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Abstract

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

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

The legal battles around these patents have attracted media attention (4, 5, Sherkow 2018). However, as pointed out by Parthasarathy (2018), "besides innovation protection the patent system can lead to higher prices for products, reduce people's access to important technologies if inventors use them to establish and maintain monopolies, and can shape innovation trajectories". Thus, a CRISPR gene editing patent landscape[6] is highly desirable for reasons that go far beyond intellectual property.

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

Can one create an exhaustive CRISPR patent list?

Patents related to the CRISPR system have been searched by the querying of 3 databases, using criteria listed in **Box 1**, up to December 31, 2017 as a priority date. This search was first limited to the patent title and abstract, in order to maximize the relevance of the data. Patent families (containing all patent extensions of a given invention) were first collected in Orbit Intelligence. A thorough manual clean-up of these results was performed to eliminate duplicates and false positives as described in **Box 1** (using inclusion and exclusion criteria exemplified in **Supplementary file 1**). Similarly, entries were collected from two other databases (PatentPulse and Patent Lens). A manual comparison of the obtained data sets showed that Orbit Intelligence provided the largest, although not completely exhaustive, set (only 1% of the patent families were not obtained via Orbit Intelligence and were identified in at least one of the other two databases). A total of 1469 patent families was thus compiled at the end of this first patent search step. However, it appeared that to ensure maximal exhaustivity, a second search querying descriptions and claims of the patents (excluding titles and abstracts) was necessary. As expected, this second search yielded many more entries (>10000) of which a large majority were false positives. A first manual clean-up removed entries unrelated to gene editing. A second sorting separated the remaining patents into two groups using the same exclusion/inclusion criteria as for the first search. The group of excluded patents contained 709 entries. Typically these patents focused on a new phenotype or production method for which CRISPR gene editing was simply mentioned as one possible means (amongst others) to implement the invention. These excluded patents, whether from the first or second search, are not further analyzed here. After removing redundancies, the second group (included patents) contained 603 patent families which were collated to the 1469 patent families selected from the first search. These 2072 patent families are considered as *bona fide* CRISPR gene editing patents since their description/claims specifically focus on a CRISPR-type system, including a more or less detailed description on how to use this system to implement the described invention (see **supplementary file 1** for criteria used for inclusion in this group). Their compilation (Table in **Supplementary File 2)** includes patent titles, abstracts, inventors, applicants, priority dates, as well as the various reference numbers of a given patent (including international extensions). Whether these patents and their extensions will finally be granted, or not, has not been included in this table since it would necessitate some time to be completed.

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

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

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

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

deposited by inventors from the USA and other countries (Switzerland (6), Japan (4), Netherlands (3), Germany (2), Russia (2), Austria (1), Belgium (1), Canada (1), China (1), France (1), Israel (1), New Zealand (1) and United Kingdom (1). 6 patents were co-deposited by other countries (China/Israel, China/United Kingdom, China/Taiwan, Denmark/Canada (2) and Switzerland/Germany).
To evaluate more accurately the respective weight of each country, it is necessary to take into account the delay of 18 months before publication of a patent (see **Box 1**) and the fact that many Chinese patents were actually published before this delay, thus artificially increasing their weight in **Supplementary File 2**. Therefore, patent numbers per countries were compared at two different time points (**Fig. 1a**). One was priority date December 31, 2017, which actually reflects those patents publicly available on November 30, 2018, the latest update of **Supplementary File 2.** The second is priority date May 2017, the most recent date for accurate geographical comparisons since it takes into account the 18 month delay in publication with respect to the latest update of Supplementary file 2. At this latter time point, inventors from the USA filed 47.8% of the patents, China 34%, Europe 10.4 %, Korea 3.8% and Japan 2.6%. 33% of these patents (up to May 2017) were deposited by private firms.

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

As already shown[5], USA major patent holders are the Massachusetts Institute of Technology (MIT, 113 patents), Harvard College (109 patents, 34 co-deposited with MIT), Broad Institute (86 patents, most of them co-deposited with MIT), University of California (73 patents) and Editas Medicine (43 patents). What has not been shown before is that China takes an important place in this ranking: Chinese Academies of Sciences and Agricultural Sciences (182 patents filed), China Agricultural University (35), Shanghai Institute for Biological Sciences (27), Shanghai Jiao Tong University (24), Sun Yat Sen University (17), University of Beijing (17) and Second Peoples Hospital of Shenzen (14). Regarding private firms well known for their marketing of transgenic products, it is interesting to note that DuPont-Pioneer filed 20 patents, Monsanto 4, Bayer 1, and Syngenta 1.

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

A technological field still in quest of technological improvements

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

The USA has not only been a pioneer in gene editing using CRISPR but is still a leader for improvements of this technical development with 479 patents compiled in this category (**Fig. 2b**). China is the second largest depositor (306 patents), while European countries again trail behind with only 91 such patents. Some patents were co-deposited by inventors from the USA and from other countries (Japan: 4 patents, Switzerland: 4, Netherlands: 2, France: 1, Austria: 1, and Germany: 1). 1 patent was co-deposited by Switzerland and Germany, and 1 patent by China and Thailand. For the reason mentioned above, when patents in this category were compared up to the priority date of May 2017 (**Fig. 2b**), it appears that the respective weights of the USA, China and Europe are 57%, 24.9% and 10.5 %. The private sector filed 32% of these patents (up to May 2017).

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

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

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

A wealth of health applications

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

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

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

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

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

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

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

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

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

Industrial applications for CRISPR

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

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

CRISPR patents in relation to agricultural organisms

Since the "GMO" controversy has largely limited agricultural applications of biotechnology and is similarly threatening CRISPR use[11], we decided to analyze as a distinct category of patents in **Supplementary File 2** those related either to “farm animals”, including aquaculture (a total of 85 patent families), or to “plants” (267 patent families). Only 5 of the “plant” patents have a dual categorization (three in both “plants” and “medical”, one for both “plants” and “farm animals” and for both “plants” and “technical improvements”). CRISPR patents in relation to agricultural organisms appeared from September 2012 for plants (Dow Agrosciences/Sangamo Biosciences, USA) and from February 2014 for farm animals and aquaculture (Qingdao Institute of Animal Husbandry Veterinary Medicine, China). As expected, the number of such patents published since has grown steadily: 11 in 2013, 35 in 2014, 63 in 2015, 112 in 2016, and 128 (data incomplete) in 2017.

As mentioned above, some patents describe general “technological improvements”, *i.e*. not linked to a precise applied goal (but which nevertheless can relate to a given species, predominantly pig for animals but also cow, buffalo, goat, sheep, chicken, birds and fish, and mainly rice for plants but also 11 other plant species). The reason for not grouping these agricultural technical improvements with the above-mentioned “technological improvement” category is that agricultural biotechnologies may be more controversial than other biotechnologies (and this could translate in differential involvement of countries).

Some other patents, without direct agricultural application, such as the use of plants for molecule production, or specific metabolic changes, or as a research model (Arabidopsis, barley and rice) were grouped in this plant category.

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

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

Discussion

The CRISPR system is at the origin of an ever increasing flux of patented inventions. Compiling all CRISPR related patents is of obvious importance for industrial strategical planning and other reasons discussed below, but has proven to be excessively difficult. The step by step method described here for CRISPR patent compilation highlights the challenges to reach exhaustivity. Consequently, most previous CRISPR patent compilations have relied on a small subset of such patents. The present compilation independently yielded a patent family number close to that of Egelie *et al.*[6] up to 2015, and extended the list up to December 31, 2017 (priority date; as publicly available on November 30, 2018). A second challenge, of semantic nature, concerns the definition of a *bona fide* CRISPR-related gene editing invention: many patents seem to mention CRISPR and other related keywords to extend the scope of their claims, while this technology is not central to the described invention. Therefore, our detailed analysis focused on what we considered as *bona fide* CRISPR patents, namely that their claims specifically focus on a CRISPR-type system to implement the invention (see our criteria in **Supplementary file 1**).

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

In our opinion, these inventions are also revolutionizing the plant and animal breeding sectors. It can be noted, for example, that CRISPR patents involve polyploid organisms such as wheat (resistance to a geminivirus) or autopolyploids such as carp (resistance to KH virus). However, the CRISPR system still has limitations. It can be seen from this present study that, to date, the modifications concern primarily single-gene characters which are often inactivated (by knock-out of the responsible gene). However, some patents do describe gene insertion or gene overexpression (*e.g*. by insertion of a particularly strong promoter or intervention on regulators / promoters such as the suppression of an interfering RNA). Although the CRISPR system is very effective for this type of operation, the number of interesting monogenic traits to be modified for agriculture remains limited. Indeed, most characters of an organism are controlled by a multitude of genes (and with a quantitative effect) and, as such, the CRISPR system cannot effectively act on the character in the present state of art (a better knowledge of the relevant genes is required). In this context, it can be noted that while the keywords 'knock-out' or 'knockout' appear 28 times in the "plant" category (**Supplementary file 2**; titles and abstract alone), 'multiplexing' or 'multi-target' (*i.e.* the simultaneous modification of several loci of the same genome) only appear 4 times highlighting the further necessity for technical improvements.

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

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

More and more voices are asking for a revision of the current European "GMO" Directive[11]. However, our present analysis shows that the damage has already been done in Europe: the number of CRISPR patents originating from this continent is trailing far behind the USA and China. This trend concerns all patent categories defined here, including those related to health (despite the fact that it is not the most controversial). Rodríguez-Navarro and Narin[13] showed that "Europe lags far behind the USA in the production of important, highly cited research". They concluded that "there is a consistent weakening of European science" which they attribute to the funding systems. The problem may be more widespread and could be attributed to a hostile cultural ("precautionary") climate against innovations, including biotechnology[17]. It would be a delusion not to consider that the GMO bans in Europe have not had a strong negative impact on the future of biotechnology in this continent (including in relation to health aspects). The definition of what is patentable (which includes "ethical" considerations) in Europe *vs*. in other parts of the world may also add to the European 'cultural' naivety in the current economical 'war'. The cost of EU patent protection was estimated to be 18-20 times more than in the U.S. Although this may no longer be the case with the new European unitary patent system (Belda et al. 2014), a reluctance to file patents may persist for all the above-mentioned factors. Whatever their relative contribution, an overall consequence is a long-term trend of patent number (all types of patents) granted by the EPO trailing far behind the number granted by the USPTO (http://www.wipo.int/edocs/pubdocs/en/wipo_pub_941_2017.pdf). Thus, the USA vs. Europe differential trend in the CRISPR case was not unexpected.

Regarding China, its patent office surpassed the EPO already in 2005 and the USPTO in 2011 in terms of patents per year. In addition, an overwhelming Chinese patent owners are Chinese, while the ratio between 'resident' and 'non-resident' are about equal for EPO and USPTO (see link above). However, it was unexpected that this general trend would reflect in the CRISPR patents so soon: there have been some earlier publications on the CRISPR patenting landscape which considered its geographical aspects[6, 10, 18], but to our knowledge none had pointed out that China has taken the lead over the USA in terms of patents per year. This can be explained by the massive investment in biotechnology in China. An example (in the agricultural field) of a technical incentive for China's investment could be the national importance of pig farming and rice cultivation, and the fact that they are threatened by diseases and pests. It is also likely to be the product of its new patenting strategy. China issued its first patent law in 1984 and revised it in 1992, 2000, 2008 and 2016 (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 economical protectionist tool[19]. The essentially domestic purpose of patents is corroborated by the fact that Chinese CRISPR patents are rarely extended to other countries. In a dense patenting landscape, foreign companies operating in this field could be deterred from exporting to China, or at least would have to pay royalties to access the Chinese market.

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

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