



**HAL**  
open science

## Worldwide CRISPR patent landscape shows strong geographical biases

Jacqueline Martin-Laffon, Marcel Kuntz, Agnès Ricroch

► **To cite this version:**

Jacqueline Martin-Laffon, Marcel Kuntz, Agnès Ricroch. Worldwide CRISPR patent landscape shows strong geographical biases. *Nature Biotechnology*, 2019, 37 (6), pp.613-620. 10.1038/s41587-019-0138-7. hal-02148307

**HAL Id: hal-02148307**

**<https://hal.science/hal-02148307>**

Submitted on 26 Oct 2020

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# 1 **Worldwide CRISPR patent landscape shows strong geographical biases**

2 Jacqueline Martin-Laffon, Marcel Kuntz and Agnès E. Ricroch

## 3 **Abstract**

4 We performed an exhaustive compilation of patents involving a CRISPR gene editing system  
5 and categorized them following a thorough analysis of their abstract, description and claims.  
6 This landscape of CRISPR patenting shows that the technology is constantly being improved  
7 and that there is a diversity of potential sectors of application (medical, industrial,  
8 agriculture), of actors (both public and private) and a novel geopolitical balance of forces in  
9 this crucial new biotechnological field. Although laboratories in the USA played a pioneer  
10 role in the original invention, and USA remains a leader in technical improvements and in the  
11 medically applied sector, China is now taking the lead in the industrial and agricultural  
12 applied sectors and in the total number of patents per year. Strikingly, in all sectors, the  
13 number of CRISPR patents originating from Europe trails far behind the USA and China.  
14 Korea and Japan are next in this ranking.

15

16

17 On August 17, 2012 Jennifer Doudna's group (University of California–Berkeley, USA) and  
18 Emmanuelle Charpentier (Umeå University, Sweden; formerly in Vienna, Austria) highlighted  
19 the underlying molecular mechanisms of the CRISPR system (Clustered Regularly Interspaced  
20 Short Palindromic Repeats)<sup>1</sup>. They demonstrated that this system can be used to produce  
21 double-stranded cuts at any precise site of DNA in prokaryotic cells by combining a RNA  
22 guide with an endonuclease protein (Cas9, CRISPR-associated protein 9 nuclease). Prior to  
23 this publication, on May 25, 2012, UC-Berkeley, the University of Vienna and Jennifer  
24 Doudna had filed a patent application (2012US-61652086) describing the methods and  
25 applications for this RNA-directed site-specific DNA modification. On the other hand, the  
26 groups of Feng Zhang at the Broad Institute of MIT and Harvard University, USA<sup>2</sup> and George  
27 Church at Harvard University, USA<sup>3</sup> demonstrated that the CRISPR system can be used to  
28 modify eukaryotic cells of mammals, including humans. On December 12, 2012, the Broad  
29 Institute, MIT and Feng Zhang filed a patent application (2012US-61736527) describing the  
30 invention of mammalian genome editing.

31 The legal battles around these patents have attracted media attention (4, 5, Sherkow 2018).

32 However, as pointed out by Parthasarathy (2018), “besides innovation protection the patent

33 system can lead to higher prices for products, reduce people’s access to important  
34 technologies if inventors use them to establish and maintain monopolies, and can shape  
35 innovation trajectories”. Thus, a CRISPR gene editing patent landscape<sup>6</sup> is highly desirable  
36 for reasons that go far beyond intellectual property.

37 Here we present a compilation of relevant patents in this field and have classified them in  
38 order to shed more light on the concerned technical fields and on the geographical origins of  
39 these patents. This unique resource can be screened for further parameters. The presented  
40 data confirms that the CRISPR system has continued to spread rapidly. It seems legitimate to  
41 say that it has revolutionized the biological science of genome editing. Our data also  
42 document the geopolitical balance of forces in this promising new biotechnological field.  
43 Two contextual aspects are particularly worth keeping in mind, namely that in recent years  
44 China has massively invested in biotechnology, while Europe suffered from disinvestment  
45 especially in agricultural biotechnology as a consequence of the “GMO” backlash.

46

#### 47 **Can one create an exhaustive CRISPR patent list?**

48 Patents related to the CRISPR system have been searched by the querying of 3 databases,  
49 using criteria listed in **Box 1**, up to December 31, 2017 as a priority date. This search was first  
50 limited to the patent title and abstract, in order to maximize the relevance of the data.  
51 Patent families (containing all patent extensions of a given invention) were first collected in  
52 Orbit Intelligence. A thorough manual clean-up of these results was performed to eliminate  
53 duplicates and false positives as described in **Box 1** (using inclusion and exclusion criteria  
54 exemplified in **Supplementary file 1**). Similarly, entries were collected from two other  
55 databases (PatentPulse and Patent Lens). A manual comparison of the obtained data sets  
56 showed that Orbit Intelligence provided the largest, although not completely exhaustive, set  
57 (only 1% of the patent families were not obtained via Orbit Intelligence and were identified  
58 in at least one of the other two databases). A total of 1469 patent families was thus  
59 compiled at the end of this first patent search step. However, it appeared that to ensure  
60 maximal exhaustivity, a second search querying descriptions and claims of the patents  
61 (excluding titles and abstracts) was necessary. As expected, this second search yielded many  
62 more entries (>10000) of which a large majority were false positives. A first manual clean-up  
63 removed entries unrelated to gene editing. A second sorting separated the remaining

64 patents into two groups using the same exclusion/inclusion criteria as for the first search.  
65 The group of excluded patents contained 709 entries. Typically these patents focused on a  
66 new phenotype or production method for which CRISPR gene editing was simply mentioned  
67 as one possible means (amongst others) to implement the invention. These excluded  
68 patents, whether from the first or second search, are not further analyzed here. After  
69 removing redundancies, the second group (included patents) contained 603 patent families  
70 which were collated to the 1469 patent families selected from the first search. These 2072  
71 patent families are considered as *bona fide* CRISPR gene editing patents since their  
72 description/claims specifically focus on a CRISPR-type system, including a more or less  
73 detailed description on how to use this system to implement the described invention (see  
74 **supplementary file 1** for criteria used for inclusion in this group). Their compilation (Table in  
75 **Supplementary File 2**) includes patent titles, abstracts, inventors, applicants, priority dates,  
76 as well as the various reference numbers of a given patent (including international  
77 extensions). Whether these patents and their extensions will finally be granted, or not, has  
78 not been included in this table since it would necessitate some time to be completed.

79 In summary, in such a dense patenting landscape, defining *bona fide* CRISPR-type gene  
80 editing inventions is a challenging task relying on defined exclusion and inclusion criteria.  
81 Establishing such a patent list necessitated searching several databases. One cannot rely on  
82 searching titles and abstracts alone and a careful manual clean-up of false positives is  
83 required. In addition, proper integration of entries in their patent families is necessary.

84 This compilation includes the milestone patents discussed in the Introduction (which can be  
85 found by copying the patent numbers in the search option of the file) and others which have  
86 attracted attention as part of the “CRISPR patent struggle” (see  
87 [https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-](https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process)  
88 [process](https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process)), including those rejected by USPTO (*i.e.* Northwestern University’s Application  
89 2008US-61099317; ToolGen’s application 2012US-61717324).

## 90 **CRISPR patent distribution: a diversity of fields but a strong geographical bias**

91 **Supplementary File 2** also compiles the country of invention and reveals that CRISPR patents  
92 were originally filed by 28 countries (**Fig. 1a**). USA and China are clearly the leaders with 872  
93 and 858 patents, respectively. Strikingly, European countries as a whole filed only 194 of  
94 these patents, followed by Korea (75 patents) and Japan (48 patents). 26 patents were co-

95 deposited by inventors from the USA and other countries (Switzerland (6), Japan (4),  
96 Netherlands (3), Germany (2), Russia (2), Austria (1), Belgium (1), Canada (1), China (1),  
97 France (1), Israel (1), New Zealand (1) and United Kingdom (1). 6 patents were co-deposited  
98 by other countries (China/Israel, China/United Kingdom, China/Taiwan, Denmark/Canada (2)  
99 and Switzerland/Germany).

100 To evaluate more accurately the respective weight of each country, it is necessary to take  
101 into account the delay of 18 months before publication of a patent (see **Box 1**) and the fact  
102 that many Chinese patents were actually published before this delay, thus artificially  
103 increasing their weight in **Supplementary File 2**. Therefore, patent numbers per countries  
104 were compared at two different time points (**Fig. 1a**). One was priority date December 31,  
105 2017, which actually reflects those patents publicly available on November 30, 2018, the  
106 latest update of **Supplementary File 2**. The second is priority date May 2017, the most  
107 recent date for accurate geographical comparisons since it takes into account the 18 month  
108 delay in publication with respect to the latest update of Supplementary file 2. At this latter  
109 time point, inventors from the USA filed 47.8% of the patents, China 34%, Europe 10.4 %,  
110 Korea 3.8% and Japan 2.6%. 33% of these patents (up to May 2017) were deposited by  
111 private firms.

112 Patenting rate per year (**Fig.1b**) shows that the USA had an early leadership, as expected, but  
113 that the patenting rate from China is steadily increasing. For this criterion, China has taken  
114 the lead over the USA in 2016.

115 As already shown<sup>6</sup> USA major patent holders are the Massachusetts Institute of Technology  
116 (MIT, 113 patents), Harvard College (109 patents, 34 co-deposited with MIT), Broad Institute  
117 (86 patents, most of them co-deposited with MIT), University of California (73 patents) and  
118 Editas Medicine (43 patents). What has not been shown before is that China takes an  
119 important place in this ranking: Chinese Academies of Sciences and Agricultural Sciences  
120 (182 patents filed), China Agricultural University (35), Shanghai Institute for Biological  
121 Sciences (27), Shanghai Jiao Tong University (24), Sun Yat Sen University (17), University of  
122 Beijing (17) and Second Peoples Hospital of Shenzhen (14). Regarding private firms well  
123 known for their marketing of transgenic products, it is interesting to note that DuPont-  
124 Pioneer filed 20 patents, Monsanto 4, Bayer 1, and Syngenta 1.

125 To refine this patenting landscape from a technical point of view, these patents were  
126 manually sorted into various categories (see color codes in **Supplementary File 2** and **Fig.**  
127 **2a**). It was obvious that many patents describe technical improvements at large of the  
128 CRISPR system, which can potentially be used for many practical purposes. Thus, such  
129 patents were classed in a specific “technical improvements” category, which contains 942  
130 out of the 2072 patent families. A second important category relates directly to medical  
131 purposes. Other patents describe industrial applications or agricultural applications; the  
132 latter can be subdivided as either related to plants or farm animals/aquaculture. An  
133 additional set of patents were classed in a category describing “other in vitro use” of  
134 components of the CRISPR system (*e.g.* DNA assembly, splicing, analysis, isolation, or linker  
135 removal, or CAS 9 assays). Using this type of categorization, only 7 patents were allocated to  
136 two categories (identified in **Supplementary File 2** by a gradient in the corresponding color  
137 codes).

138

### 139 **A technological field still in quest of technological improvements**

140 Admittedly, there is a certain level of subjectivity in this classification since all CRISPR  
141 patents could be considered as providing “technical improvements”. However, patents  
142 included in this category focus their claims on general methods (often for research), while  
143 patents with claims directly related to one of the above-mentioned specific applications (*i.e.*  
144 medical, industrial or agricultural) were excluded. Inclusion and exclusion selection criteria  
145 are exemplified in **Supplementary file 1**.

146 The USA has not only been a pioneer in gene editing using CRISPR but is still a leader for  
147 improvements of this technical development with 479 patents compiled in this category (**Fig.**  
148 **2b**). China is the second largest depositor (306 patents), while European countries again trail  
149 behind with only 91 such patents. Some patents were co-deposited by inventors from the  
150 USA and from other countries (Japan: 4 patents, Switzerland: 4, Netherlands: 2, France: 1,  
151 Austria: 1, and Germany: 1). 1 patent was co-deposited by Switzerland and Germany, and 1  
152 patent by China and Thailand. For the reason mentioned above, when patents in this  
153 category were compared up to the priority date of May 2017 (**Fig. 2b**), it appears that the

154 respective weights of the USA, China and Europe are 57%, 24.9% and 10.5 %. The private  
155 sector filed 32% of these patents (up to May 2017).

156 By nature, this category is quite diverse and it required further sorting into sub-categories  
157 (see **Supplementary File 2** and its color codes). They consist of either general methods for  
158 improving CRISPR/cas9-mediated genome-editing without species restriction, or are linked  
159 to a given species or a group of species (namely mammals including humans, fish, other  
160 animals, fungi, micro-algae, or prokaryotes) or to mitochondria, or methods to favor knock-  
161 out or rather homologous types of editing, or chromosome translocation. Other sub-  
162 categories were created as follows. Although most patents in the previous sub-categories  
163 include methods for delivery to cells, some patents specifically focus on improvements of  
164 such delivery. Other patents describe CAS9 variants or the use of other nucleases (including  
165 Cpf1) or improvements in the guide RNAs and multiple gene editing (multiplexing).  
166 Importantly, some patents claim reducing off-target editing (or detection of off-target  
167 editing). Other applications are also described such as epigenome editing, RNA editing or  
168 other miscellaneous uses (including genomic screening/gene detection, cell sorting and gene  
169 drive).

170 Patents filed before the milestone inventions mentioned in the Introduction were also  
171 included as a sub-category (and termed “early development” in **Supplementary File 2**).  
172 These include descriptions of CAS nucleases, guide RNA delivery vehicles, or use of CRISPR  
173 sequences. Included in this sub-category is the Vilnius University’s patent (2012US-  
174 61613373) describing *in vitro* “RNA-directed DNA cleavage by the Cas9-crRNA complex”  
175 (which was filed just before the Berkeley patent mentioned in the Introduction).

176 Note that we have chosen to include technical improvements directly related to agricultural  
177 organisms (131 patent families) as a sub-category in the agricultural category for reasons  
178 explained below. However, when added to the “technical improvement” category, the total  
179 amount of patents in the latter category is then 1073 patents out of 2072 in **Supplementary**  
180 **File 2**.

181 **A wealth of health applications**

182 This “medical” category groups patents (554 patent families out of 2072 in **Supplementary**  
183 **File 2**) claiming the use of CRISPR for a wide spectrum of explicit health goals, such as  
184 engineering human cells to treat a disease or controlling a human pathogen. Patents  
185 describing upstream medical research tools, such as edited human cell lines, or animal  
186 models for human diseases, or animal sources for xenotransplantation were also included in  
187 this category. Patents related to classical pharmaceutical purposes or nutrition are analyzed  
188 separately (see below). Three patents were classed in both ‘medical’ and ‘plants’ categories  
189 and one in both ‘medical’ and industrial applications’. Five patents were co-deposited by  
190 inventors from the USA and either from Belgium, China, Germany and Switzerland (2  
191 patents).

192 For geographical comparison (**Fig. 2c**) comparison was also up to May 2017 (502 patents).  
193 The USA is the leader with 49% of patents deposited, followed by China (32%), Korea  
194 (13.5%), Europe (10.5%, with Switzerland alone representing 7%), Japan and Canada (7.4%  
195 each). Private companies filed 37.6% of these 502 patents.

196 An impressive number of a hundred diseases covering most categories of the international  
197 classification of diseases (<http://www.who.int/classifications/icd/en/>) are concerned with  
198 CRISPR technology patents (see color codes in **Supplementary File 2**). Cancer alone  
199 represents 131 patent families, of which 31 describe immunotherapy approaches (*e.g.* using  
200 chimeric antigen receptor (CAR)-modified T lymphocytes; see<sup>7</sup>) for selectively eliminating  
201 cancerous or other pathogenic cells. 59 patent families on cancer applications of CRISPR  
202 technology were filed by China, dominated by the public sector (Universities, Chinese  
203 Academy of Science, Research Institutes). It is important to note the recent creation of  
204 around fifteen Chinese private firms, which have filed patents concerning cancer  
205 applications of CRISPR technology since June 2015 (such as Anhui Kedgene Biotechnology,  
206 Biotowntek, Chengdu Keli Bo Biotechnology, Chongqing Gaosheng Biological Pharmaceutical,  
207 Guangzhou Huiyuanyuan Pharmaceutical Technology, Nanjing Kaidi Biotechnology, & Yuan  
208 Biotechnology). The USA is the second country filing such “cancer” patents (54 patent  
209 families), mainly represented by universities or research institutes, but also by private firms,  
210 such as Agenovir, Batu Biologics, Editas Medicine, Intima Bioscience, Juno Therapeutics,  
211 Grail, Nantomics, Nuon Therapeutics, Sandia Corporation. Europe is only represented by  
212 Denmark (1 patent filed by Frost Habib), France (4 patents filed by Collectis, 1 patent filed by



213 Inserm/Rennes and Bordeaux Universities/Institute Bergonie), Germany (1 patent filed by  
214 Amgen Research Munich), Switzerland (1 patent co-deposited with USA Novartis/Intellia  
215 Therapeutics) and United Kingdom (1 patent filed by Phoremest).

216 112 patents in Supplementary file 2 describe methods for treating viral infections:  
217 Cytomegalovirus, Hepatitis B, Hepatitis C, Herpes simplex, Human immunodeficiency virus  
218 (HIV), Human papilloma virus, Human T-cell Leukemia, Influenza B, Poliovirus, Varicella  
219 zoster, and Zika virus. An often used strategy is the *ex vivo* modification of T-cells to knock  
220 out the *CCR5* gene, resulting in resistance to HIV infection<sup>7</sup>. Out of the patents claiming  
221 treatment of viral diseases using CRISPR technology, 62 originated from USA and are well  
222 distributed between public (University of Temple alone holds 18 patents) and private sectors  
223 (Agenovir, 11 patents; Editas Medicine, 7 patents; Excision Biotherapeutics, 6 patents;  
224 Nantomics, 1 patent). 41 such patents originate from China, mostly filed by the public sector,  
225 but also by private firms such as Biotowntek, Guangdong Chi Meng Medical Technology,  
226 Guangzhou Zeesan Biotechnology, Shanghai Jie Yi Biotechnology, Shanghai Jinwei  
227 Biotechnology, and Wuhu Inno Biotechnology. Only 5 other countries are included in this  
228 sub-category: France (Cellestis, 3 patents; INSERM/ Nantes University, 1 patent), Canada  
229 (Protiva Biotherapeutics, 1 patent), Japan (Aichi Prefecture, 1 patent), Korea (Yonsei  
230 University, 1 patent) and Russia (Federalnoe Byudzhetnoe Uchrezhdenie Institute  
231 Epidemiologii, 1 patent).

232 Other patents describe gene therapy methods, such as gene replacement in somatic cells<sup>7</sup>.  
233 They concern Alzheimer's disease and other nervous system disorders such as Huntington's  
234 disease, autism and other psychiatric diseases, autosomal dominant diseases, blood diseases  
235 (e.g. beta-thalassemia, anemia), diseases of the musculoskeletal system (e.g. bone diseases  
236 and rheumatoid arthritis), muscular dystrophies (e.g. Duchenne's disease), nucleotide repeat  
237 disorders, retina or other ocular diseases (e.g. glaucoma). Some patents describe induced  
238 pluripotent stem cells (iPSC) modifications for *ex vivo* therapy<sup>7</sup>.

239 Other patent claims include gene knock-out use, for example to treat allergic, endocrine,  
240 nutritional and metabolic diseases (diabetes, cystic fibrosis, hypercholesterolemia,  
241 hyperlipidemia, obesity, etc.), coronary atherosclerotic heart disease and other  
242 cardiovascular disease prevention, destruction of senescent cells, or targeting metastasis-  
243 related genes. Other patents concern treatment of infection by resistant bacteria. Some

244 patents claim improved delivery to cells of gene editing components, or transplantation  
245 improvements.

246 The USA and China are again dominant for these medical patent sub-categories (excluding  
247 cancer or virus applications) with respectively 134 and 113 patents filed. As for the cancer  
248 and virus sub-categories, USA and China are mainly represented by public research  
249 institutes or universities, but also by private firms, such as Editas Medicine, Sangamo  
250 Therapeutics, Intellia Therapeutics (USA), and Beijing Biocytogen, Generos Biopharma,  
251 Suzhou Tongshan Biotechnology (China). 45 of such patents were filed by European  
252 countries, mostly represented by Switzerland with 33 patents filed (CRISPR Therapeutics: 29  
253 patents for several neurological, blood and metabolic diseases; Centre Hospitalier  
254 Universitaire Vaudois: 1 patent for Huntington' Disease; University of Basel: 1 patent on cell  
255 therapy; University of Lausanne: 1 patent for DNA-triplet repeat diseases; Novartis/Intellia  
256 Therapeutics (co-deposited with USA): 1 patent for blood disease). Korea is taking a growing  
257 place with 19 patents recently filed by public and private sectors, concerning a wide range  
258 of diseases (Industry Academic Cooperation Foundation, Institute for Basic Science, Korea  
259 Research Institute of Bioscience and Biotechnology, Moogene Medi, MGEN Plus, Seoul  
260 National University Hospital, Toolgen and Yonsei University). Canada is also represented  
261 with 8 patents (University of Laval, Hospital for Sick Children and Protiva Biotherapeutics)  
262 concerning neurological and muscular diseases and delivery of CRISPR therapeutics.

263 Note that 187 patent families in the sub-categories "Mammals, including Humans" or  
264 "Knockout technique (mammals)" of the above-mentioned "technical improvements"  
265 category of **Supplementary File 2** may have implications for human health (although less  
266 direct, hence their classification as "technical improvements"). This also holds true for a sub-  
267 category in the "industrial applications" category (see below) describing a number of  
268 pharmaceutical applications (65 patent families). These health-related sub-categories can be  
269 identified by the same specific color code as the patents in the "medical" category in  
270 **Supplementary File 2**. Taking into account all these patents leads to a noteworthy number  
271 of 806 patent families out of 2072 directly or indirectly related to human health.

272 **Industrial applications for CRISPR**

273 Industrial applications of the CRISPR system through metabolic engineering has been  
274 reviewed<sup>10</sup>. In our compilation this category contains fewer patents (167 patent families;  
275 **Supplementary File 2, Fig.2a**) than the previous ones, most likely because it often involves  
276 microorganisms for which there are many other effective methods of genome modification  
277 including homologous recombination. Microorganisms are either fungi or bacteria  
278 (*Lactobacillus buchneri*, *Riemerella anatipestifer*, *Saccharomyces cerevisiae*, *Salmonella*,  
279 *Streptomyces virginiae*). Patent claims include the identification of serotypes, growth of  
280 microorganisms and suppression of resistance to antibiotics, biofuel production or increased  
281 production of molecules of interest. Two patents classed in an “aroma/taste” sub-category  
282 involve mammalian cells: one filed from Switzerland describes the use of human embryonic  
283 kidney cells to functionally express odorant receptor proteins on the cell surface for high-  
284 throughput screens of volatile flavor and fragrance compounds and one filed from Germany  
285 describes the activation of taste receptor genes in mammalian cells. Use of animal cells is  
286 also described for manufacturing skeletal muscle for dietary consumption, as well as a  
287 method using edited mouse or human cells as part of a kit for detecting pyrogen, not to  
288 forget hypoallergenic cats. Some patents are also related to silk production. Pharmaceutical  
289 applications (65 patent families) relate to production of antibodies, vaccines or other  
290 product (note that a majority, 31 patents, originated from China, and only 18 from the USA,  
291 7 from Europe, 6 from Korea, 1 from Israel, Japan, and Singapore). 9 patents are related to  
292 nutrition (*i.e.* 5 patents from China, 2 from the USA and 2 from Korea).

293 Considering all patents in this “industrial” category shows that they originated from China,  
294 USA, Europe and 6 other countries (**Figure 2d**). After comparison up to May 2017 as a  
295 priority date (148 patents), it appears that China is leading this category (38.5%), followed by  
296 the USA (33%), while patents from European origin represent only 15.5% (of which Denmark  
297 alone contributes to 5.4%) for this category. One patent was co-deposited by inventors from  
298 the USA and from New Zealand. Private firms filed 34.5% of these patents.

299

### 300 **CRISPR patents in relation to agricultural organisms**

301 Since the “GMO” controversy has largely limited agricultural applications of biotechnology  
302 and is similarly threatening CRISPR use<sup>11</sup>, we decided to analyze as a distinct category of

303 patents in **Supplementary File 2** those related either to “farm animals”, including  
304 aquaculture (a total of 85 patent families), or to “plants” (267 patent families). Only 5 of the  
305 “plant” patents have a dual categorization (three in both “plants” and “medical”, one for  
306 both “plants” and “farm animals” and for both “plants” and “technical improvements”).  
307 CRISPR patents in relation to agricultural organisms appeared from September 2012 for  
308 plants (Dow Agrosiences/Sangamo Biosciences, USA) and from February 2014 for farm  
309 animals and aquaculture (Qingdao Institute of Animal Husbandry Veterinary Medicine,  
310 China). As expected, the number of such patents published since has grown steadily: 11 in  
311 2013, 35 in 2014, 63 in 2015, 112 in 2016, and 128 (data incomplete) in 2017.

312 As mentioned above, some patents describe general “technological improvements”, *i.e.* not  
313 linked to a precise applied goal (but which nevertheless can relate to a given species,  
314 predominantly pig for animals but also cow, buffalo, goat, sheep, chicken, birds and fish, and  
315 mainly rice for plants but also 11 other plant species). The reason for not grouping these  
316 agricultural technical improvements with the above-mentioned “technological  
317 improvement” category is that agricultural biotechnologies may be more controversial than  
318 other biotechnologies (and this could translate in differential involvement of countries).  
319 Some other patents, without direct agricultural application, such as the use of plants for  
320 molecule production, or specific metabolic changes, or as a research model (Arabidopsis,  
321 barley and rice) were grouped in this plant category.

322 The largest plant sub-category describes direct claims for plant breeding (130 patents), with  
323 rice being dominant (64 patents). Only 11 patents were filed for maize, 5 for wheat, 4 for  
324 tomato, 3 for potato, 2 for tobacco and 1 each for cotton, nut grass, oilseed plants, sorghum,  
325 and pasture plants. These patents concern male-sterility (16 patents), herbicide-tolerance (6  
326 patents), virus resistance or detection (9 patents, including 1 for detection and 2 for tobacco  
327 and tomato), fungi, bacteria and pests resistance, plant stature/architecture, flowering time,  
328 pollination and fertility parameters, plant aging and fruit shelf-life, haploid breeding, seed  
329 quality or shattering, metabolic changes, yield, stress resistance and plant crossing.  
330 Considering the potential of genome editing for improved animal breeding<sup>12</sup> it was to be  
331 expected that the largest animal sub-category also relates to breeding (50 patents), with pig  
332 being dominant (22 patents), followed by sheep (12 patents), mammals in general (5  
333 patents), fish (4 patents), birds (3 patents), goat (2 patents), cow and rabbit (one patent

334 each). Applications concern fertility, meat production, milk quality, resistance to various  
335 diseases, including resistance to viruses, and sheep wool color.

336 The geographical origins of these patents are shown in **Fig. 2e**. After analysis up to the  
337 priority date of May 2017 (215 'plant' patents and 64 for 'farm animal' patents), it appears  
338 that China is leading this plant category (60.5%), followed by the USA (26%), while patents  
339 from European origin represent only 8% (17 patents of which Germany and The Netherlands  
340 contributed to 6 and 5 patents, respectively). Japan and Korea represent 2.3% each (5  
341 patents). For farm animals, the Chinese leadership amounts to 87.5%, with 8% for the USA,  
342 and a single patent for Australia, Israel, Japan and UK. Three patents were co-deposited  
343 respectively by inventors from China and UK, Denmark and Canada; USA and Netherlands for  
344 'plants'. One was co-deposited (UK and USA) for 'farm animals'. Private companies filed 27%  
345 and 5% of these 'plant' and 'farm animal' patents, respectively. Private companies with the  
346 most deposits are Dupont Pioneer (USA; 12 patents), KWS Saat (Germany; 5 patents),  
347 Keygene (Netherlands; 4 patents), Dow Agrosiences (USA; 3 patents), Beijing DBN  
348 Technology (China; 3 patents). Public depositors are mostly represented by Chinese public  
349 organizations: China Agricultural University and Institute of Genetics and Development  
350 Biology/Chinese Academy of Sciences (14 patents each), Anhui Academy of Agricultural  
351 Sciences (11 patents), Institute of Cropscience/Chinese Academy of Agricultural Sciences (10  
352 patents). University of California is the most important USA depositor for agricultural sector  
353 with 9 patents filed.

## 354 **Discussion**

355 The CRISPR system is at the origin of an ever increasing flux of patented inventions.  
356 Compiling all CRISPR related patents is of obvious importance for industrial strategical  
357 planning and other reasons discussed below, but has proven to be excessively difficult. The  
358 step by step method described here for CRISPR patent compilation highlights the challenges  
359 to reach exhaustivity. Consequently, most previous CRISPR patent compilations have relied  
360 on a small subset of such patents. The present compilation independently yielded a patent  
361 family number close to that of Egelie *et al.*<sup>6</sup> up to 2015, and extended the list up to  
362 December 31, 2017 (priority date; as publicly available on November 30, 2018). A second  
363 challenge, of semantic nature, concerns the definition of a *bona fide* CRISPR-related gene

364 editing invention: many patents seem to mention CRISPR and other related keywords to  
365 extend the scope of their claims, while this technology is not central to the described  
366 invention. Therefore, our detailed analysis focused on what we considered as *bona fide*  
367 CRISPR patents, namely that their claims specifically focus on a CRISPR-type system to  
368 implement the invention (see our criteria in **Supplementary file 1**).

369 A more detailed analysis of these patents revealed what can be described as a rush to  
370 improve the technology itself (942 patent families out of a total of 2072), while other  
371 patents claimed a direct specific applied purpose. Therefore, we classed the first group as  
372 'general technical improvements', and subdivided the other CRISPR patents as either directly  
373 related to medical purposes, or to industrial (including pharmaceutical) applications, or to  
374 agricultural purposes, following technical criteria explained above. Such a separation is  
375 inevitably a matter of interpretation but a classification into categories and then into sub-  
376 categories appeared useful to highlight the diverse applications of CRISPR gene editing. Note  
377 that **Supplementary file 2** contains specific color codes which help the visualization of  
378 related patents despite the fact they were classed in different categories (*e.g.* for health:  
379 medical- and pharmaceutical-related patents share the same color code; farm animal/plant  
380 patents with technical improvements share the same color code as the technical  
381 improvements category). It should also be noted that the categorization chosen here on a  
382 technical basis is not at odds with our geographical comparison (for example, 'medical'  
383 patents are dominated by the USA, while "industrial" patents are dominated by China, as are  
384 pharmaceutical patents that we chose to add to this "industrial" category).

385 In our opinion, these inventions are also revolutionizing the plant and animal breeding  
386 sectors. It can be noted, for example, that CRISPR patents involve polyploid organisms such  
387 as wheat (resistance to a geminivirus) or autopolyploids such as carp (resistance to KH virus).  
388 However, the CRISPR system still has limitations. It can be seen from this present study that,  
389 to date, the modifications concern primarily single-gene characters which are often  
390 inactivated (by knock-out of the responsible gene). However, some patents do describe  
391 gene insertion or gene overexpression (*e.g.* by insertion of a particularly strong promoter or  
392 intervention on regulators / promoters such as the suppression of an interfering RNA).  
393 Although the CRISPR system is very effective for this type of operation, the number of

394 interesting monogenic traits to be modified for agriculture remains limited. Indeed, most  
395 characters of an organism are controlled by a multitude of genes (and with a quantitative  
396 effect) and, as such, the CRISPR system cannot effectively act on the character in the present  
397 state of art (a better knowledge of the relevant genes is required). In this context, it can be  
398 noted that while the keywords ‘knock-out’ or ‘knockout’ appear 28 times in the “plant”  
399 category (**Supplementary file 2**; titles and abstract alone), ‘multiplexing’ or ‘multi-target’ (*i.e.*  
400 the simultaneous modification of several loci of the same genome) only appear 4 times  
401 highlighting the further necessity for technical improvements.

402 The current licensing strategy of various companies regarding patents in the CRISPR field has  
403 already been analyzed<sup>6,10</sup> and will not be discussed here. The fact that this molecular chisel  
404 operates directly on the genome raises ethical issues that will affect the development of  
405 CRISPR research and the publication of patents, particularly in animals  
406 (<http://nuffieldbioethics.org/project/genome-editing>). Regarding public health, Sherkow<sup>14</sup>  
407 argued that health-related patents may contribute to high prices for novel therapies which  
408 may limit their availability for patients and may also lead to the allocation of research and  
409 development resources to profitable diseases. The same author also discussed the ethical  
410 implications of CRISPR patenting<sup>15</sup> and “lessons about science and society”<sup>16</sup>. The present  
411 compilation and further updates will allow documented discussions about these ethical  
412 issues.

413 Obviously, the regulatory status of gene-edited organisms will impact on further  
414 developments of the technology. The recent ruling by the Court of Justice of the European  
415 Union that precise gene-editing technologies, such as CRISPR–Cas9, would not be exempted  
416 from European “GMO” law will be detrimental to this respect (Callaway 2018). Their  
417 marketing as “GMOs” will be very costly and submitted to political opposition. This will limit  
418 public laboratory research, which filed most CRISPR patents to date (1344 patent families  
419 out of 2072; 70 by individuals and 64 by both public and private sectors).

420 More and more voices are asking for a revision of the current European “GMO” Directive<sup>11</sup>.  
421 However, our present analysis shows that the damage has already been done in Europe: the  
422 number of CRISPR patents originating from this continent is trailing far behind the USA and  
423 China. This trend concerns all patent categories defined here, including those related to

424 health (despite the fact that it is not the most controversial). Rodríguez-Navarro and Narin<sup>13</sup>  
425 showed that “Europe lags far behind the USA in the production of important, highly cited  
426 research”. They concluded that “there is a consistent weakening of European science” which  
427 they attribute to the funding systems. The problem may be more widespread and could be  
428 attributed to a hostile cultural (“precautionary”) climate against innovations, including  
429 biotechnology<sup>17</sup>. It would be a delusion not to consider that the GMO bans in Europe have  
430 not had a strong negative impact on the future of biotechnology in this continent (including  
431 in relation to health aspects). The definition of what is patentable (which includes “ethical”  
432 considerations) in Europe vs. in other parts of the world may also add to the European  
433 ‘cultural’ naivety in the current economical ‘war’. The cost of EU patent protection was  
434 estimated to be 18-20 times more than in the U.S. Although this may no longer be the case  
435 with the new European unitary patent system (Belda et al. 2014), a reluctance to file patents  
436 may persist for all the above-mentioned factors. Whatever their relative contribution, an  
437 overall consequence is a long-term trend of patent number (all types of patents) granted by  
438 the EPO trailing far behind the number granted by the USPTO  
439 ([http://www.wipo.int/edocs/pubdocs/en/wipo\\_pub\\_941\\_2017.pdf](http://www.wipo.int/edocs/pubdocs/en/wipo_pub_941_2017.pdf)). Thus, the USA vs. Europe  
440 differential trend in the CRISPR case was not unexpected.

441 Regarding China, its patent office surpassed the EPO already in 2005 and the USPTO in 2011  
442 in terms of patents per year. In addition, an overwhelming Chinese patent owners are  
443 Chinese, while the ratio between ‘resident’ and ‘non-resident’ are about equal for EPO and  
444 USPTO (see link above). However, it was unexpected that this general trend would reflect in  
445 the CRISPR patents so soon: there have been some earlier publications on the CRISPR  
446 patenting landscape which considered its geographical aspects<sup>6, 10, 18</sup>, but to our knowledge  
447 none had pointed out that China has taken the lead over the USA in terms of patents per  
448 year. This can be explained by the massive investment in biotechnology in China. An  
449 example (in the agricultural field) of a technical incentive for China’s investment could be the  
450 national importance of pig farming and rice cultivation, and the fact that they are threatened  
451 by diseases and pests. It is also likely to be the product of its new patenting strategy. China  
452 issued its first patent law in 1984 and revised it in 1992, 2000, 2008 and 2016  
453 ([http://www.ipwatchdog.com/2015/12/18/chinese-patent-law-amendments-  
454 proposed/id=63981/](http://www.ipwatchdog.com/2015/12/18/chinese-patent-law-amendments-proposed/id=63981/)). China enacted a patenting system which can be considered as an



455 economical protectionist tool<sup>19</sup>. The essentially domestic purpose of patents is corroborated  
456 by the fact that Chinese CRISPR patents are rarely extended to other countries. In a dense  
457 patenting landscape, foreign companies operating in this field could be deterred from  
458 exporting to China, or at least would have to pay royalties to access the Chinese market.

459 In conclusion, this compilation and classification of CRISPR-type gene editing patents  
460 worldwide shows an impressive stream of highly diverse applications and an unexpected  
461 switch in the balance of forces in favor of China, while providing no indication that Europe,  
462 which has lost the “GMO” battle, is in a position of regaining forces in this new biotech  
463 battlefield. The information provided here makes it possible to identify key inventors, the  
464 most prolific actors, and to further analyze innovative environments. It could be  
465 complemented by analyzing the maturity of the technology, the strategic trajectories of  
466 actors in the field and of those how fund these actors. It also remains to be determined how  
467 many of these patents will actually be exploited. Since many inventions listed here are  
468 improvements of prior inventions, it will interesting to see how these improvement patents  
469 will lead to litigation, especially in the context of the legal battle surrounding the original  
470 inventions. Although it is not always the case, regulation should be particularly reactive in  
471 order to adapt to the fast evolution of such innovative domains and we believe that such a  
472 patent landscape can contribute to adapt regulation in many regions of the world.

473

#### 474 **Acknowledgements**

475 The contribution of Ulysse Del Ghingaro and Marguerite Jamet to early stages of this work is  
476 gratefully acknowledged. We also thank Michaël Brites Teixeira for helpful comments and  
477 Patent Pulse for having allowed us temporary free access to their database.

#### 478 **References**

- 479 1. Jinek, M. et al. A programmable dual-RNA-guided DNA endonuclease in adaptive  
480 bacterial immunity. *Science* **337**, 816-821 (2012).
- 481 2. Cong, L. et al. Multiplex genome engineering using CRISPR/Cas systems. *Science* **339**,  
482 819-823 (2013).
- 483 3. Mali, P. et al. RNA-guided human genome engineering via Cas9. *Science* **339**, 823-826  
484 (2013).

- 485 4. Harrison, C. EPO revokes Broad's CRISPR patent. *Nat. Biotechnol.* **36**, 209 (2018).
- 486 5. Lim, D. Disruption and development: the evolving CRISPR patent and technology
- 487 landscape. *Pharm. Pat. Anal.* (2018).
- 488 6. Egelie, K.J., Graff, G.D., Strand, S.P. & Johansen, B. The emerging patent landscape of
- 489 CRISPR-Cas gene editing technology. *Nat. Biotechnol.* **34**, 1025-1031 (2016).
- 490 7. Kim, E.J., Kang, K.H. & Ju, J.H. CRISPR-Cas9: a promising tool for gene editing on
- 491 induced pluripotent stem cells. *Korean J. Intern. Med.* **32**, 42-61 (2017).
- 492 8. Maus, M.V. & Levine, B.L. Chimeric antigen receptor T-Cell therapy for the
- 493 community oncologist. *Oncologist* **21**, 608-617 (2016).
- 494 9. Feng, W. et al. The potential of the combination of CRISPR/Cas9 and pluripotent stem
- 495 cells to provide human organs from chimaeric pigs. *Int. J. Mol. Sci.* **16**, 6545-6556
- 496 (2015).
- 497 10. Ferreira, R., David, F. & Nielsen, J. Advancing biotechnology with CRISPR/Cas9: recent
- 498 applications and patent landscape. *J. Ind. Microbiol. Biotechnol.* **45**, 467-480
- 499 (2018).
- 500 11. Ricroch, A.E., Ammann, K. & Kuntz, M. Editing EU legislation to fit plant genome
- 501 editing: The use of genome editing technologies in plant breeding requires a
- 502 novel regulatory approach for new plant varieties that involves farmers. *EMBO*
- 503 *Rep.* **17**, 1365-1369 (2016).
- 504 12. Bhat, S.A. et al. Advances in genome editing for improved animal breeding: A review.
- 505 *Vet. World* **10**, 1361-1366 (2017)
- 506 13. Rodriguez-Navarro, A. & Narin, F. European Paradox or Delusion-Are European
- 507 Science and Economy Outdated? *Science and Public Policy* **45**, 14-23 (2018).
- 508 14. Sherkow, J.S. CRISPR, Patents, and the Public Health. *Yale J. Biol. Med.* **90**, 667-672
- 509 (2017a).
- 510 15. Sherkow, J.S. Patent protection for CRISPR: an ELSI review. *J. Law Biosci.* **4**, 565-576
- 511 (2017b).
- 512 16. Sherkow, J.S., Benahmed-Miniuk, F., Kresz, M., Kanaujiya, J.K. & Southgate, C.D.
- 513 Inventive steps: the CRISPR patent dispute and scientific progress: The recent
- 514 patent decisions about CRISPR tell us a lot about how advances in biology are
- 515 actually made-and how they are not. *EMBO Rep.* **18**, 1047-1051 (2017c).
- 516 17. Kuntz, M. & Berezow, A. Timidity and a hostility to competition have left Europe a
- 517 scientific wasteland. *The Telegraph*, 5 September 2017.
- 518 18. Brinegar, K. et al. The commercialization of genome-editing technologies. *Crit. Rev.*
- 519 *Biotechnol.* 1-12 (2017).
- 520 19. De Rassenfosse, G. & Raiteri, E. Technology protectionism and the patent system: strategic
- 521 technologies in China. *SSRN*, <http://dx.doi.org/10.2139/ssrn.2803379> (2016).