarget	1
Technical University of Munich (TUM)	1
Thermo Fisher Scientific GeneArt	1
University of Cologne	1
University of Giessen	1
University of Tübingen	1

Table 5: Top German CRISPR patent family applicants

C. CRISPR COMPANIES DATABASE

As described in Section III, 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.

Of the 724 CRISPR companies, 57.0% (413/724) were discovered through having their name listed as an applicant on a CRISPR patent family. There was no further public evidence that the company made or sold CRISPR-related products beyond the patent. In most cases, basic information on these companies could not be located either. **Figure 27** shows that companies with only patent information are located mostly in China, illustrating the opaque nature of Chinese companies.

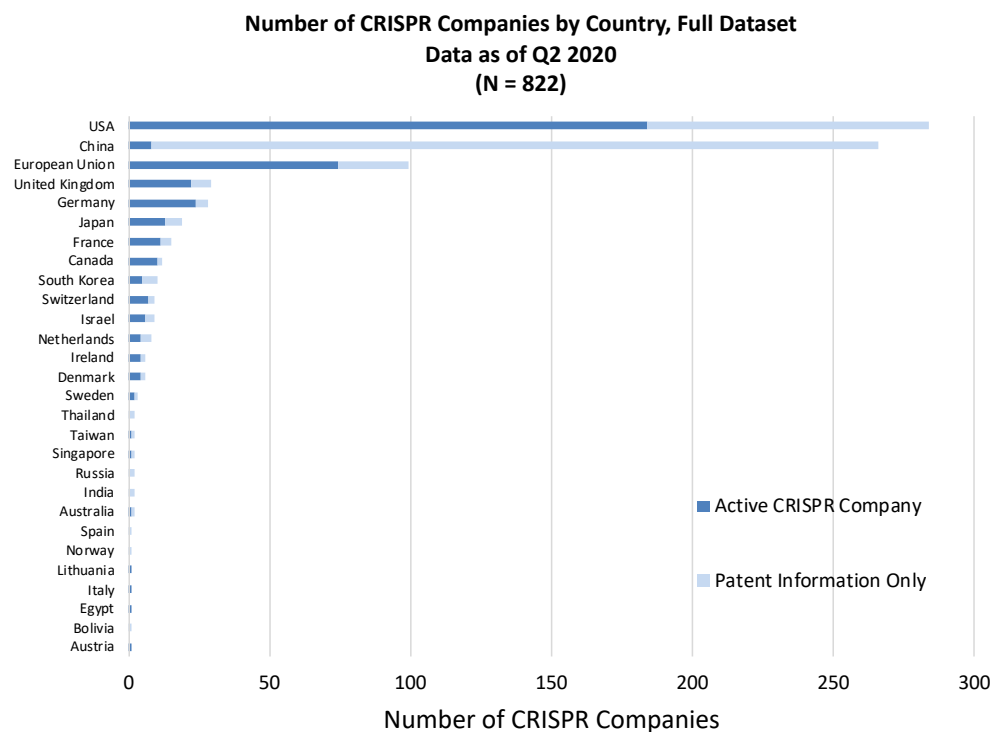


Figure 27: All CRISPR companies by country of headquarters
Note: The European Union includes the United Kingdom.

Given the missing data, we focus the remainder of the discussion on the 311 active CRISPR companies that had additional information on how they made, used, or sold CRISPR and CRISPR-related products.

i. Worldwide Active Companies

a. Founding Dates

As of August 2020, the Database included 311 unique active companies in 21 countries. Although CRISPR commercialization appears relatively healthy, the uncertainty surrounding the patent and regulatory landscape may be stifling some activity or corporate willingness to advertise the tool's use. In its primer on its technology, for example, CRISPR-engaged company Hera Biolabs notes that "CRISPR/Cas9 has demonstrated high efficiency gene editing in non-commercial settings, however, there are still questions about the commercial freedom to operate of [sic] the system, leaving many potential users on the sidelines" (Hera Biolabs n.d.).

Nevertheless, the active companies in the Database include both new startups and established private and public companies. Many working on CRISPR are relatively small (as measured by number of employees), but the Database also includes a number of larger firms.

Around 2012, seminal academic publications on CRISPR as a tool paved the way for commercialization. Entrepreneurs began forming new companies to leverage the technique: 40% of the active companies were founded between 2010 and 2019 (125/311) (**Figure 28**), either just prior to or just after the tool's literature debut. But existing companies also took note and began incorporating CRISPR into their business plans: An additional third (33% = 102/311) of the active companies were founded between 1990 and 2009, while 22% (68/311) were founded prior to 1990.

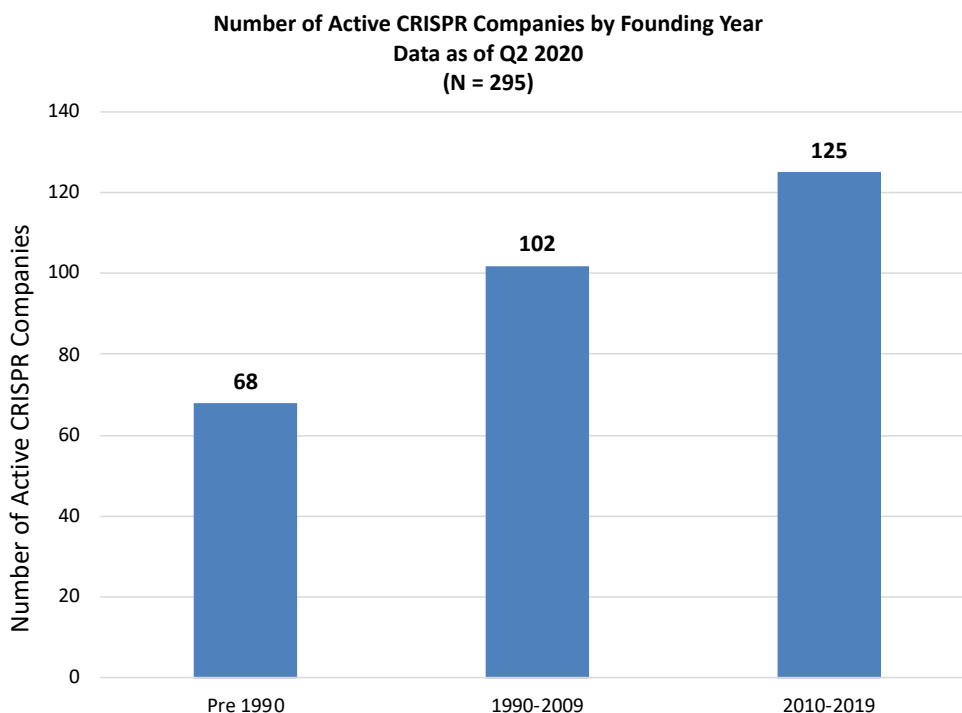


Figure 28: Active companies in the CRISPR Companies Database by founding year
Note: Sixteen companies whose founding year could not be determined were excluded from this chart.

The timing of CRISPR’s introduction as a tool (2012) is key to understanding how and why companies began to use the technique, but other critical events in the gene editing field also provide insight. Notably, 1990 was a landmark date—the first gene editing clinical research took place at the U.S. National Institutes of Health in September of that year (Philippidis 2016). It is possible that many of the companies founded in the subsequent decade sought to capitalize on the burgeoning discipline. And having established themselves as pioneers in the gene editing space, they may have been well-positioned to incorporate CRISPR when the new tool subsequently emerged. Another crucial development came approximately two decades later: A critical paper that helped clarify the gene editing potential of a separate system—TALENs (transcription activator-like effector nucleases)—was published in 2009 (Boch et al. 2009). A number of the firms founded between 2010 and 2019 were established based on the potential of TALENs or CRISPR.

Among the companies founded between 2010 and 2019, nearly half (49% = 61/125) were founded between 2014 and 2016, more than during any period during that time span (**Figure 29**). This signals that CRISPR commercialization efforts progressed substantially in the years following the tool’s 2012 introduction—an insight further supported by the fact that a number of companies created by CRISPR pioneering researchers (including Editas Medicine, Intellia Therapeutics, and CRISPR Therapeutics) all went public in 2016. The

general upward trend between 2013 and 2016 following the tool’s 2012 introduction is not surprising—the pipeline between basic research and commercialization has a natural delay. But the ripening of the field may have been accelerated by a key 2013 paper suggesting that CRISPR was superior to other gene editing techniques available at the time (Ding et al. 2013; Cohen 2017).

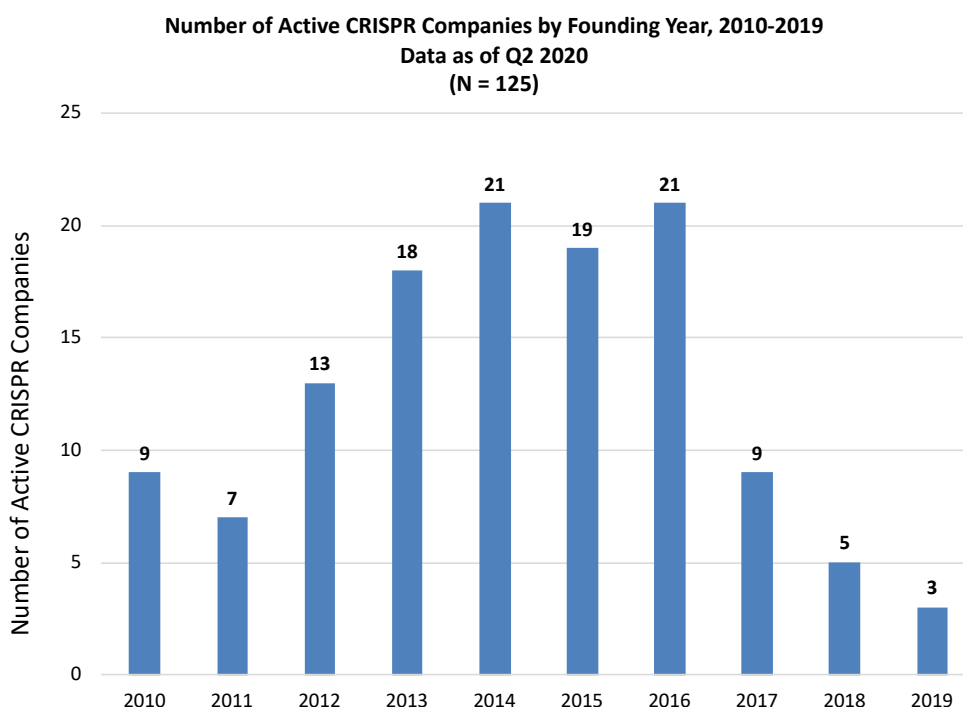


Figure 29: Active companies in the CRISPR Companies Database by founding year, 2010-2019

But the 2014 - 2016 peak was followed by a decrease in the number of companies founded annually. No definitive conclusions can be drawn, but it could be a result of chilling attitudes toward CRISPR after academic papers began to question its safety for therapeutic uses (e.g., Kosicki, Tomberg, and Bradley 2018). The decrease could also be due to more recent companies choosing to keep their involvement in CRISPR secret as a way to protect their nascent ideas.

b. Company Type and Size

The active CRISPR companies include companies of various types and sizes. Most are private (72% = 225/311)—acquired (10% = 32/311), established (27% = 83/311), or startup (35% = 110/311)—while roughly a third are public (27% = 85/311) as shown in **Figure 30**.

Active CRISPR Companies by Company Type
Data as of Q2 2020
(N = 310)

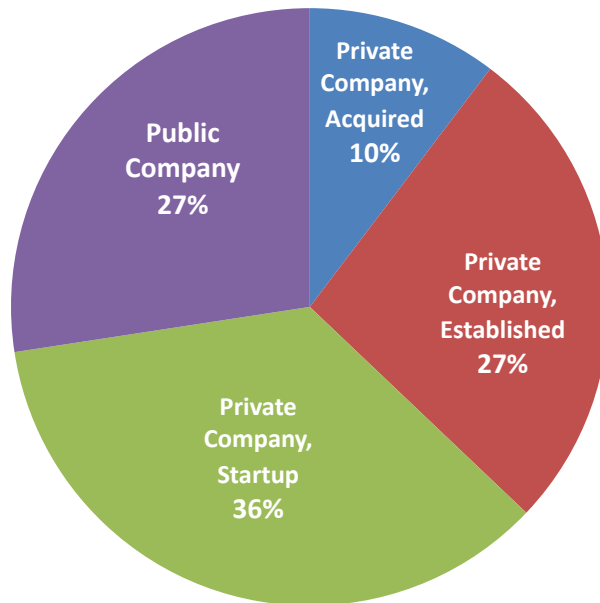


Figure 30: Active companies in the CRISPR Companies Database by company type
Note: One company whose type could not be determined was excluded from this chart.

Company type is correlated with year of founding. Most public companies (75% = 62/29) were founded 2009 or earlier (**Figure 31**). This is not surprising; in 2016, the median time between founding and an initial public offering (IPO) was 7.7 years (Der Marderosian 2017), so many companies founded in the last decade simply have not matured sufficiently to make an IPO feasible. Still, as is typical for CRISPR, the pace of progress has been rapid for some players—a small number (21) of companies founded in 2010 or later have managed to go public in that relatively short time period. Although there are fewer public companies founded after 2010, more CRISPR-engaged private companies were founded between 2010 and 2019 than were founded before 1990 or between 1990 and 2010 (92, as compared to 63 between 1990 and 2009 and 25 before 1990). The number of companies that were subsequently acquired remained the same across the three time periods (11 before 1990, 9 between 1990 and 2009, 11 between 2010 and 2019).

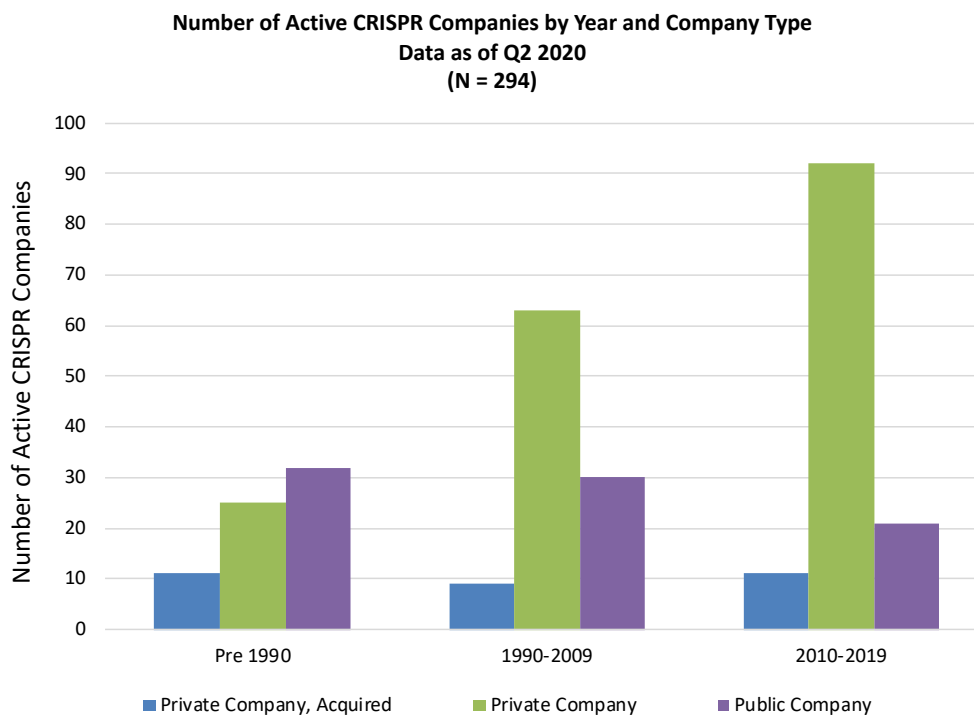


Figure 31: Active companies in the CRISPR Companies Database by year and company type

Note: Sixteen companies whose founding year could not be determined were excluded from this chart, as was one additional company whose type could not be determined.

Many of the active companies are relatively small. Forty percent (123/311) have 100 or fewer employees; this includes 29 companies with only 1-10 employees (9% of the 311 active companies) (Figure 32). These smaller companies tend to be younger—25 of the 29 companies with 1-10 employees, for example, were founded between 2010 and 2019. But there are a number of companies at the other end of the spectrum as well: The active companies includes 85 companies (27%) with over 500 employees and 45 of those have over 10,000 employees (14% of the 311 active companies). The majority of these large companies (500+ employees) were founded before 1990 (53/85, 62%). Many are major pharmaceutical, chemical, or agricultural companies, such as Merck, DuPont, and Monsanto. Still, a small number (5) of companies founded after 2010 have grown quickly to have over 500 employees. The CRISPR-engaged U.S. biopharmaceutical company AbbVie, for example, was founded in 2013 and has over 10,000 employees; in 2020, it acquired Allergan, a pharmaceutical company collaborating with Editas Medicine on CRISPR-based treatments for inherited eye diseases (Terry 2020).

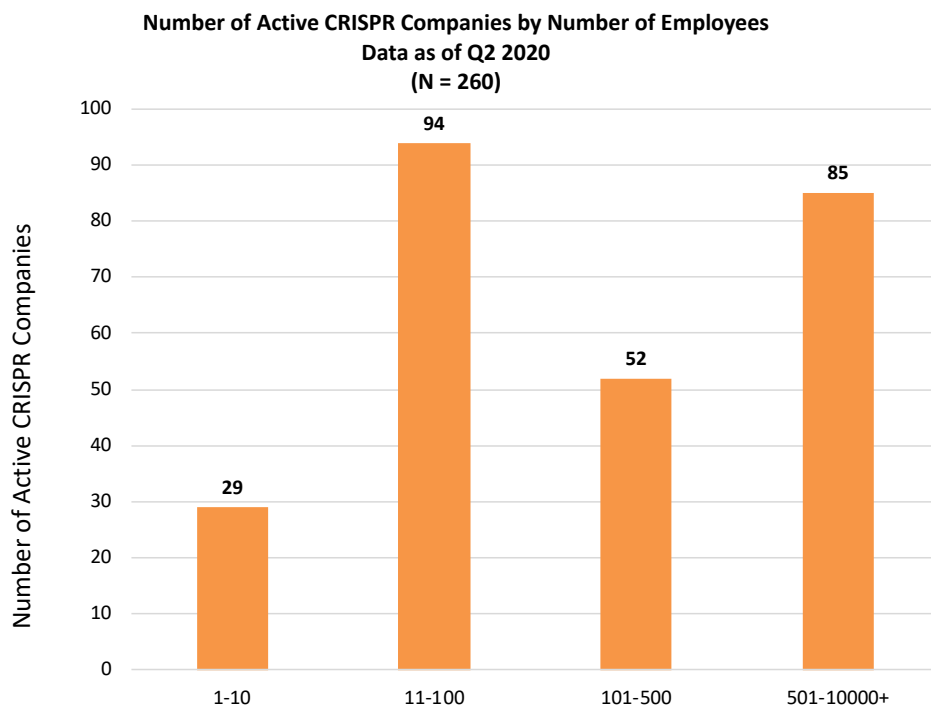


Figure 32: Active companies in the CRISPR Companies Database by number of employees
Note: Fifty-one companies whose size could not be determined were excluded from this chart.

c. Companies by Country Headquarters

The United States dominates the active CRISPR company landscape. Nearly 60% (184/311) of the active companies in the Database are based in the United States, while 24% (74/311) are based in the European Union (**Figure 33**). On an individual country basis, Germany has the second-highest percentage of companies, though its proportion (8% = 24/311) still pales relative to that of the United States.

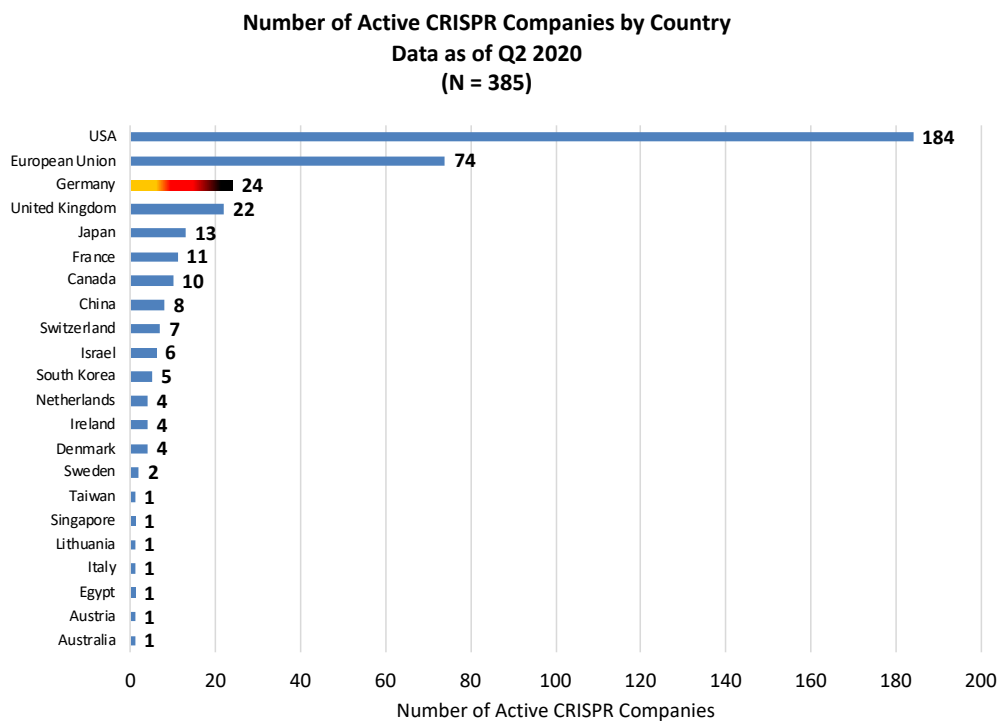


Figure 33: Active companies in the CRISPR Companies Database by country

Note: The European Union includes the United Kingdom.

The United States dominates in the number of active CRISPR companies and the size and structure of its companies varies somewhat from other locations around the world. For example, U.S. CRISPR companies tend to be smaller than their European counterparts: In the European Union, about 30% of the active companies in the Database have 501-10000+ employees, while 42% of those in the United States have fewer than 100 employees and 7% have fewer than ten employees (**Figure 34**). German active companies, like others in Europe, tend to skew larger with 38% of them employing over 501 people.

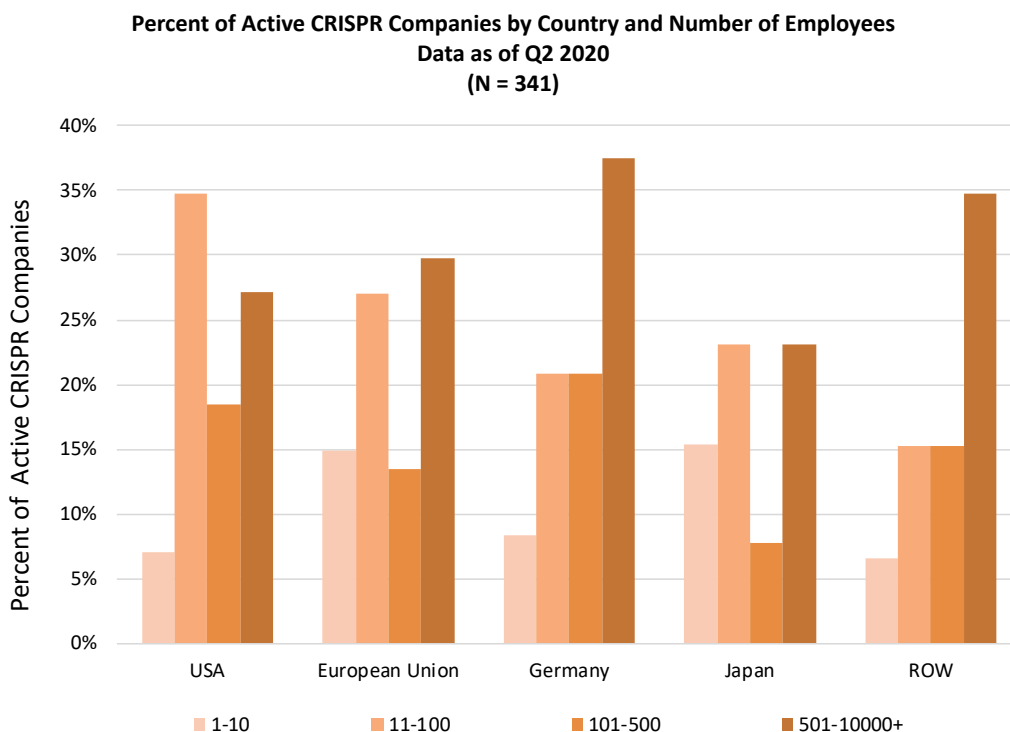


Figure 34: Active companies in the CRISPR Companies Database by company size, as a percentage of companies in each geographic region

Note: Fifty-one companies whose size could not be determined were omitted. The European Union includes the United Kingdom.

Given their smaller size, it is not surprising that United States companies also tend to be younger: 44% of the active U.S. companies were founded between 2010 and 2019 (**Figure 35**). Companies in other parts of the world are generally older. In the European Union, for instance, only 32% of companies were founded between 2010 and 2019, while 43% were founded between 1991 and 2009. Again, Germany follows Europe, with 71% of its active CRISPR companies being founded before 2010 (most of those were founded between 1991 and 2009).

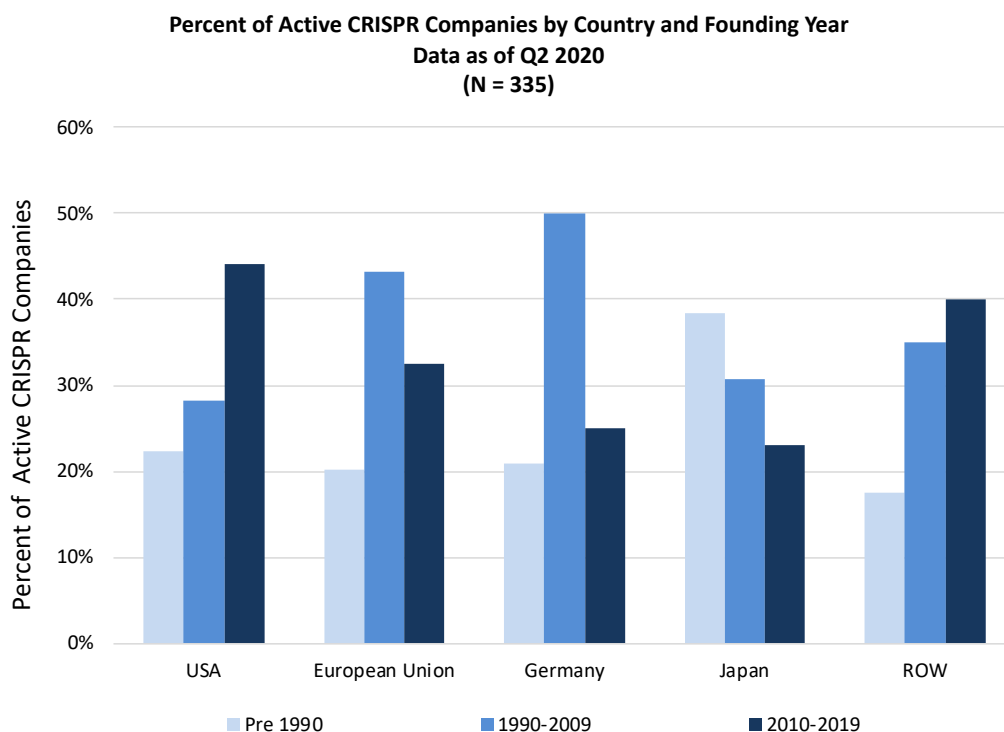


Figure 35: Active companies in the CRISPR Companies Database by founding year, as a percentage of companies in each geographic region

Note: Sixteen companies whose founding year could not be determined were omitted from this chart. The European Union includes the United Kingdom.

ii. Active Company Application Categories

Active companies in the Database use CRISPR in a variety of ways. The companies were classified manually using the same categories used for CRISPR Papers and Patents: Health/Medicine (including medical applications), Agriculture/Livestock (including plants and livestock), Industrial Applications (including biofuels and food manufacturing), and Technical Improvements (improvements made to the CRISPR tool, including new delivery mechanisms). Two new categories were added to capture corporate activities that would not be present in papers and patents. 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 can be classified into several categories depending on how they described their CRISPR activities.

Health/Medicine, Technical Improvements, and Research Services dominate the landscape: Each is an application category for approximately a third of the active companies (**Figure 36**). Other companies focus

on Agriculture/Livestock (14% = 42/311) or Industrial Applications (7% = 22/311), or are owners or investors of other CRISPR-engaged companies (11% = 34/311).

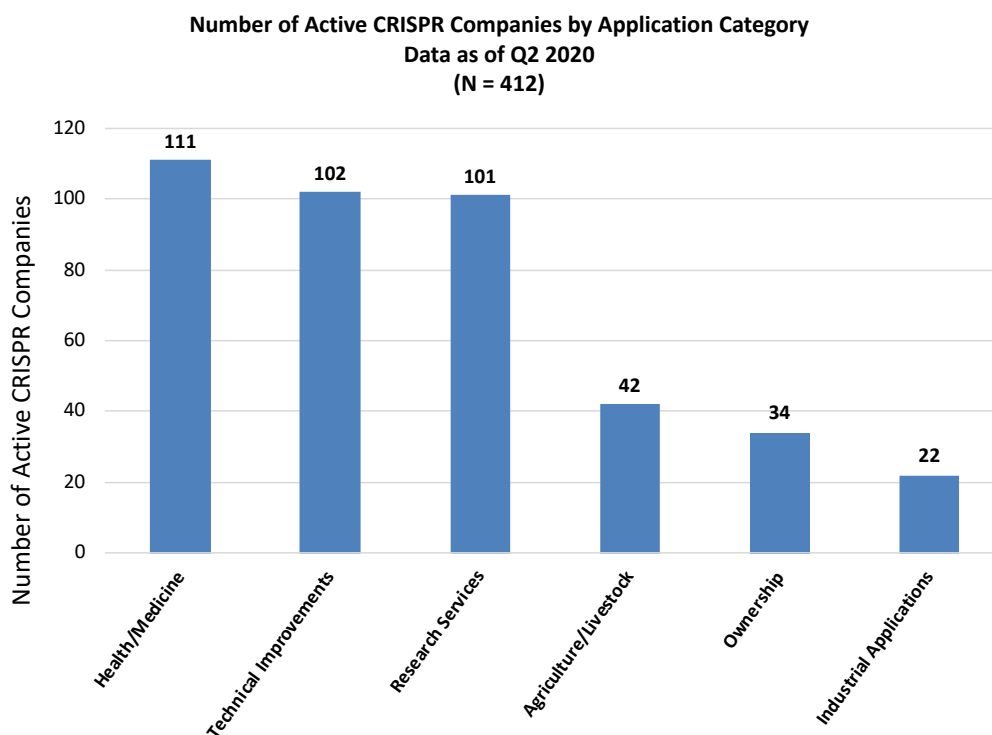


Figure 36: Active companies in the CRISPR Companies Database by Application Category

The application categories of the active companies vary somewhat with founding date. For example, a larger proportion of companies focused on Health/Medicine were founded between 2010 and 2019 (60%) than were founded before 1990 (16%) or between 1990 and 2009 (18%) (likely because using CRISPR for human therapeutics is a relatively recent advance) (**Figure 37**). Companies providing Technical Improvements and Research Services also tend to be somewhat younger (only 15% of the companies in each category were founded before 1990). But Ownership relationships are more likely to arise among older companies (35% of Ownership companies were founded between 1990 and 2009 and 47% before 1990, compared to 15% between 2010 and 2019).

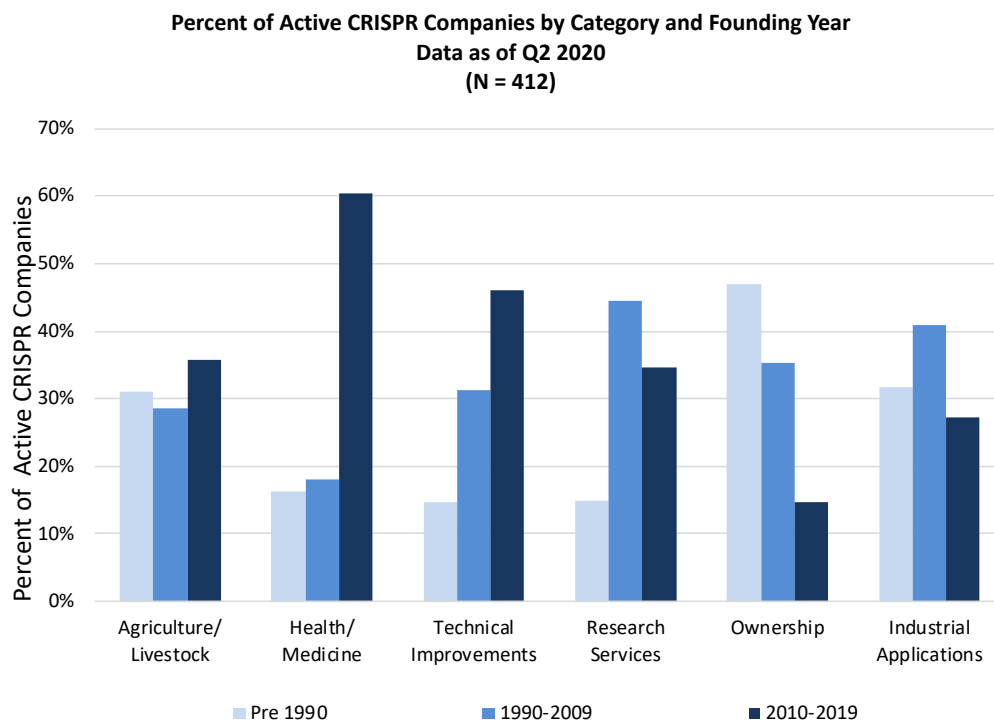


Figure 37: Active companies in the CRISPR Companies Database by founding year as a percent of Application Category grouping

Note: Companies focused on more than one area are double counted in this chart. In addition, sixteen companies whose founding year could not be determined were excluded.

Application categories also vary somewhat by company size (**Figure 38**). Particularly noteworthy is that most companies engaged in Ownership relationships are large firms (71% of companies in that category have over 500 employees and none have fewer than 10 employees). This result is not surprising. The category captures parent companies with subsidiaries engaged in CRISPR work or firms in joint agreements with companies involved in developing CRISPR products. Such arrangements are a common strategy of large biotech firms (*e.g.*, Lerner and Merges 1998).

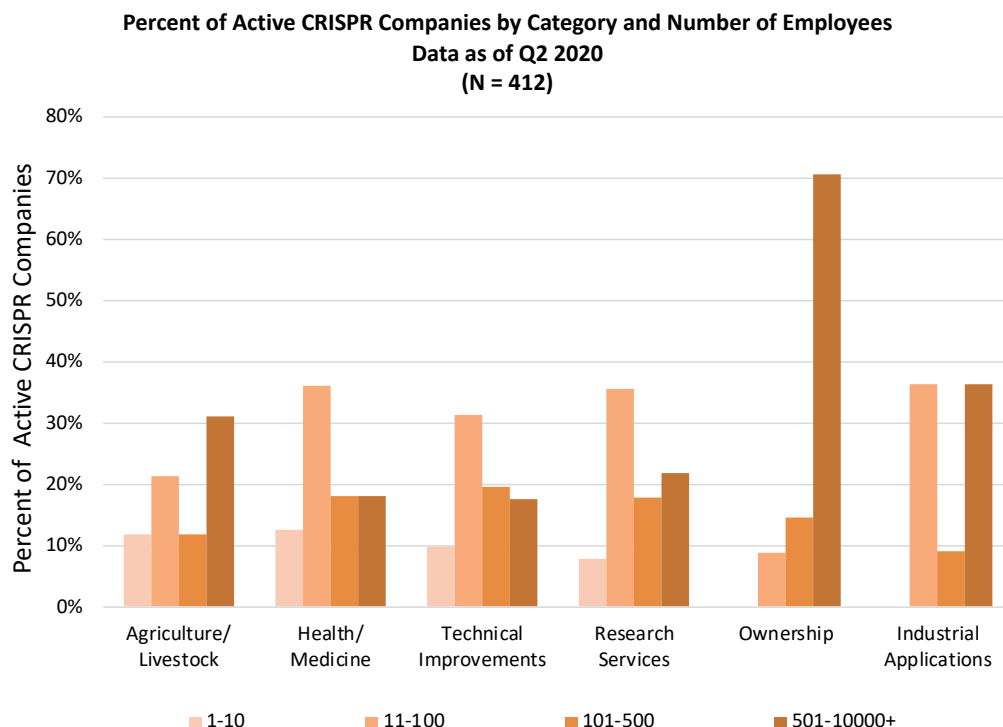


Figure 38: Active companies in the CRISPR Companies Database by number of employees, as a percentage of Application Category grouping

Note: Companies focused on more than one area are double counted in this chart. Fifty-one companies whose size could not be determined were excluded from this chart.

Finally, application categories varies to some degree with location. The United States leads every category (**Figure 39**) due to its dominance in terms of overall quantity of active CRISPR companies. But the U.S.'s main focus is in Health/Medicine as compared to Agriculture/Livestock or Ownership. In contrast, German companies contribute to more of the Ownership and Research Services categories than any others.

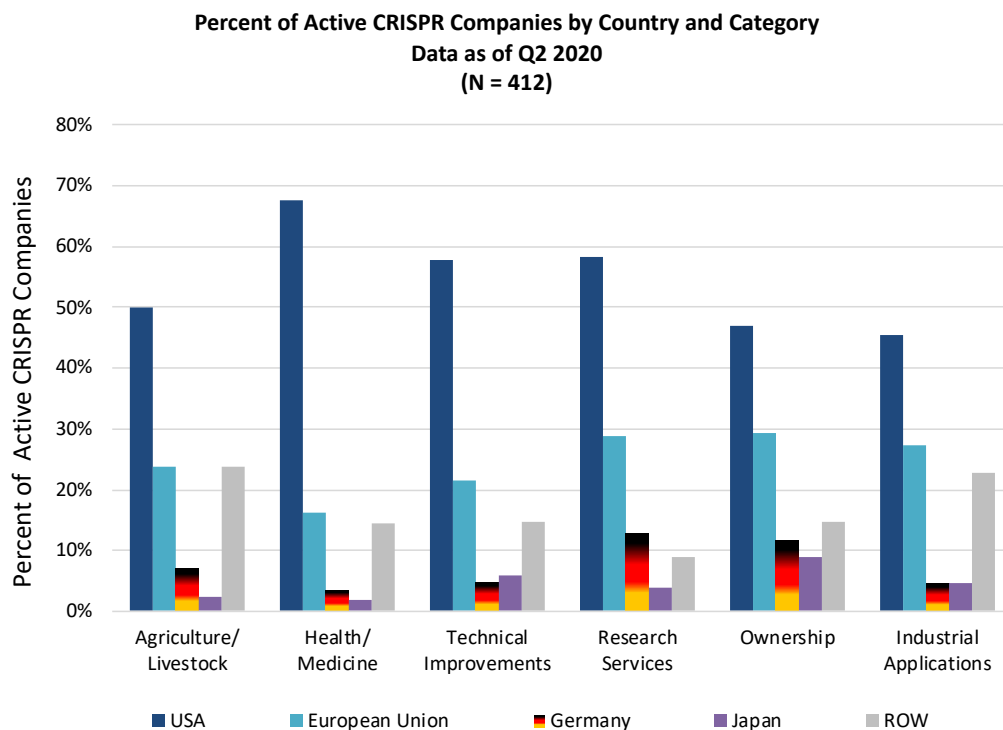


Figure 39: Active companies in the CRISPR Companies Database by country, as a percentage of Application Category grouping
Note: Companies focused on more than one area are double counted in this chart. The European Union includes the United Kingdom.

iii. Notable Active Companies

The Database includes the commercialization efforts of pioneering CRISPR researchers Jennifer Doudna, Emmanuelle Charpentier, Feng Zhang, and George Church (**Table 6**). These are relatively young companies, founded either just prior to or shortly after the seminal papers on CRISPR were published in 2012. All are based in the United States or Europe (generally in the same city as that of the associated CRISPR pioneer’s institution). Most of these companies not only license the original CRISPR technology but also work on potential applications, primarily in medicine. A number of the earliest employees at these firms came from the founders’ academic labs.

Company	Location	Founding CRISPR Pioneers	Focus Area	Founding Year
Editas Medicine	Cambridge, MA, USA	Zhang, Church	Health, Research Services	2013
Caribou Biosciences	Berkeley, CA, USA	Doudna	Health, Farm Animals/Plants, Research Services	2011
Intellia Therapeutics	Cambridge, MA, USA	Charpentier	Health, Research Services	2014
ERS Genomics	Dublin, Ireland	Charpentier	Research Services	2014
CRISPR Therapeutics	Zug, Switzerland	Charpentier	Health, Research Services	2013

Table 6: Notable companies in the Database founded by CRISPR pioneers

As might be expected given CRISPR's therapeutic potential, some of the major CRISPR-engaged firms are large pharmaceutical companies, such as Merck (Germany) or Bristol-Myers Squibb (United States). These firms have invested in CRISPR—either directly or via subsidiaries—for medical applications. But many of the companies working on CRISPR-based medicine are much smaller. Compared to their larger counterparts, smaller companies may be less risk averse and have more agility to embrace new and emerging technologies such as CRISPR. The San Francisco-based biotechnology company Ligandal, for example, works on CRISPR cancer therapeutics; it was founded in 2013 and has fewer than ten employees but is still active in the CRISPR space.

Although CRISPR is often portrayed primarily as a tool for medical or agricultural applications, firms in the Database work in many areas outside of these fields. Specifically, a large number of companies license CRISPR technologies or offer products or services to facilitate research. The U.S. company Santa Cruz Biotechnology, for instance, offers a range of CRISPR plasmid products. Other firms, classified under Ownership, own subsidiaries engaged in CRISPR work or are otherwise financially involved in partnership arrangements. The Egyptian company Minapharm Pharmaceuticals, for example, owns ProBioGen, a German technology provider that is collaborating with the Swiss company CRISPR Therapeutics to develop in vivo CRISPR delivery methods (CRISPR Therapeutics 2019).

iv. Germany

CRISPR-engaged companies in Germany differ somewhat in character from those headquartered in other countries. First, German CRISPR-engaged companies tend to be larger—nearly 40% (9/24) have more than

500 employees while less than 10% have fewer than 100 employees (2/24). Although they trend toward being larger, active German CRISPR companies are distributed approximately evenly across company types—eight are private companies, established or acquired; seven are public firms; and nine are startups.

Half of the active German companies in the Database (12/24) were founded between 1990 and 2010, while roughly a fifth (5/24) were founded before 1990 and a quarter between 2010 and 2019 (6/24).

Over half (13/24,) of the active CRISPR-engaged companies in Germany focus on Research Services, while Health, Technical Improvements, and Ownership each account for approximately 15-20% of the German companies in the Database (17%, 21%, and 17%, respectively). German companies represent 13% of all active companies focused on Technical Improvements, as well as 12% of all Ownership companies. German companies also account for 7% of the companies focused on Agriculture, despite the European Union's classification of CRISPR as a technology requiring compliance with genetically modified organism regulations.

The active CRISPR companies in Germany are similar to the list of patent applicants in **Table 5**, but with the addition of established companies like Merck and Bayer and a set of newer startups and private companies offering Research Services like Eupheria Biotech, Cytena, GeneWerk, Genomics Online, Vivlion, ChromoTek, ProBiogen, siTOOLS Biotech.

D. CRISPR CLINICAL TRIALS DATABASE

Although the CRISPR tool was introduced in 2012, as of May 2020 the CRISPR Clinical Trials Database already included forty-nine unique trials with start dates spanning 2015 to 2021 and sponsors in seven countries. The dataset is small, limiting the power of statistical analyses; nonetheless, the field has rapid progressed rapidly toward clinical trials, speaking to the therapeutic potential of CRISPR applications. The studies currently in the Database are early stage trials, and the majority have start dates of 2018 or later. Most are not for new CRISPR-based drugs or therapeutics just yet; those that do assess treatments are mostly targeted at diseases also targeted by conventional gene therapies, such as cancers and blood disorders. The vast majority of the studies in the Database are sponsored by institutions in China and the United States. Despite its prominence in CRISPR-related publications, Germany sponsors only a single CRISPR clinical trial.

i. *Clinical Trials: Time, Trial Type, and Disease Target*

a. Time

Of the 49 clinical trials in the CRISPR Clinical Trials Database, the majority (53% = 26/49) were initiated¹⁹ in 2018 and 2019 (**Figure 40**).

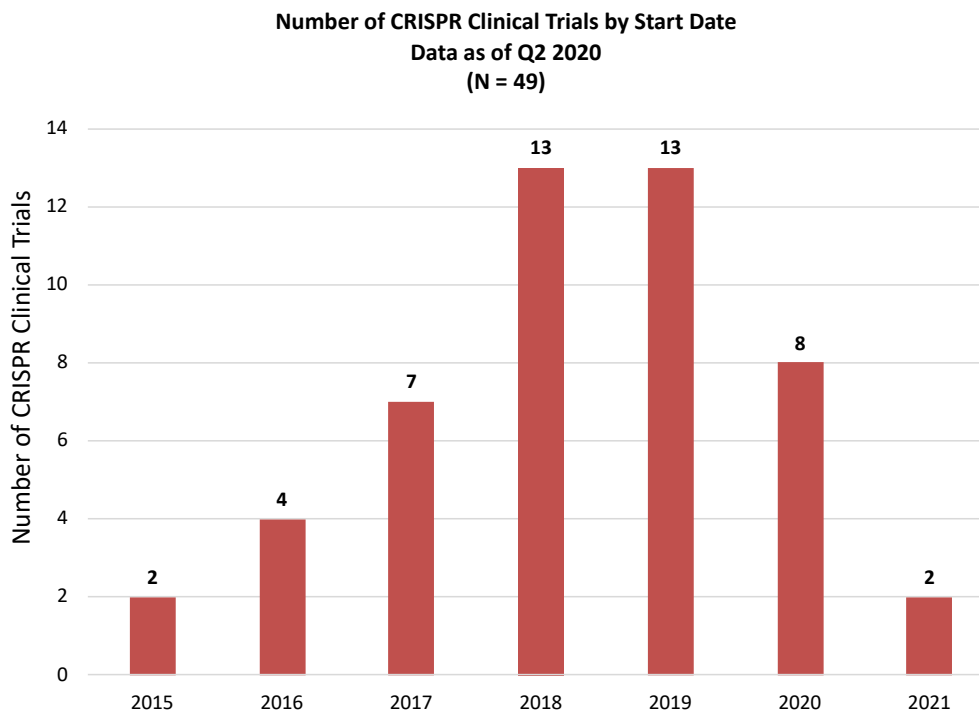


Figure 40: Clinical trials in the CRISPR Clinical Trials Database by start year

Generally, 2018—the year the United States approved the first human trial for a CRISPR-based treatment²⁰—is considered the beginning of CRISPR clinical trials for new therapies (Henderson, 2019). Researchers in China, however, were conducting human studies several years earlier. In 2016, for instance, Sichuan University and Chengdu MedGen Cell, Co. sponsored a trial to evaluate a CRISPR-based therapy for lung cancer (NCT02793856). This study is cited as the first clinical trial using a CRISPR-based therapy globally (Li et al. 2020). The CRISPR Clinical Trials Database also includes two studies prior to even China’s early work: Both are U.S. studies using CRISPR to develop induced pluripotent stem cell banks.²¹

¹⁹ The date of clinical trial registration was unavailable, so we use trial initiation date for all time analyses.

²⁰ The trial, NCT03399448, was designed to test the safety and efficacy of using modified T cells to treat various malignancies. It was subsequently terminated.

²¹ The first trial (NCT02964481) aims to create a registry of children and adults exposed to malignant hyperthermia trigger agents to examine genetic variance that may contribute to susceptibility; CRISPR will be used as part of an effort to create a stem cell bank. The second trial (NCT03332030) aims to establish a stem cell bank for patients with NF1 and central nervous system tumors.

b. Trial type

Four general types of studies appear in the Database: (1) trials using CRISPR-edited cells therapeutically (“CRISPR-edited cells”), (2) studies using CRISPR to create cell lines, databases, or models for future research (“CRISPR cell line creation/modeling”), (3) studies using CRISPR as a genome sequencing or screening tool (“CRISPR genome sequencing/tests”), and (4) studies assessing health attitudes or behaviors related to CRISPR (“surveys”). The majority of the studies in the Database use CRISPR to edit cells (65% = 32/49) (**Figure 41**), work that began appearing around 2016 (**Figure 42**).

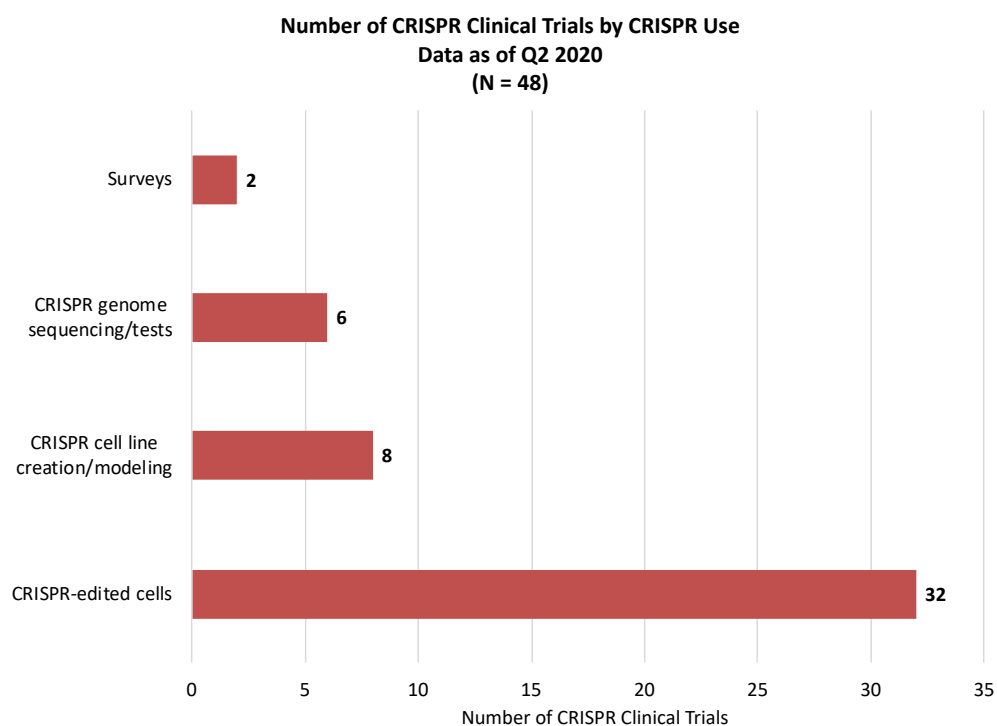


Figure 41: Clinical trials in the CRISPR Clinical Trials Database by CRISPR use

Note: Information for one trial in the Database (CHICTR1800014941) was too limited to characterize CRISPR use. It was therefore excluded from this analysis.

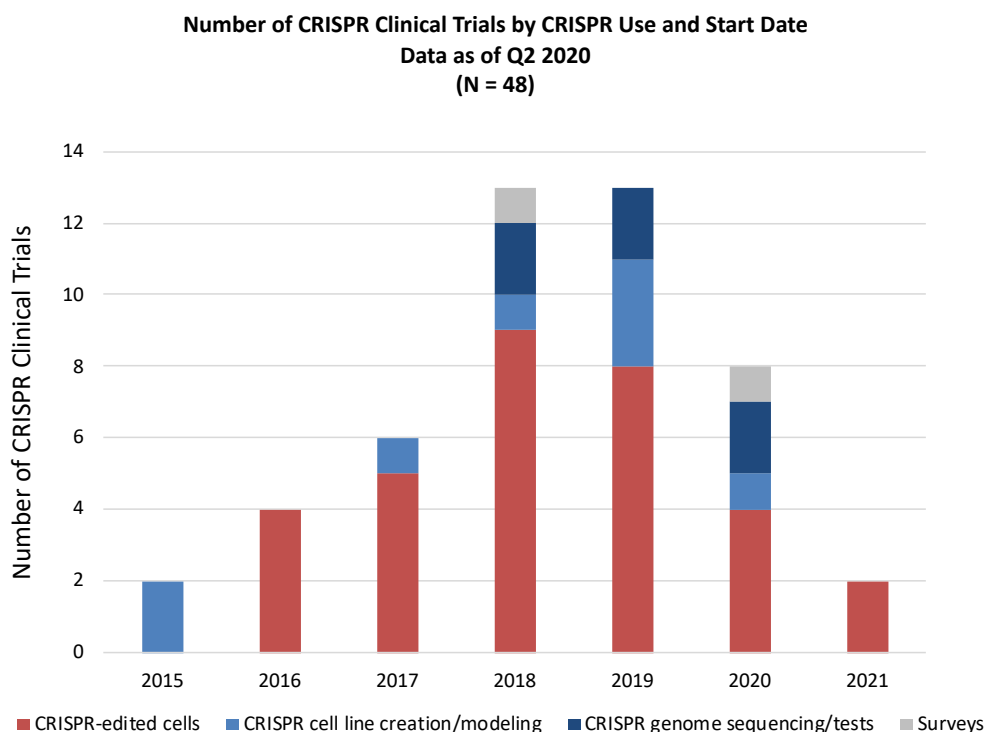


Figure 42: Clinical trials in the CRISPR Clinical Trials Database by CRISPR use and year

Note: Information for one trial in the Database (CHICTR1800014941) was too limited to characterize CRISPR use. It was therefore excluded from this analysis.

To create a comprehensive dataset, the strategy used to collect trials for the Database erred toward inclusivity: The Database includes *all* studies returned from queries for key search terms in various clinical trial databases (see Section III.d for more detail). Accordingly, not every trial in the Database meets stricter criteria often used to define clinical trials. The U.S. National Institutes of Health (NIH), for example, defines a clinical trial as “A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes” (U.S. National Library of Medicine 2020).²² Among the four categories of trials in the Database, only a subset of trials meet this intervention-focused definition. This difference explains the discrepancy between the first CRISPR clinical trials as

²² Although this is the formal definition supplied by NIH, it is not strictly applied even internally. For example, the definition suggests that clinical trials must be interventional, but ClinicalTrials.gov (hosted by the NIH National Library of Medicine) accepts registrations for both interventional and observational studies.

reported in the literature and that captured in the Database: The 2015 U.S. trials used CRISPR to help create stem cell banks, efforts that may not be categorized as clinical trials using a stricter definition.

Moreover, even among those trials likely to meet an intervention-focused definition, CRISPR is used in a variety of ways. For example, it can be applied therapeutically, where CRISPR-edited cells are used as a drug or CRISPR is delivered to patient cells to make specified edits (these are the trials described as “CRISPR-edited cell trials” in this study). But it can also be used as a diagnostic tool or screening device in trials assessing other types of interventions (a subset of the “CRISPR genome sequencing/test” trials fall into this category). Because much of the enthusiasm for CRISPR as a tool stems from its potential for use in drugs or treatments, this study analyzes the CRISPR-edited cell trials separately at certain points. When the Database is restricted to these trials, there are a total of twenty-nine studies. All are early phase²³ trials: around half (14/29, 48%) are Phase I trials, and most of the remaining studies (38% = 11/29) are Phase 1/2 trials.

c. Disease target

Most (51% = 25/49) studies in the CRISPR Clinical Trials Database are geared toward cancer treatment (**Figure 43**). Another seven trials (14%) target blood diseases—all of these address sickle cell disease or β -thalassemia. Infectious diseases are also fairly well-represented (12% = 6/49). When the dataset is restricted to only the CRISPR-edited cell trials, 91% (29/32) are focused on therapies for either cancers or blood diseases (**Figure 44**).

²³ The U.S. Food and Drug Administration categorizes clinical trials based on study characteristics, including size and study objective. An explanation of the phases can be found at <https://www.clinicaltrials.gov/ct2/help/glossary/phase>.

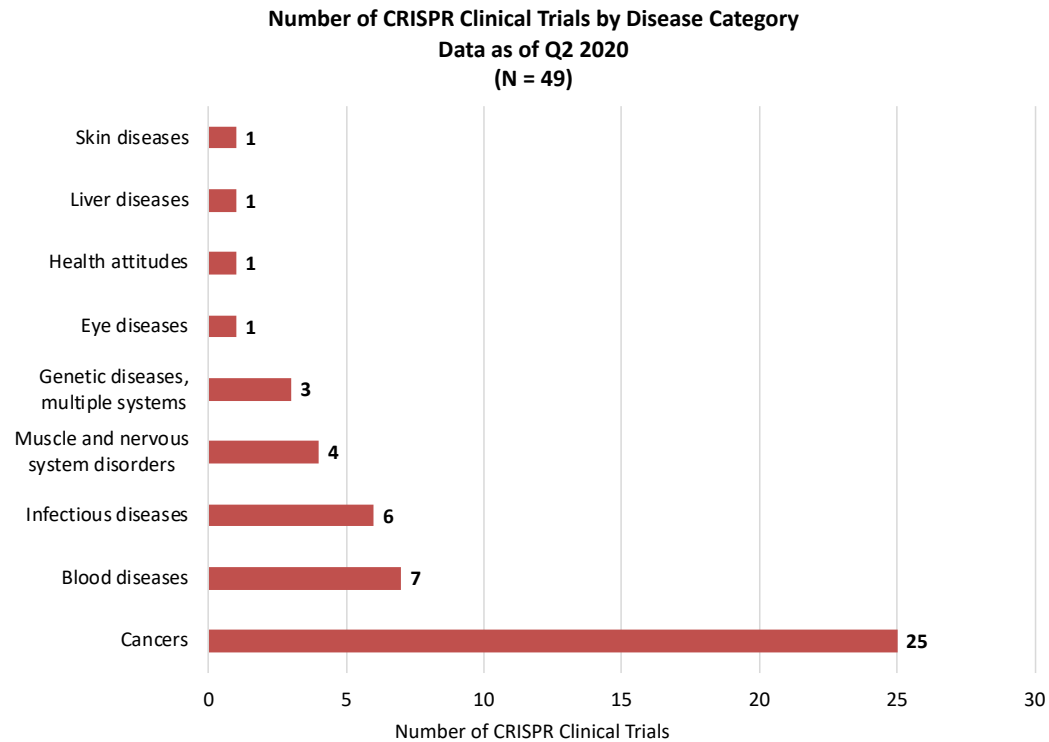


Figure 43: Clinical trials in the CRISPR Clinical Trials Database by disease category

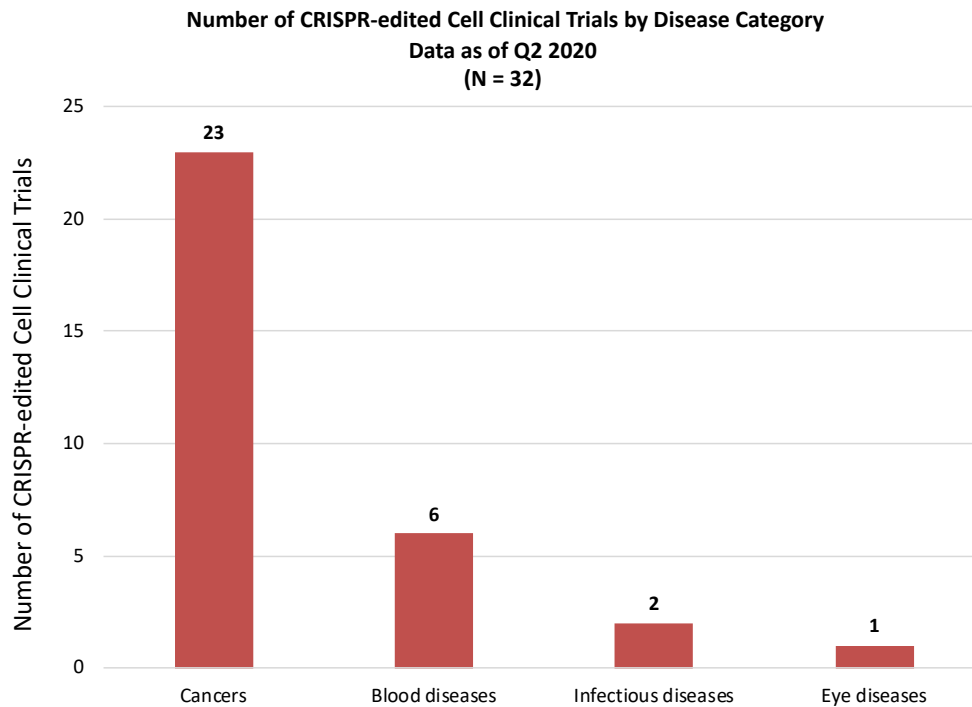


Figure 44: CRISPR-edited cell trials in the CRISPR Clinical Trials Database by disease category

These results are not surprising: CRISPR is a form of gene therapy, so the attributes that make certain diseases promising targets for conventional gene therapy are likely to confer similar advantages in the realm of CRISPR-based treatments. Generally, gene therapy researchers target diseases because they are particularly prevalent and fatal (e.g., cancer, cardiovascular diseases, HIV) or because the underlying mechanisms are well-understood and relatively simple to correct by supplying, replacing, or silencing a defective gene (e.g., a number of monogenic diseases). The Database suggests that, as expected, the most common disease targets for CRISPR-based therapies (**Figure 43 43**) are similar to the most common targets for conventional gene therapies; the trend is even more pronounced when the dataset is restricted to trials using CRISPR-edited cells (**Figure 44**).

In addition, the type of cell that must be targeted to treat the disease can impact the ease of treatment using CRISPR-based therapies. More specifically, the cell type influences the method of delivery to the nucleus, one of the “greatest challenges” in CRISPR applications (Doudna and Sternberg 2017; Zyontz 2019). Other cellular characteristics that can influence the utility of CRISPR as a treatment include amenability to *ex vivo* editing and speed of self-replication. Broadly speaking, the easier it is to edit the cell *ex vivo* and the greater the speed of replication, the better the target for CRISPR treatment. Unsurprisingly, then, the vast majority of the studies using CRISPR to edit cells do so *ex vivo* (94% = 30/32). Only two studies in the Database attempt to edit *in vivo*.²⁴

d. Notable trials and early results

Notable among the 49 trials in the Database is NCT03399448, the first interventional CRISPR trial in the United States. The study, conducted by the University of Pennsylvania in collaboration with the Parker Institute for Cancer Immunotherapy and the American biotherapeutics company Tmunity Therapeutics, was a Phase I study designed to investigate a CRISPR-based immunotherapy for cancer treatment. The researchers recently (February 2020) published initial results that demonstrate safety and feasibility following treatment of three patients (Stadtmauer et al. 2020).

In the realm of genetic diseases, a series of studies sponsored by the American biopharmaceutical company Vertex Pharmaceuticals Inc. and the Swiss gene editing company CRISPR Therapeutics is being closely watched. They are multi-site Phase 1/2 trials designed to evaluate CRISPR-based therapies for severe hemoglobinopathies (sickle cell disease [NCT03745287] and β -thalassemia [NCT03655678]). These

²⁴ One study, NCT03872479, is a U.S. trial using CRISPR to treat Leber Congenital Amaurosis Type 10. The other, NCT03057912, is a Chinese study evaluating a CRISPR-based therapy for human papillomavirus (HPV).

studies are considered by many to be the first uses of *ex vivo* CRISPR-based therapies to treat genetic diseases (Henderson 2019). A follow-on study (NCT04208529) will assess longer-term outcomes. As recently as June 2020, the companies reported interim data that suggest positive safety and efficacy outcomes (Vertex 2020). The promising initial results have attracted media attention: In June 2020, National Public Radio featured one of the patients in the trial who has reportedly experienced substantial improvements in sickle cell disease symptoms following treatment (Stein 2020).

Although most trials are focused on *ex vivo* CRISPR-based therapies, one notable study in the Database (NCT03872479) is exploring an *in vivo* treatment for Leber Congenital Amaurosis Type 10, an inherited eye disorder. Doses of a CRISPR-based therapy are administered via subretinal injection. The trial is sponsored by the U.S. companies Allergan and Editas Medicine, Inc.

The Database also includes the notorious Chinese “CRISPR babies” trial (ChiCTR1800019378). This is the only trial in the Database targeting germline (rather than somatic) cells, creating edits that can be inherited in subsequent generations. The study resulted in the birth of three CRISPR-edited human babies. The lead researcher, He Jiankui, claims to have disabled the CCR5 gene in the embryos in an attempt to confer protection against HIV. Following widespread scientific and ethical criticism, the trial was withdrawn. In a proposal highly reminiscent of He’s work, Russian scientist Denis Rebrikov has been vocal about his attempts to obtain approval to use CRISPR to edit human embryos prior to implantation (Cyranoski 2019). As of this writing, his proposal has not been approved, and Russia currently has no CRISPR clinical trials in the Database.

ii. Clinical Trials: Location

a. Trials by Location

Most CRISPR clinical trials are administered by sponsors in China or the United States (**Figure 45**). China alone sponsors over half of the trials in the Database (55% = 27/49), while the United States sponsors roughly a third (35% = 17/49). Switzerland sponsors around 10% (5/49), and all of these are led by CRISPR Therapeutics (including the three ongoing evaluations of CRISPR therapies for hemoglobinopathies). Germany sponsors one trial in the Database.

The geographic concentration of CRISPR clinical trials is amplified when examining only trials that use CRISPR-edited cells (**Figure 46**). All but one of the trials that uses CRISPR-edited cells is sponsored by at least one of the three leading countries (97% = 31/32). Other countries, including France, Germany, and

India, appear to focus their clinical trial efforts on CRISPR cell line creation and modeling, though the United Kingdom does sponsor one CRISPR-edited cell trial (**Figure 45**).

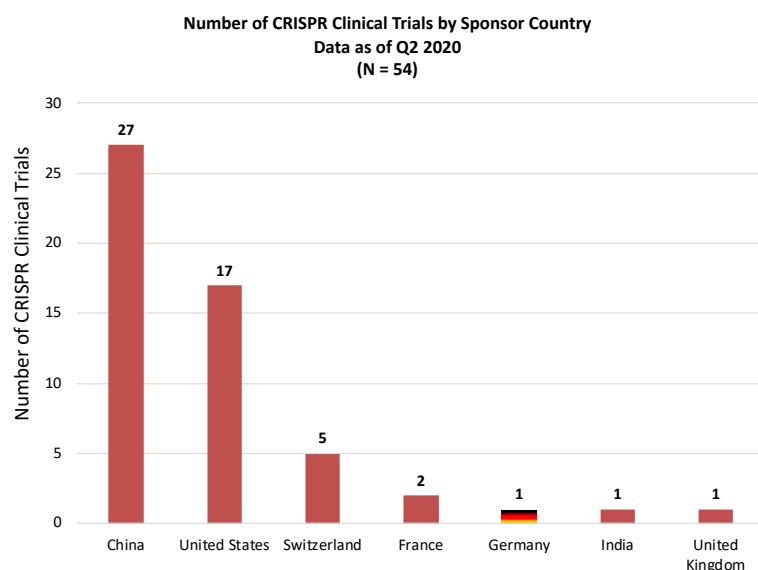


Figure 45: Clinical trials in the CRISPR Clinical Trials Database by country of sponsor

Note: A number of trials have sponsors from more than one country; these are counted more than once for the purposes of this analysis.

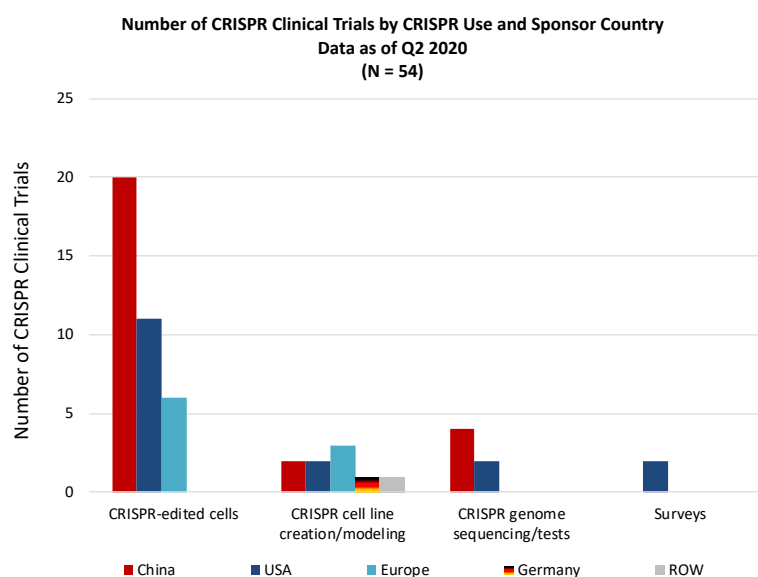


Figure 46: Clinical trials in CRISPR Clinical Trials Database by CRISPR use and country

Note: Information trial CHICTR1800014941 was too limited to characterize CRISPR and was therefore excluded. In addition, a number of trials have sponsors from more than one country; these are counted more than once for the purposes of this analysis. Europe here includes France, Germany, Switzerland, and the United Kingdom.

The dominance of China and the United States in overall quantity of CRISPR clinical trials comports with trends for clinical trials more generally, though China's lead over the United States is anomalous. According to World Health Organization (WHO) data on clinical trials between 1999 and 2019, the United States conducts roughly a quarter of all clinical trials worldwide (WHO 2020). China ranks second, conducting 8.8% of studies globally. It is closely followed by Japan (whose lack of participation in CRISPR clinical trials is conspicuous) at 8.7%. Germany appears fourth on the WHO ranking, sponsoring around 7.6% of the world's clinical trials; by contrast it sponsors only 2% of the trials appearing in the CRISPR Clinical Trials Database. Given the limited number of CRISPR clinical trials in the Database and differences in the underlying data sources²⁵, CRISPR clinical trials should be compared to the WHO clinical trial data cautiously; nevertheless, the WHO data offer a rough comparative benchmark (**Figure 47**).

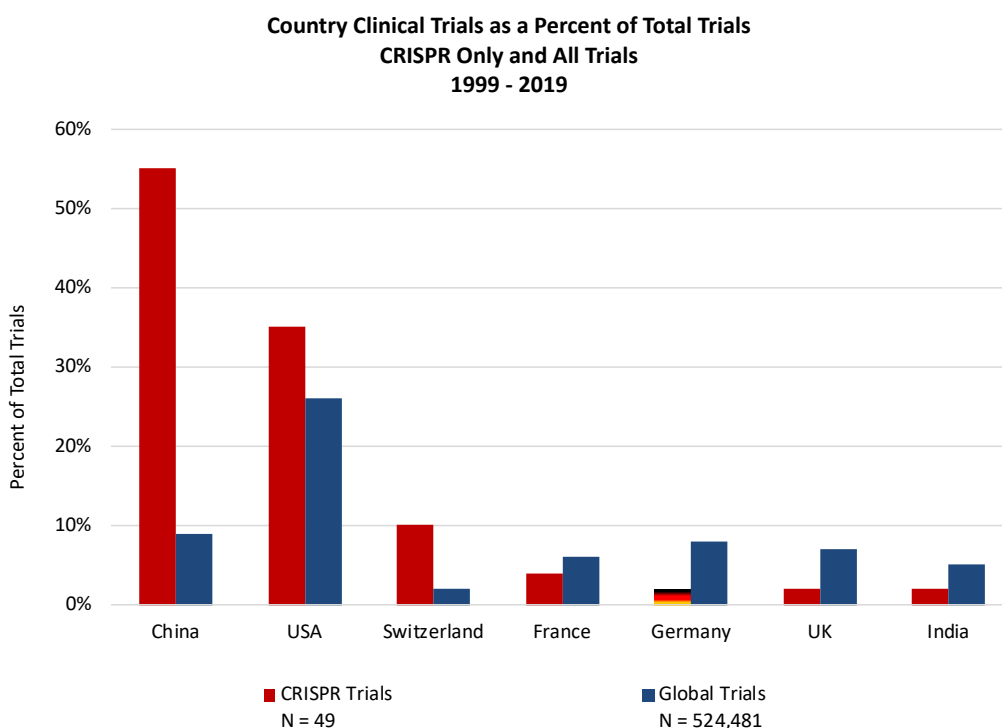


Figure 47: Percentage of CRISPR clinical trials by country compared to global clinical trial rates
Note: A number of trials have sponsors for trials in the CRISPR Clinical Trial Database have from more than one country; as a result, the percentages of CRISPR clinical trials sum to greater than 100%.

China's advantage in terms of overall quantity of CRISPR clinical trials may be explained in part by its early activity in this space. In 2015, 2016, and 2017, China and the United States were the only countries initiating CRISPR clinical trials (**Figure 48**). But while the United States sponsored some early work, after

²⁵ The WHO data reflect registrations in the International Clinical Trials Registry Platform, 1999 - 2019. The CRISPR Clinical Trials Database uses the Dimensions database, supplemented with Global Clinical Trials Data, as well as other databases for the United States, Europe, and China (see Section III for more details).

two studies in 2015, its participation dropped off until 2018. Meanwhile, China initiated eleven trials in 2016 and 2017. These trials alone can account for most of China's ten-trial lead over the United States. Germany's sole trial did not begin until 2019.

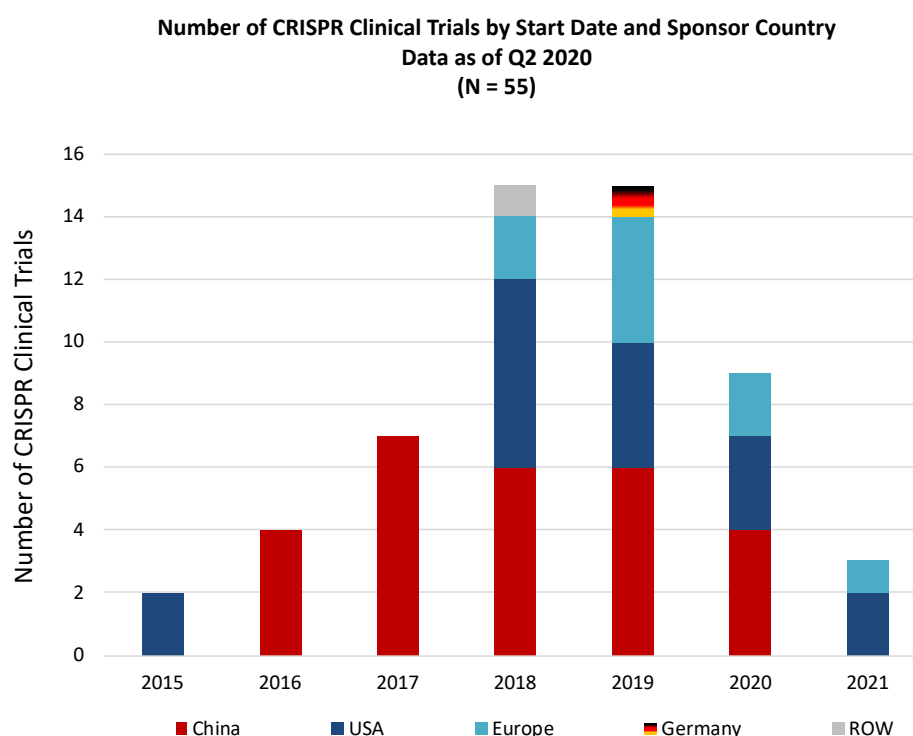


Figure 48: Clinical trials in the CRISPR Clinical Trials Database by start year and country of sponsor
Note: A number of trials have sponsors from more than one country; these are counted more than once for the purposes of this analysis. Europe here includes France, Germany, Switzerland, and the United Kingdom.

China's head start on CRISPR clinical trials may be due to its willingness to delve into human trials relatively early—China began interventional clinical trials a full two years before any other country (2016 vs. 2018). For their parts, the United States and Europe have proceeded to human trials cautiously. In some cases, the work being conducted in China would be unlikely to obtain U.S. or European approval, particularly given the lack of transparency surrounding some of the Chinese research.²⁶ Most infamous, of course, are He Jiankui's "CRISPR babies." He's work was shrouded in secrecy: News of the trial did not break until after the first two babies were already born (Davies 2019b).²⁷ China's head start may also be the product of a deliberate national strategy: China's 13th Five Year Plan (2015-2020), for example, indicated

²⁶ Although the United States and Europe are generally seen as relatively transparent regarding research the U.S. Food and Drug Administration and NIH have recently been accused of tolerating lapses in mandatory clinical trial reporting (Piller 2020).

²⁷ He's institution has subsequently fired him, and He has been criminally sanctioned (Cyranoski 2020).

that the biotechnology industry should exceed 4% of GDP by 2020. The country has invested heavily in its biotechnology sector, and it has focused, in particular, on medical biotechnology (UBS 2018).

As discussed above, most CRISPR clinical trials (78% = 38/49) target cancers, blood diseases, or infectious diseases (**Figure 49**): China, the United States, and Switzerland are responsible for all but one of the CRISPR clinical trials in these categories. To the extent that other countries sponsor CRISPR clinical trials, most focus exclusively on other disease types (and, as noted above, these trials are CRISPR cell line creation/modeling studies). Germany's sole trial is focused on CRISPR cell line creation/modeling for muscle and nervous system disorders.

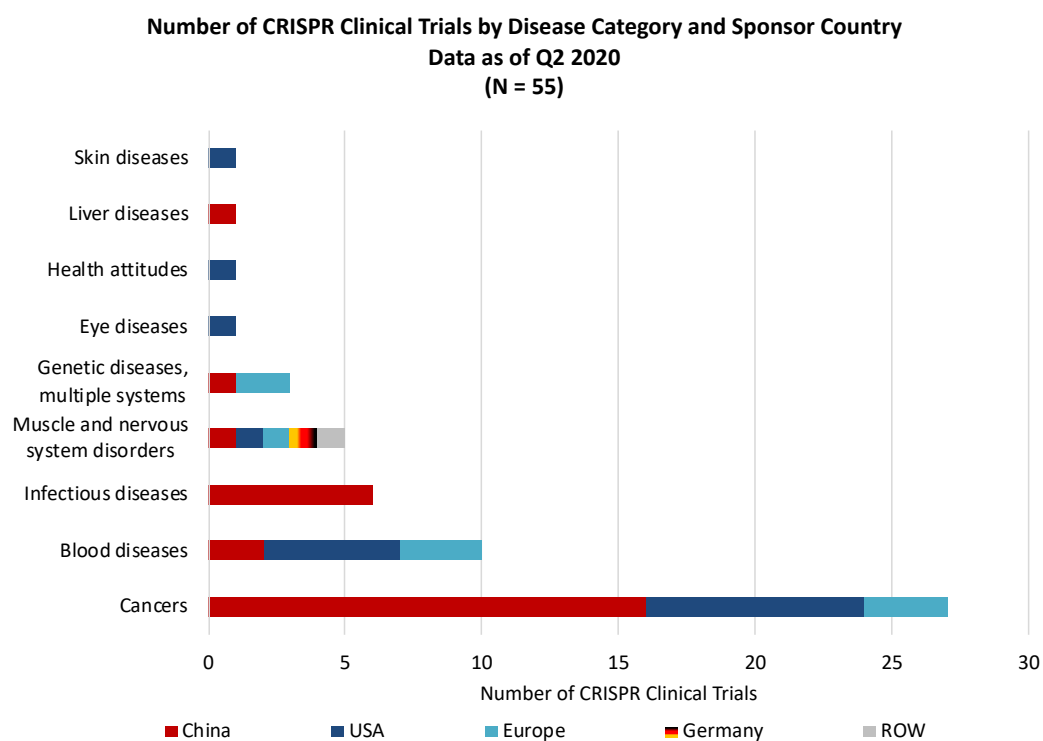


Figure 49: Clinical trials in the CRISPR Clinical Trials Database by disease category and country
Note: A number of trials have sponsors from more than one country; these are counted more than once for the purposes of this analysis. Europe here includes France, Germany, Switzerland, and the United Kingdom.

b. Institutions

There are fifty-nine unique sponsoring institutions represented in the Database. The vast majority of these institutions sponsor only a single trial. A small number (15% = 9/59), however, sponsor more than one; these are listed in **Table 7**.

Most clinical trials in the Database are sponsored by non-industry institutions (65% = 32/49), though around one fifth of the studies include partnerships between industry and non-industry sponsors (21% = 10/49) (**Figure 50**). All three leaders in the CRISPR clinical trials space (China, the United States, and Switzerland) have industry-led trials and partnerships between industry and non-industry sponsors; other countries represented in the Database rely solely on non-industry sponsors (**Figure 51**).

Institution	Country	Number of trials
CRISPR Therapeutics	Switzerland	5
Chinese PLA General Hospital	China	4
Peking University	China	4
Shanghai Bioray Laboratory Inc.	China	4
Vertex Pharmaceuticals	United States	3
Xiangya Hospital of Central South University	China	3
National Cancer Institute	United States	2
South University of Science and Technology, China	China	2
University of Minnesota	United States	2

Table 7: Institutions sponsoring more than one trial in the CRISPR Clinical Trials Database

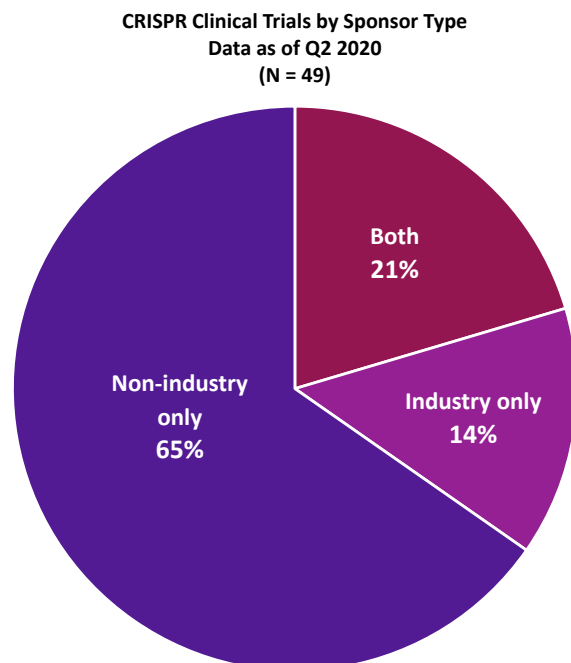
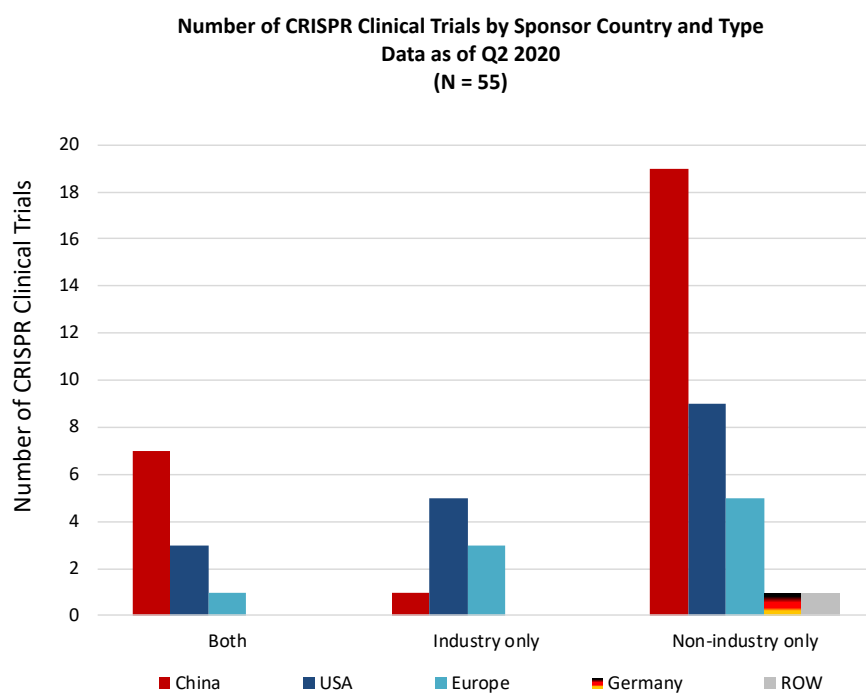


Figure 50: Clinical trials in the CRISPR Clinical Trial Database by sponsor type



S

Figure 51: Clinical trials in the CRISPR Clinical Trial Database by sponsor country and type
Note: A number of trials have sponsors from more than one country; these are counted more than once for the purposes of this analysis. Europe includes France, Germany, Switzerland, and the United Kingdom.

c. Germany

Despite the fact that Germany ranks fourth on the WHO list for global clinical trial sponsorship, only one trial in the Database is sponsored by an institution in Germany (though these data should be interpreted cautiously given the small number of CRISPR clinical trials). On the whole, China and the United States, dominate the CRISPR clinical trial landscape; many countries, including most of Europe, lag well behind them. But in light of Germany's CRISPR publication record, its lack of clinical trials in this area is not surprising given its patenting behavior and publication focus.

Germany's sole trial (DRKS00019110) aims to create controls for future studies. The study will collect samples from patients who have or carry mutations associated with dystonia, a movement disorder. The disease-causing mutations can be corrected using CRISPR/Cas9 to produce healthy controls: Other than the corrected mutation, the cells will be genetically identical to patient samples and can be used for comparisons in subsequent studies. The trial, sponsored by the Zentrum für Kinder-und Jugendmedizin Heidelberg, started in 2019 and is currently recruiting patients.

In addition, although Germany sponsors only one study in the Database, some of the larger clinical trials do recruit patients in Germany. Very few trials in the Database recruit patients outside of their sponsors' countries: Among the five that do, four include Germany as a trial site. Notably, the Vertex Pharmaceuticals/CRISPR Therapeutics trials recruit German patients.

V. DISCUSSION

The results of the four databases constructed for this report reveal a number of important trends in the global CRISPR innovation ecosystem for the EFI to consider. First, only a few countries dominate the CRISPR landscape and they are leaders in all measured aspects including papers, patent families, companies, and clinical trials. Second, Germany is a strong player in generating new ideas but is not as active in the commercial aspects of CRISPR. Third, countries in the CRISPR innovation ecosystem participate in niche areas, which could be used as a reference when formulating an innovation strategy for Germany going forward.

The CRISPR innovation ecosystem is dominated by organizations and individuals in two countries: the United States and China. These two countries are the largest players in publishing CRISPR academic

articles, filing CRISPR patent families, encouraging companies that create CRISPR products or services, and running CRISPR clinical trials. However, they have starkly different relationships with the technology.

CRISPR in the United States is often a story of discovery and entrepreneurship. Some of the most prominent early CRISPR discoveries were in the United States, so researchers there had a first mover advantage, especially the original CRISPR pioneers like Jennifer Doudna, Emmanuelle Charpentier, and Feng Zhang and the academic scientists around them (Thompson and Zyontz 2020). The United States' dominance in CRISPR innovation was further helped by the entrepreneurial ecosystems for biotechnology, located in Silicon Valley (near UC Berkeley in California) and Kendall Square (near MIT in Massachusetts), as well as the Technology Transfer Offices (TTOs) at large research universities in the United States. 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. Although translating technology from the lab bench to the market can be difficult, the environments in which CRISPR pioneers operated supported them in patenting their technology and founding their own CRISPR startup companies. These surrogate companies, including Caribou Biosciences (Berkeley, CA), Editas Medicine (Cambridge, MA), CRISPR Therapeutics (Basel, Switzerland), and Intellia Therapeutics (Cambridge, MA), were given rights by the CRISPR pioneers to not only develop CRISPR products but to license them to others (Contreras and Sherkow 2017). Today, the CRISPR pioneer founders remain involved in their companies serving as scientific advisors and often employing former graduate and postdoctoral students at the corporate labs. This involvement has strengthened the tie between the academic and corporate labs, making it easier to innovate with the new technology quickly. It has also likely contributed to the increase in additional CRISPR startups in the United States.

CRISPR in China followed a very different path. Chinese academics and organizations were fast followers in CRISPR as they were not involved in the initial development of the technology. This is reflected in China's initially low rates of publishing and patenting and then explosive growth in both in later years. This extraordinary growth is likely related to the government's 13th Five-Year Plan (2016-2020) that emphasized becoming a dominant hub 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). However, as shown in Section IV, the CRISPR work coming from China seems to be more about quantity than quality since the top-down encouragement from the Chinese government may incentivize Chinese scientists to quickly produce observable measures of innovation such as papers and patents. 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 has also led to some serious ethical dilemmas in the use of CRISPR in the country. The genetic modification of viable human embryos using CRISPR by Dr. He Jiankui producing living babies rocked the scientific community when He announced his results in late 2018 (Regalado 2019).

Germany seems to be following a different innovation model in CRISPR than either the United States or China. Although Germany has the academic and corporate infrastructure and experience in biotechnology and pharmaceuticals necessary for CRISPR commercialization, Germany remains a dominant player in academic research but is less active in patenting, clinical trials, and new CRISPR companies. Although CRISPR was not initially discovered in Germany, research organizations in the country were early participants in producing novel CRISPR research, although the growth rate in papers was slower than other countries'. The German CRISPR companies that do exist are larger, more established, and more likely to offer CRISPR research services or follow a partnership/acquisition strategy for CRISPR innovation. This is entirely consistent with the literature on the use of strategic alliances for R&D in established biopharma companies (Lerner and Merges 1998). These organizations are comfortable working with foreign organizations and are able to identify exciting new technologies from others. For example, the joint venture between Bayer and CRISPR Therapeutics gives Bayer opt-in rights for CRISPR treatments in hemophilia, ophthalmology and autoimmune diseases without having to do their own R&D (CRISPR Therapeutics 2019b). However, there are only a small number of research and product relationships between academia and corporations in Germany, which may be why Germany has only a few startup companies making or selling CRISPR technology, unlike the United States. Germany's model appears to be similar to Japan's, another country that is a top publisher, but patents relatively less, and has fewer and more established CRISPR companies.

The three countries' different paths seem to be largely influenced by the existing academic, business, and cultural environments at the time CRISPR was introduced. This is not surprising since CRISPR's rapid diffusion did not provide much time for established ecosystems to adapt. These existing environments might also explain why countries focus on different niche areas within CRISPR. For example, the United States, although top in most areas, focuses on Health/Medicine and Technical Improvements. This is consistent with its role in early CRISPR discovery, the interest in scientific tools and medical applications of the CRISPR pioneers, and the entrepreneurial environment. China focuses mostly on Agriculture/Livestock, which is consistent with the government's push to develop technology in that area. Germany focuses mostly on Technical Improvements and other Business-to-Business applications of CRISPR which is consistent with the types of established companies in the country such as Bayer, Merck

KGaA, Thermo Fisher, KWS, and BASF. The application areas of each country seem to hold over the four databases. Thus any future CRISPR innovation strategy should carefully consider whether the necessary environment to expand to other areas exists. For example, innovation strategies should consider current academic and corporate resources; regulations and government support; and culture and risk preferences.

VI. IMPLICATIONS FOR GERMANY'S CRISPR INNOVATION STRATEGIES

Based on the results and discussion above, there are a number of implications for a future CRISPR innovation strategy. There are also several related questions this report cannot address, and future studies are suggested to better answer them.

A. IMPLICATIONS

First, the translation from academic ideas to commercial outcomes through academic and corporate partnerships may be an opportunity for Germany, especially if considering entering Health and Medicine. German universities and corporations in CRISPR both focus on Technical Improvements, but there is little to no evidence of corporate and academic organizations co-authoring, patenting, or forming other alliances even outside Germany. Given the importance of the academic-corporate relationships to CRISPR development in the United States, it may be difficult to compete without building these relationships. In order to find solutions, diagnosing the exact problem is imperative. This leads to questions such as: Why might this disconnect be occurring in Germany? Are there barriers to academics and post-docs engaging in commercializing behaviors? Is it challenging to develop public-private partnerships? Could this lead to German ideas being commercialized elsewhere?

Second, it is worth considering how Germany should position itself in the CRISPR space. Germany already has a strong base for technical improvements and services in CRISPR as well as established and experienced companies with capabilities in scientific tools and services related to health applications. Currently, German companies tend to offer CRISPR services or support CRISPR innovations in subsidiaries or R&D partners. Given Germany's current strengths, it could consider incentivizing a particular niche-- creating quality solutions for the biggest challenges with CRISPR tools (e.g., delivery mechanisms or improving editing efficiency). Note that much of the work in CRISPR drugs, therapeutics, and diagnostics is being conducted by United States startups. If Germany is interested encouraging its organizations to enter Health and Medicine, it would be a follower in this space broadly. It is also important to identify and address any regulatory barriers that German organizations might face in Health/Medicine (or Agricultural) applications.

Third, as a longer term strategy, Germany may choose to consider incentivizing the creation of more German-headquartered CRISPR startups. However, without a strong entrepreneurial support structure like those in the United States, this strategy could be more difficult. Before encouraging the creation of new ventures it will be important to understand the current barriers to founding new firms. For example, is there no interest? Is there interest, but a lack of Venture Capital funds? Who is trying but failing to start a new CRISPR firm? Alternatively, Germany may not need to directly encourage new ventures, but could help current established companies leverage their experience in finding and supporting new technologies from others or further developing these capabilities in-house. For example, the acquisition and partnership experience of established firms could be used to support new startups or more intrapreneurship. Established firms could also be encouraged to create more strategic alliances with existing CRISPR companies around the world.

Fourth, Germany has the experience and standing to go beyond just new CRISPR innovation and become a global thought leader creating regulatory frameworks for the ethical development and use of the future tools. Germany could also create thought leadership in the social sciences, for example, by encouraging research on personal attitudes and behaviors around CRISPR. As the CRISPR technology matures, understanding the societal implications and ethics of this exciting technology will become increasingly important.

B. SUGGESTED FUTURE STUDIES

To develop a comprehensive innovation strategy, questions arising from the implications above suggest potential future studies that will help to better understand Germany's CRISPR environment, but that are not covered by the results in this report.

To support a CRISPR Technology Improvement strategy in Germany, a future study would identify the biggest concerns with CRISPR tools where German companies or academics could be encouraged to focus their efforts. Results from Tender 1 could be used to guide the development of this study.

Another important area of study not addressed in this report is identifying who funds CRISPR research in Germany and where the funds are going.

Survey and interviews with academic scientists (PIs and postdoctoral students) in CRISPR, would help discover some of the underlying barriers to academic-corporate relationships and attitudes towards starting a new venture. Example questions:

1. How did you decide to study CRISPR? How do you use CRISPR?
2. Have you worked with other labs on CRISPR experiments?
3. Have you worked with corporations on CRISPR experiments of products? Why or why not?
4. Have you considered commercializing a CRISPR product?
5. Have you considered starting a CRISPR company?
 - a. If yes, did you start to (or successfully) create a company?
 - b. If you considered it but chose not to, why?

A companion set of surveys and interviews should also be conducted with individuals from biotech, pharma, and CRISPR startups (including failed organizations). Example questions:

1. How do you use CRISPR? Did your company develop the products? Did you partner with or acquire another company?
2. Have you worked with academic labs on CRISPR products? Why or why not?
3. For startups, what encouraged you to create a startup? What was the process?

Additionally, tracing out in detail the CRISPR collaborations and networks, both domestic and international as well as between corporate and non-corporate entities will help identify common paths of collaboration and the benefits of sharing new innovations. This final proposed study would provide a richer understanding of the CRISPR ecosystem and identify opportunities and constraints for Germany's strategic initiatives moving forward.

REFERENCES

- Addgene. 2020. “CRISPR Guide.” Addgene Science Guides, available at: <https://www.addgene.org/guides/crispr/>.
- Alvarez, J. 2020. “New CRISPR-Based COVID-19 Test Kit Can Diagnose Infection in Less Than an Hour.” UCSF Press Release (April 16) available at: <https://www.ucsf.edu/news/2020/04/417181/new-crispr-based-covid-19-test-kit-can-diagnose-infection-less-hour>.
- Barrangou, R., C. Fremaux, H. Deveau, M. Richards, P. Boyaval, S. Moineau, D. Romero, P. Horvath. 2007. “CRISPR provides acquired resistance against viruses in prokaryotes.” *Science* 315(5819): 1709–1712.
- Begley, S. 2020. “CRISPR Tracker.” STAT News (accessed August 24) available at: <https://www.statnews.com/feature/crispr/tracker/>.
- Boch J, et al. 2009. “Breaking the code of DNA binding specificity of TAL-type III effectors.” *Science* 326:1509–1512.
- Brinegar K, K Yetisen A, Choi S, et al. 2017. The commercialization of genome-editing technologies. *Crit Rev Biotechnol.* 37(7):924-932.
- Broad Communications. 2020. “For Journalists: Statement and Background on the CRISPR Patent Process (updated May 18), available at: <https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process>
- Central Committee of the Communist Party of China. 2016. *The 13th Five-Year Plan for economic and Social Development of the People’s Republic of China: 2016-2020*. Translated by the Compilation and Translation Bureau, Central Committee of the Communist Party of China, China. Available at: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKewjfid-krrnqAhWUITQIHQrYBUAQFjADegQIARAB&url=https%3A%2F%2Fen.ndrc.gov.cn%2Fpolicyrelease_8233%2F201612%2FP020191101482242850325.pdf&usq=AOvVaw3O7cmrDbWB4ajvhUflf7Ab
- Chen JS, Ma E, Harrington LB, Da Costa M, Tian X, Palefsky JM, and Doudna JA. 2018. “CRISPR-Cas12a target binding unleashes indiscriminate single-stranded DNase activity.” *Science* 360 (6387): 436–439.
- Chinese Academy of Sciences. 2020. “About Us.” (accessed August 24) available at: http://english.cas.cn/about_us/introduction/201501/t20150114_135284.shtml.
- Cohen, J. 2017. “How the battle lines over CRISPR were drawn.” *Science Magazine*, available at: <https://www.sciencemag.org/news/2017/02/how-battle-lines-over-crispr-were-drawn>.
- Cong, L., F. A. Ran, D. Cox, S. Lin, R. Barretto, N. Habib, P. D. Hsu, X. Wu, W. Jiang, L. A. Marraffini, and F. Zhang. 2013. “Multiplex genome engineering using CRISPR/Cas systems.” *Science* 339(6121): 819-823.
- Conti A, Thursby J G and Thursby MC., 2014. “Patents as Signals for Startup Financing.”. NBER Working Paper No. w19191, Available at SSRN: <https://ssrn.com/abstract=2287049>.
- Contreras, JL and JS Sherkow. 2017. “CRISPR, surrogate licensing, and scientific discovery,” *Science* 355 (6326), 698-700.
- CRISPR Therapeutics. 2019a. “CRISPR Therapeutics and ProBioGen Sign Collaboration and License Agreement to Develop Novel In Vivo Delivery Technologies.” Press release, available at: <http://www.crisprtx.com/about-us/press-releases-and-presentations/crispr-therapeutics-and-pro-bio-gen-sign-collaboration-and-license-agreement-to-develop-novel-in-vivo-delivery-technologies>.

- CRISPR Therapeutics. 2019b. “CRISPR Therapeutics and Bayer Announce an Update on Casebia Therapeutics.” Press release, (October 19) available at: <http://www.crisprtx.com/about-us/press-releases-and-presentations/crispr-therapeutics-and-bayer-announce-an-update-on-casebia-therapeutics>.
- Cyranoski, D. 2018. “CRISPR-baby scientist fails to satisfy critics.” *Nature* 564: 13-14.
- Cyranoski, D. 2019. “Russian biologist plans more CRISPR-edited babies.” *Nature News*, available at: <https://www.nature.com/articles/d41586-019-01770-x>
- Cyranoski, D. 2020. “What CRISPR-baby prison sentences mean for research.” *Nature News*, available at: <https://www.nature.com/articles/d41586-020-00001-y>.
- Davies, K. 2019a. “All About That Base Editing.” Genetic Engineering and Biotechnology News, available at: <https://www.genengnews.com/insights/all-about-that-base-editing/>.
- Davies, K. 2019b. “CRISPR’s China Crisis.” Genetic Engineering and Biotechnology News, available at: <https://www.genengnews.com/insights/crisprs-china-crisis/>.
- Der Marderosian, L. 2017. “2017 IPO Report.” *Harvard Law School Forum on Corporate Governance*, available at: <https://corpgov.law.harvard.edu/2017/05/25/2017-ipo-report/>.
- Ding, Q., Regan, S.N., Xia, Y., Oostrom, L.A., Cowan, C.A., and Musunuru, K. 2013. “Enhanced efficiency of human pluripotent stem cell genome editing through replacing TALENs with CRISPRs.” *Cell Stem Cell* 12(4):393–394.
- Doudna, J. 2015. “Genomic Engineering and the Future of Medicine.” *JAMA*. 313(8):791-792.
- Doudna, J. and S. Sternberg. 2017. *A Crack in Creation: Gene Editing and the Unthinkable Power to Control Evolution*. Houghton Mifflin Harcourt.
- Egelie KJ, Graff GD, Strand SP, Johansen B. 2016. The emerging patent landscape of CRISPR-Cas gene editing technology. *Nat Biotechnol*. 34(10):1025-1031.
- European Patent Office Board of Appeal. 2020. “Decision in Case T 844/18 on the CRISPR Gene Editing Technology.” (January 17) available at: <https://www.epo.org/law-practice/case-law-appeals/communications/2020/20200117.html>.
- Fan, M., J. Tsai, B. Chen, K. Fan, and J. LaBaer. 2005. “A central repository for published plasmids.” *Science* 307(5717): 1877.
- Fernandez, C.R. 2020. “Broad Institute Loses Appeal on European CRISPR Patent.” (January 24) available at: <https://www.labiotech.eu/crispr/crispr-patent-europe/>.
- Ferreira R, David F, Nielsen J. 2018. “Advancing biotechnology with CRISPR/Cas9: recent applications and patent landscape.” *J Ind Microbiol Biotechnol*.;45(7):467-480.
- Gans, J.S, D.H. Hsu, and S. Stern. 2008. “The impact of uncertain intellectual property rights on the market for ideas: Evidence from patent grant delays.” *Management Science* 54(5): 982-997.
- Gans, Joshua S., and Scott Stern. 2003. “The Product Market and the Market for Ideas: Commercialization Strategies for Technology Entrepreneurs.” *Research Policy* 32: 333-350.
- Gantz, V., N. Jasinskiene, O. Tatarenkova, A. Fazekas, V. Macias, E. Bier, and A. James. 2015. “Highly Efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito *Anopheles stephensi*.” *PNAS* 112(49): E6736–E6743.

- Gasiunas, G., Barrangou, R., Horvath, P., and Siksnys, V. 2012. "Cas9–crRNA ribonucleoprotein complex mediates specific DNA cleavage for adaptive immunity in bacteria." *PNAS* 109, E2579–E2586.
- Gaudelli NM, Komor AC, Rees HA, Packer MS, Badran AH, Bryson DI, Liu DR. 2017. "Programmable base editing of A-T to G-C in genomic DNA without DNA cleavage." *Nature* 551:464–471.
- Gootenberg JS, Abudayyeh OO, Lee JW, Essletzbichler P, Dy AJ, Joung J, Verdine V, Donghia N, Daringer NM, Freije CA, Myhrvold C, Bhattacharyya RP, Livny J, Regev A, Koonin EV, Hung DT, Sabeti PC, Collins JJ, and Zhang F. 2017. "Nucleic acid detection with CRISPR-Cas13a/C2c2." *Science* 356(6336): 438–442.
- Haeussler C., Harhoff D., Mueller E., 2014. "How Patenting informs VC investors – The Case of Biotechnology," *Research Policy* 43(8), p. 1286-1298.
- Henderson, H. 2019. "CRISPR Clinical Trials: A 2019 Update." *SynBioBeta*, available at: <https://synbiobeta.com/crispr-clinical-trials-a-2019-update/>.
- Hirakawa MP, Krishnakumar R, Timlin JA, Carney JP, Butler KS. 2020. Gene editing and CRISPR in the clinic: current and future perspectives. *Biosci Rep.* Apr 30;40(4).
- Hera Biolabs. n.d. "Cas-CLOVER nucleases – the clean alternative to CRISPR/Cas9." Available at: <https://www.herabiolabs.com/cas-clover/>.
- Ishino Y, Shinagawa H, Makino K, Amemura M, Nakata A. 1987. "Nucleotide sequence of the iap gene, responsible for alkaline phosphatase isozyme conversion in *Escherichia coli*, and identification of the gene product". *Journal of Bacteriology*. 169 (12): 5429–5433.
- Jinek, M., K. Chylinski, I. Fonfara, M. Hauer, J. A. Doudna, and E. Charpentier. 2012. "A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity." *Science* 337(6096): 816-21.
- Koleski, K. 2017. The 13th Five-Year Plan, U.S.-China Economic and Security Review Commission, available at: <https://www.uscc.gov/research/13th-five-year-plan>.
- Komor AC, Kim YB, Packer MS, Zuris JA, Liu DR. 2016. "Programmable editing of a target base in genomic DNA without double-stranded DNA cleavage." *Nature* 533:420–424.
- Kosicki, M., Tomberg, K., and Bradley, A. 2018. "Repair of double-strand breaks induced by CRISPR–Cas9 leads to large deletions and complex rearrangements." *Nature Biotechnology* 36:765–1771.
- LaManna M. Pyhtila B, and Barrangou R. 2020. "Sharing the CRISPR Toolbox with an Expanding Community." *The CRISPR Journal* 3(4): 248=252.
- Ledford, H. 2015. "CRISPR, the disruptor." *Nature* (522): 20–24.
- Lerner J. and Merges R.P. 1998. "The control of technology alliances: An empirical analysis of the biotechnology industry." *Journal of Industrial Economics* 46(2):125–156.
- Li, Y., Glass, Z., Huang, M., Chen, Z.-Y., and Xu, Q. 2020. "Ex vivo cell-based CRISPR/Cas9 genome editing for therapeutic applications." *Biomaterials* 234: 119711.
- Ma, H., N. Marti-Gutierrez, S. W. Park, J. Wu, Y. Lee, K. Suzuki, A. Koski, D. Ji, T. Hayama, R. Ahmed, H. Darby, C. Dyken, Y. Li, E. Kang, A. R. Park, D. Kim, S. T. Kim, J. Gong, Y. Gu, X. Xu, D. Battaglia, S. Krieg, D. Lee, D. Wu, D. Wolf, S. Heitner, J. C. Belmonte, P. Amato, J. S. Kim, S. Kaul, and S. Mitalipov. 2017. "Correction of a pathogenic gene mutation in human embryos." *Nature* 548(7668): 413-419.
- Mali, P., Yang, L., Esvelt, K.M., Aach, J., Guell, M., DiCarlo, J.E., Norville, J.E., and Church, G.M. (2013). RNA-guided human genome engineering via Cas9. *Science* 339, 823–826

- Martin-Laffon J, Kuntz M and Ricroch. 2019. "Worldwide CRISPR patent landscape shows strong geographical biases." *Nature Biotechnology* 37, 613–620.
- Merton RK. 1973. *The Sociology of Science: Theoretical and Empirical Investigations*. University of Chicago Press, Chicago.
- MPEG LA. 2020. "The Initiative: MPEG LA Calls on CRISPR-Cas9 Patent Holders to Solve the CRISPR IP Conundrum." (accessed August 24) available at: <https://www.mpegla.com/crispr/initiative/>.
- Moon SB, Kim DY, Ko JH, and Kim YS. 2019. "Recent Advances in the CRISPR Genome Editing Tool Set," *Experimental and Molecular Medicine* 51:1-11.
- National Science Foundation. 2019. Publication Output: U.S. Trends and International Comparisons. Science and Engineering Indicators 2020. NSB-2020-6. Alexandria, VA. Available at <https://nces.nsf.gov/pubs/nsb20206/>.
- Patent Trial and Appeal Board. 2019. "Notice to Declare Interference." Regents of the University of California, University of Vienna, Emmanuelle Charpentier v. Broad Institute, Inc., Massachusetts Institute of Technology, President and Fellows of Harvard College (filed June 24, Interference # 106,115).
- Pennisi, E. 2013. "The CRISPR craze." *Science* 341(6148): 833-836.
- Philippidis, A. 2016. "Making history with the 1990 gene therapy trial." *Genetic Engineering and Biotechnology News*, available at: <https://www.genengnews.com/magazine/269/making-history-with-the-1990-gene-therapy-trial/>.
- Piller, C. 2020. "FDA and NIH let clinical trial sponsors secret and break the law." *Science Magazine*, available at <https://www.sciencemag.org/news/2020/01/fda-and-nih-let-clinical-trial-sponsors-keep-results-secret-and-break-law>.
- Platt, R.J., S. Chen, Y. Zhou, M. J. Yim, L. Swiech, H. R. Kempton, J. E. Dahlman, O. Parnas, T. M. Eisenhaure, M. Jovanovic, D. B. Graham, S. Jhunjhunwala, M. Heidenreich, R. J. Xavier, R. Langer, D. G. Anderson, N. Hacohen, A. Regev, G. Feng, P. A. Sharp, and F. Zhang. 2014. "CRISPR-Cas9 knockin mice for genome editing and cancer modeling." *Cell*. 159(2):440-55.
- Regalado, A. 2019. "China's CRISPR babies: Read exclusive excerpts from the unseen original research." *MIT Technology Review* (December 3). Available at: <https://www.technologyreview.com/2019/12/03/131752/chinas-crispr-babies-read-exclusive-excerpts-he-jiankui-paper/>.
- Regents of the University of California, University of Vienna, Emmanuelle Charpentier v. Broad Institute, Inc., Massachusetts Institute of Technology, President and Fellows of Harvard College, 903 F.3d 1286 (CAFC 2018).
- Samy M. 2018. "CRISPR Genome-Editing: The Value of CRISPR's Intellectual Property." ARK Invest Research. White Paper. (August 17).
- Sauermann H and Stephan P. 2013. "Conflicting Logics? A Multidimensional View of Industrial and Academic Science." *Organization Science* 24(3):889-909.
- Sherlock Biosciences. 2020. "Sherlock Biosciences Receives FDA Emergency Use Authorization for CRISPR SARS-CoV-2 Rapid Diagnostic." (May 7) available at: <https://sherlock.bio/sherlock-biosciences-receives-fda-emergency-use-authorization-for-crispr-sars-cov-2-rapid-diagnostic/>.
- Specter, M. 2015. "The Gene Hackers: A powerful new technology enables us to manipulate our DNA more easily than ever before." *The New Yorker* (16 November).

- Stadtmauer, E.A., Fraietta, J.A., Davis, M.M., Cohen, A.D., Weber, K.L., Lancaster E., Mangan, P.A., Kulikovskaya, I., Gupta, M., Chen, F., Tian, L., Gonzalez, V.E., Xu, J., Jung, I., Melenhorst, J.J., Plesa, G., Shea, J., Matlawski, T., Cervini, A., Gaymon, A.L., Desjardins, S., Lamontagne, A., Salas-Mckee, J., Fesnak, A., Siegal, D.L., Levine, B.L., Jadowsky, J.K., Young, R.M., Chew, A., Hwang, W.-T., Hexner, E.O., Carreno, B.M., Nobles, C.L., Bushman, F.D., Parker, K.R., Qi, Y., Satpathy, A.T., Chang, H.Y., Zhao, Y., Lacey, S.F., and June, C.H. 2020. "CRISPR-engineered T cells in patients with refractory cancer." *Science* 06 Feb 2020: eaba7365.
- Stein, R. 2020. "A year in, 1st patient to get gene editing for sickle cell disease is thriving." *National Public Radio*, available at: https://www.npr.org/sections/health-shots/2020/06/23/877543610/a-year-in-1st-patient-to-get-gene-editing-for-sickle-cell-disease-is-thriving?utm_campaign=storyshare&utm_source=twitter.com&utm_medium=social.
- Stockton, N. 2017. "CRISPR kills HIV and eats Zia 'like Pac-man'. It's Next Target? Cancer." *WIRED*.
- Synthego Blog. 2019. "CRISPR's Animals: Uncommon Model Organisms in Genetic Research," available at: <https://www.synthego.com/blog/crispr-animals>.
- Terry, M. 2020. "Allergan and Editas dose first patient in historic CRISPR trial for inherited blindness." *Biospace*, available at: <https://www.biospace.com/article/allergan-and-editas-dose-1st-patient-in-crispr-trial/>.
- Thompson N and Zyontz S. 2020. "Decomposing the "Tacit Knowledge Problem." Codification of Knowledge and Access in CRISPR Gene-Editing". Available at SSRN: <https://ssrn.com/abstract=3073227> or <http://dx.doi.org/10.2139/ssrn.3073227>.
- UBS. 2018. "China's biotech revolution." *UBS Chief Investment Office*, available at: <https://www.ubs.com/global/en/wealth-management/chief-investment-office/market-insights/regional-outlook/2018/china-biotech.html>.
- U.S. National Library of Medicine. n.d. "Trends, charts, and maps." *ClinicalTrials.gov*, available at: <https://clinicaltrials.gov/ct2/resources/trends#TypesOfRegisteredStudies>.
- Vertex. 2020. "CRISPR Therapeutics and Vertex Announce New Clinical Data for Investigational Gene-Editing Therapy CTX001™ in Severe Hemoglobinopathies at the 25th Annual European Hematology Association (EHA) Congress." Press release, available at: <https://investors.vrtx.com/news-releases/news-release-details/crispr-therapeutics-and-vertex-announce-new-clinical-data>.
- Wang, Y., X. Cheng, Q. Shan, Y. Zhang, J. Liu, C. Gao, and J. L. Qiu. 2014. "Simultaneous editing of Three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew." *Nature Biotechnology* 32(9): 947–951.
- World Health Organization (WHO). 2020. "Number of clinical trials by year, country, WHO region and income group (1999-2019)." Available at https://www.who.int/research-observatory/monitoring/processes/clinical_trials_1/en/.
- World Intellectual Property Organization (WIPO). 2020. "Patent family by origin (2012-2018)." WIPO IP Statistics Data Center, (updated April 2020). Available at: <https://www3.wipo.int/ipstats/index.htm?tab=patent>
- Zyontz S. 2016. "Technological breakthroughs, entry, and the direct of scientific progress: Evidence from CRISPR/Cas9." Working paper.
- Zyontz S. 2019. "Making the Cut: The Rate and Direction of CRISPR Innovation." MIT PhD Thesis. Available at: <https://dspace.mit.edu/handle/1721.1/123571>.
- Zyontz S and Neil T. 2020. "Who Experiments vs. Expands the Research Frontier? Evidence from the DNA-editing technology, CRISPR." Working paper.