PATENTS

Worldwide CRISPR patent landscape shows strong geographical biases

A survey of the CRISPR patent landscape shows the improvement of technology, a diversity of potential sectors of application, and a new geopolitical balance of forces in the field.

On 17 August 2012 Jennifer Doudna's group at the University of California, Berkeley and Emmanuelle Charpentier at Umeå University and formerly at the University of Vienna highlighted the underlying molecular mechanisms of the CRISPR (clustered regularly interspaced short palindromic repeats) system[1]. They demonstrated that this system can be used to produce double-stranded cuts at any precise DNA site in prokaryotic cells by combining a RNA guide with an endonuclease protein, CRISPR-associated protein 9 nuclease, or Cas9. Prior to this publication, on 25 May 2012, 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. Meanwhile, groups led by Feng Zhang at the Broad Institute of MIT and Harvard University[2] and George Church at Harvard[3] demonstrated that the CRISPR system can be used to modify eukaryotic mammalian cells, including those of humans. On 12 December 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[4–6]. However, as pointed out by Parthasarathy, "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."[7] Thus, a CRISPR gene-editing patent landscape[8] is highly desirable for reasons that go far beyond intellectual property.

We present a compilation of relevant patents in this field and have classified them to shed more light on the technical fields concerned and on the geographical origins of these patents. This unique resource can be screened for further parameters. The data confirm that CRISPR research has continued to spread rapidly and has revolutionized the field of genome editing. Our data also

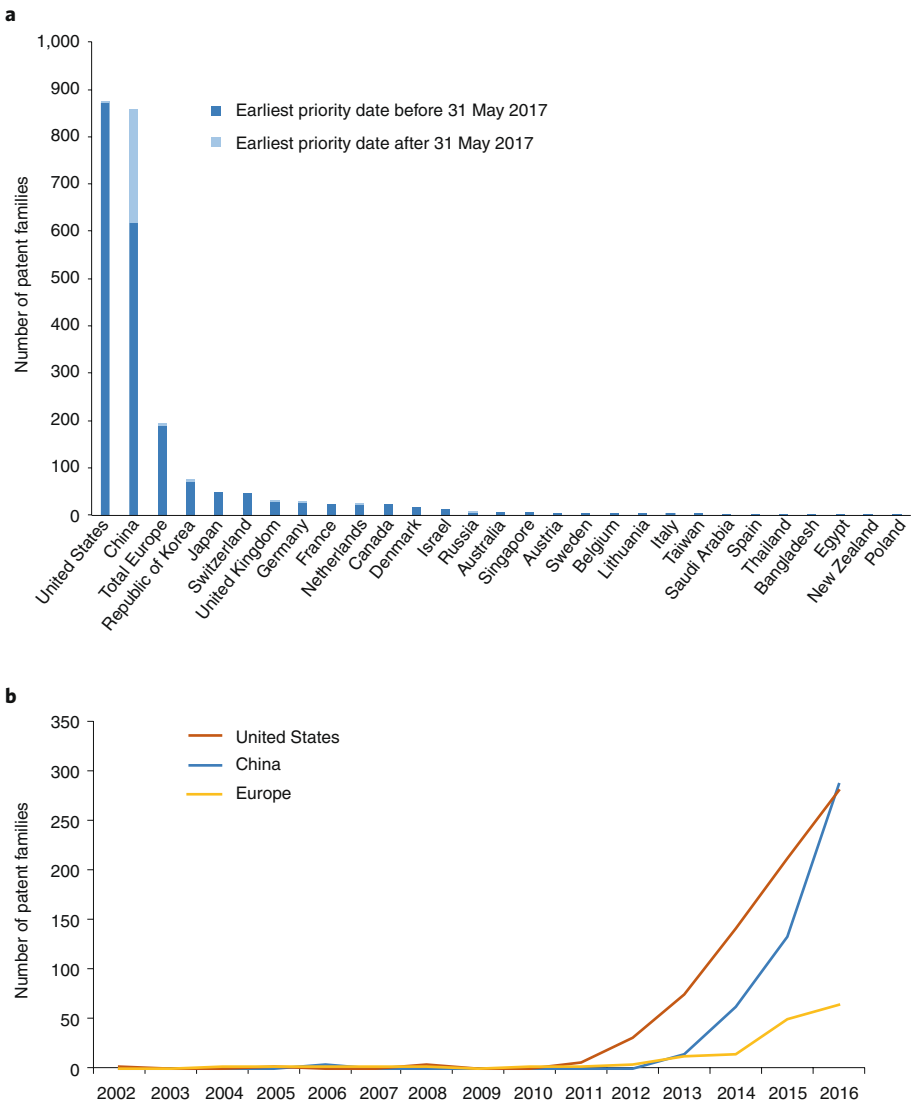

Fig. 1 | Geographical repartition and evolution of patent families related to the CRISPR gene editing system. By convention, the earliest priority date was used for the patent collection as a whole, as displayed in Supplementary Table 1 (priority date limited to 31 December 2017). **a**, Number of patent families related to the CRISPR–Cas system per country. Values correspond to the total amounts of patent families compiled in Supplementary Table 1. Dark blue indicates patents with a priority date up to 31 May 2017. Light blue indicates additional patents publicly available at the date of last update (priority date up to 31 December 2017). **b**, Evolution of number of patent families per year in three geographical zones (according to earliest date of priority, from 2002 until 2016 inclusive). Year 2017 was not included since these data are not available in all cases.

Box 1 | Methodology

Patents related to the CRISPR system of gene editing were obtained from the following databases: Orbit Intelligence (https://www.orbit.com; marketed by Questel), PatentPulse (https://www.patent-pulse.com) and the open database Patent Lens (https://www.lens.org/). The search strategy was based on keywords in the following query equation: CRISPR OR Cas9 OR Cpf1 OR gRNA(s) OR sgRNA(s) OR "RNA(s) guide(d)" OR "guide(d) RNA(s)". Searches were also performed using other nucleases (namely CAS1 to CAS10, CSY1 to CSY3, CSE1, CSE2, CSA5, CSN2, and CSM2 to CSM5) but did not yield entries not already identified using the previous searches (yielding instead many false positives due to the use of the same acronyms in different contexts). The search was limited to patent priority dates up to 31 December 2017. Patent records were listed according to the databases' grouping as patent families (i.e., all available worldwide patent applications and granted patents considered to cover a single invention, as defined by the Documentation Database (DocDB) simple patent family classification).

A manual cleanup of these results was performed to remove duplicates and false positives, using patent titles, abstracts, applicants, inventors, earliest priority date and technology classification codes, and the full text of the patent when necessary. Some patents that were not correctly classified automatically by the databases as belonging to a particular patent family were identified during this cleanup and were added to their patent family. Patent families selected manually as being directly related to the CRISPR system were compiled in Supplementary Table 1 and their features were added manually in the various columns, including technological categories and subcategories, as discussed in the text. (See the Supplementary Note for examples of criteria for patent rejection or inclusion during the manual cleanup.) A manual reconciliation of inconsistently spelled and formatted assignee names was also performed to harmonize presentation and facilitate further analyses. Although initiated before the publication of guidelines by Smith et al.[9], the present patenting landscape study was revised accordingly.

While technical analyses used all publicly available patents (i.e., those compiled in Supplementary Table 1), meaningful comparison of the geographical origins of patents must take into account that a patent application will typically be published after a delay of 18 months but there may be exceptions: namely, that in some jurisdictions the applicant can request an earlier publication. To take into account these disparities, patents with earliest priority date at least 18 months ago (i.e., up to 31 May 2017) were considered for geographical comparisons (expressed as a percentage throughout this article).

document the geopolitical balance of forces in this promising new biotechnological field, including the observations that in recent years China has massively invested in biotechnology, while Europe has suffered from disinvestment, especially in agricultural biotechnology as a consequence of the backlash against genetically modified organisms (GMOs).

Can one create an exhaustive CRISPR patent list?

We searched patents related to the CRISPR system by querying three databases using criteria[9] listed in Box 1, up to 31 December 2017 as a priority date. This search was first limited to the patent title and abstract 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 cleanup of these results was performed to eliminate duplicates and false positives as described in Box 1 (using inclusion and exclusion criteria exemplified in the Supplementary Note). Entries were collected similarly from two other databases (PatentPulse and Patent Lens). A manual comparison of the datasets obtained showed that Orbit Intelligence provided the largest, although not completely exhaustive, set (only 1% of the patent families were not obtained via Orbit Intelligence but were identified in at least one of the other two databases). A total of 1,469 patent families was thus compiled at the end of this first patent search step. However, to ensure maximal exhaustivity, we conducted a second search querying descriptions and claims of the patents (excluding titles and abstracts). As expected, this second search yielded many more entries (>10,000), of which a large majority were false positives. A first manual cleanup 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 (among 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 with the 1,469 patent families selected from the first search. These 2,072 patent families are considered as bona fide CRISPR gene editing patents since their descriptions or 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 the Supplementary Note for inclusion criteria for this group). Their compilation (Supplementary Table 1) includes patent titles, abstracts, inventors, applicants, priority dates and 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 not yet be known.

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 cleanup of false positives is required. In addition, proper integration of entries in their patent families is necessary.

This compilation includes the milestone patents discussed above (which can be found by searching on the patent numbers) and others that have attracted attention as part of the CRISPR-related patent struggle (see https://www.broadinstitute.org/crispr/journalists-statement-and-background-crispr-patent-process), including those rejected by the US Patent and Trademark Office (USPTO) (e.g., Northwestern University's application 2008US-61099317 and ToolGen's application 2012US-61717324).

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

Supplementary Table 1 also compiles the country of invention and reveals that CRISPR patents were originally filed by 28 countries (Fig. 1a). The United States

and China lead with 872 and 858 patents, respectively. Strikingly, European countries as a whole filed only 194 such patents, followed by the Republic of Korea (75 patents) and Japan (48 patents). Twenty-six patents were co-deposited by inventors from the United States and other countries (Switzerland (6), Japan (4), the Netherlands (3), Germany (2), Russia (2), Austria (1), Belgium (1), Canada (1), China (1), France (1), Israel (1), New Zealand (1) and the United Kingdom (1). Six patents were co-deposited by other pairs of 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 Table 1. Therefore, we compared patent numbers per country at two different time points (Fig. 1a). One was priority date 31 December 2017, which actually reflects those patents publicly available on 30 November 2018, the latest update of Supplementary Table 1. The second is priority date 31 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 Table 1. At this latter time point, inventors from the United States had filed 47.8% of the patents, China 34%, Europe 10.4%, the Republic of Korea 3.8% and Japan 2.6%. Thirty-three percent of these patents (up to 31 May 2017) were deposited by private firms.

Patenting rate per year (Fig. 1b) shows that the United States had an early leadership, as expected, but that the patenting rate from China is steadily increasing. In this criterion, China took the lead over the United States in 2016.

As previously shown[8], major patent holders in the United States include the Massachusetts Institute of Technology (MIT; 113 patents), Harvard College (109 patents, 34 co-deposited with MIT), the Broad Institute (86 patents, most of them co-deposited with MIT), the University of California (73 patents) and Editas Medicine (43 patents). We further find that China takes an important place in this ranking: the 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, we 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, we manually sorted these patents into various categories (see color codes in Fig. 2a and Supplementary Table 1). It was obvious that many patents describe technical improvements at large in the CRISPR system, which could potentially be used for many practical purposes. Thus, we classed such patents in a 'technical improvements' category, which contains 942 out of the 2,072 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 (for example, DNA assembly, splicing, analysis, isolation or linker removal, or Cas9 assays). Using this type of categorization, only 7 patents were allocated to two categories (identified in Supplementary Table 1 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 can 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 the Supplementary Note.

The United States not only has 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 with only 91 such patents. Some patents were co-deposited by inventors from the United States and from other countries: Japan (4 patents), Switzerland (4), the Netherlands (2), Austria (1), France (1), and Germany (1). One patent was co-deposited by Switzerland and Germany, and 1 patent by China and Thailand. When patents in this category are compared up to the priority date of 31 May 2017 (Fig. 2b), the respective weights of the United States, China and Europe are 57%, 24.9% and 10.5%. The private sector filed 32% of these patents (up to 31 May 2017).

By nature, this category is diverse, and it merited further sorting into subcategories (see Supplementary Table 1 and its color codes). They consist of either general methods for improving CRISPR–Cas9-mediated genome editing, without species restriction, or those linked to a given species or a group of species (namely, mammals including humans, fish, other animals, fungi, microalgae or prokaryotes) or to mitochondria, or methods to favor either knockout or homologous types of editing, or chromosome translocation. Other subcategories were created as follows. Although most patents in the previous subcategories 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 the reduction of 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 and gene detection, cell sorting, and gene drive).

Patents filed before the milestone inventions mentioned in the first paragraph above were also included as a subcategory (termed 'early development' in Supplementary Table 1). These include descriptions of Cas nucleases, guide RNA delivery vehicles, or use of CRISPR sequences. Included in this subcategory is 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 above).

Note that we have chosen to include technical improvements directly related to agricultural organisms (131 patent families) as a subcategory in the agricultural category for reasons explained below. However, when added to the 'technical improvement' category, the total number of patents in the latter category is then 1,073 patents out of 2,072 in Supplementary Table 1.

A wealth of health applications

The 'medical' category groups patents (554 patent families out of 2,072 in Supplementary Table 1) 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

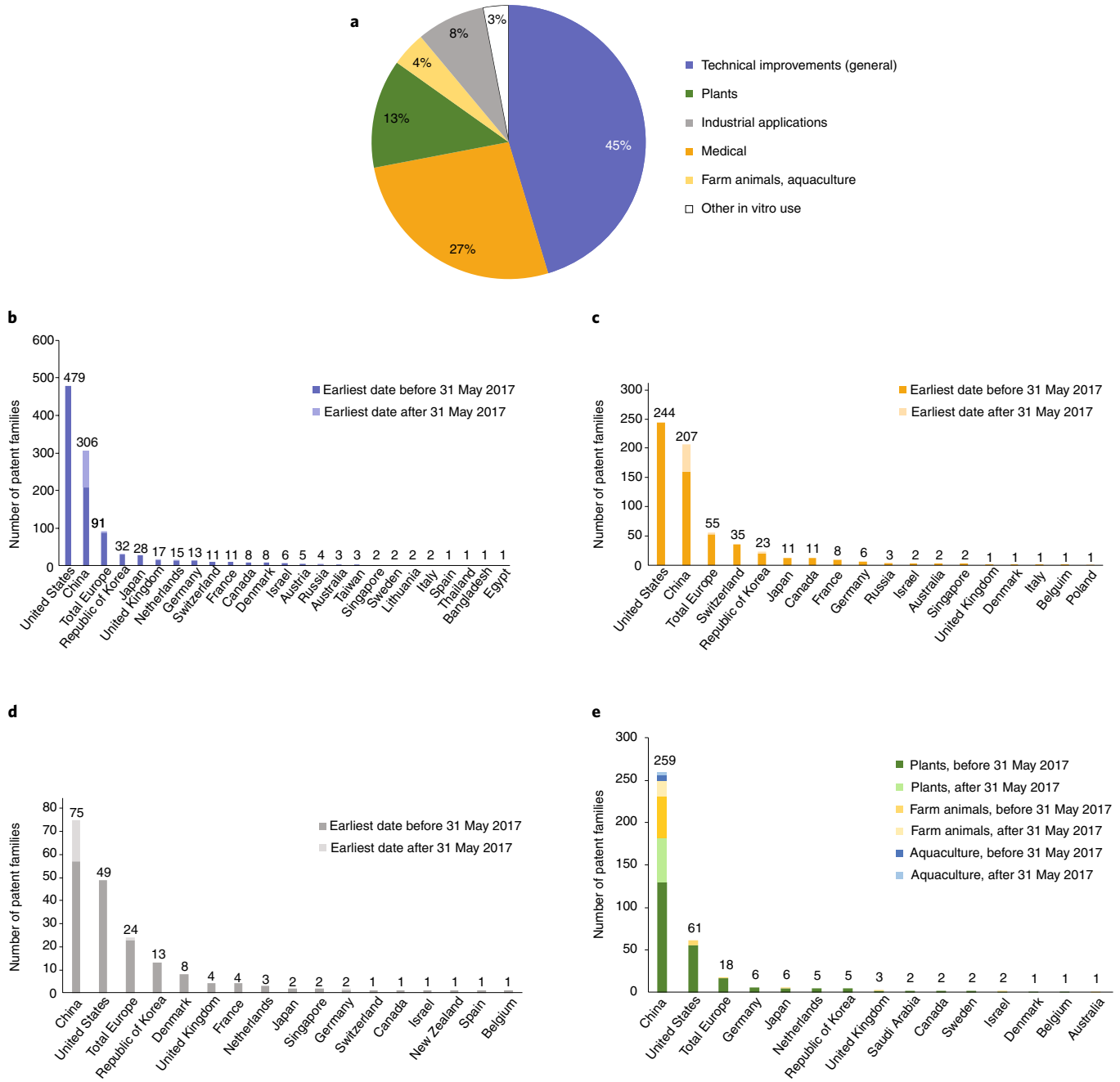

Fig. 2 | Number of patent families related to the CRISPR system per technical category. By convention, the earliest priority date was used for the patent collection as a whole, as displayed in Supplementary Table 1. The dark part of each bar corresponds to patents with a priority date up to 31 May 2017, while the light part corresponds to additional patents publicly available at the date of last update. **a**, Total patent families sorted by categories as defined in the text. **b**, Number of patent families per country related to the 'technical improvement' category. **c**, Number of patent families per country directly related to 'medical applications'. **d**, Number of patent families per country related to 'industrial applications'. **e**, Number of patent families per country related to 'agricultural applications'. Patents are separated into 'plant', 'farm animal' and 'aquaculture' categories.

upstream medical research tools, such as edited human cell lines, 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 United States and either Belgium, China, Germany or Switzerland (2 patents).

For geographical comparison (Fig. 2c), we analyzed patents up to 31 May 2017 (502 patents). The United States is the leader with 49% of patents deposited, followed by China (32%), the Republic of Korea (4%), Europe (10.5%, with Switzerland alone representing 7%), Canada and Japan (2.2% each). Private companies filed 37.6% of these 502 patents.

An impressive number of 100 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 Table 1). Cancer alone represents 131 patent families, of which 31 describe immunotherapy approaches (for example, using chimeric antigen receptor (CAR)-modified T lymphocytes[10]) for selectively eliminating cancerous or other pathogenic cells. Fifty-nine patent families on cancer applications of CRISPR technology were filed by China, dominated by the public sector (Chinese Academy of Sciences, universities, and research institutes). It is important to note the recent creation of around 15 Chinese private firms (such as Anhui Kedgene Biotechnology, Biotowntek, Chengdu Keli Bo Biotechnology, Chongqing Gaosheng Biological Pharmaceutical, Guangzhou Huiyuanyuan Pharmaceutical Technology, Nanjing Kaidi Biotechnology and Yuan Biotechnology) that have filed patents concerning cancer applications of CRISPR technology since June 2015. The United States ranks second in filing 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 and Sandia Corporation. Europe is represented only by Denmark (1 patent filed by Frost Habib), France (4 patents filed by Cellectis, 1 patent filed by Inserm/Rennes and Bordeaux Universities/Institut Bergonié), Germany (1 patent filed by Amgen Research Munich), Switzerland (1 patent co-deposited with US Novartis/Intellia Therapeutics) and the United Kingdom (1 patent filed by PhoreMost).

One hundred and twelve patents in Supplementary Table 1 describe methods for treating viral infections: cytomegalovirus, hepatitis B, hepatitis C, herpes simplex, HIV, human papilloma virus, human T-cell leukemia virus, influenza B, polyomavirus, 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. Out of the patents claiming treatment of viral diseases using CRISPR technology, 62 originated from the United States, well distributed between the public sector (with Temple University alone holding 18 patents) and private sector (Agenovir, 11 patents; Editas Medicine, 7 patents; Excision Biotherapeutics, 6 patents; Nantomics, 1 patent). Forty-one 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 five other countries are included in this subcategory: France (Cellectis, 3 patents; Inserm/Nantes University, 1 patent), Canada (Protiva Biotherapeutics, 1 patent), Japan (Aichi Prefecture, 1 patent), the Republic of 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. They concern Alzheimer's disease and other nervous system disorders, such as Huntington's disease, autism and psychiatric diseases; autosomal dominant diseases; blood diseases (for example, β-thalassemia and anemia); diseases of the musculoskeletal system (for example, bone diseases and rheumatoid arthritis) and muscular dystrophies (for example, Duchenne's disease); nucleotide repeat disorders; and retinal or other ocular diseases (for example, glaucoma). Some patents describe induced pluripotent stem cell (iPSC) modifications for ex vivo therapy[11].

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

The United States and China again dominate these medical patent subcategories (excluding cancer or virus applications), with 134 and 113 patents filed, respectively. As in the cancer and virus subcategories, the United States and China are represented mainly by public research institutes or universities, but also by private firms, such as Editas Medicine, Sangamo Therapeutics and Intellia Therapeutics (United States) and Beijing Biocytogen, Generos Biopharma and Suzhou Tongshan Biotechnology (China). Forty-five 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's 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 the United States), 1 patent for blood disease). The Republic of Korea has 19 patents recently filed by members of the 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.

In addition, 187 patent families in the subcategories 'mammals, including humans' or 'knockout technique (mammals)' of the above-mentioned 'technical improvements' category of Supplementary Table 1 may have implications for human health (although less direct ones, hence their classification as 'technical improvements'). This also holds true for a subcategory in the 'industrial applications' category (see below) describing a number of pharmaceutical applications (65 patent families). These health-related subcategories can be identified by the same color code as the patents in the 'medical' category in Supplementary Table 1. Taking into account all these patents leads to a noteworthy number of 806 patent families out of 2,072 directly or indirectly related to human health.

Industrial applications for CRISPR

Industrial applications of the CRISPR system through metabolic engineering have been reviewed[12]. In our compilation, this category contains fewer patents (167 patent families; Fig. 2a and Supplementary Table 1) than the previous ones, likely because it often involves microorganisms for which there are many other effective methods of genome modification, including homologous recombination. These 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' subcategory 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 another, 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, and even the production of hypoallergenic cats. Some patents are also related to silk production. Pharmaceutical applications (65 patent families) relate to the production of antibodies, vaccines or other products; a majority, 31 patents, originated from China, and only 18 from the United States, 7 from Europe, 6 from the Republic of Korea, 1 from Israel, Japan, and Singapore. Nine patents are related to nutrition: 5 from China, 2 from the United States and 2 from the Republic of Korea.

Examining all patents in this 'industrial' category shows that they originated from China, the United States, Europe and six countries from elsewhere in the world (Fig. 2d). When comparing up to 31 May 2017 as a priority date (148 patents), China leads this category (38.5%), followed by the United States (33%), while patents of European origin represent only 15.5% (of which Denmark alone contributes 5.4%). One patent was co-deposited by inventors from the United States and 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[13], we decided to analyze, as a distinct category of patents in Supplementary Table 1, 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 (3 in both 'plants' and 'medical,' 1 each in both 'plants' and 'farm animals' and in both 'plants' and 'technical improvements'). CRISPR patents in relation to agricultural organisms appeared from September 2012 for plants (Dow Agrosciences/Sangamo Biosciences) and from February 2014 for farm animals and aquaculture (Qingdao Institute of Animal Husbandry Veterinary Medicine). 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,' that is, those not linked to a precise applied goal, but which nevertheless can relate to a given species (predominantly pigs for animals, but also cows, buffalo, goats, sheep, chickens, 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 also grouped in the 'plants' category.

The largest plant subcategory 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 pest resistance, plant stature or 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[14], it was to be expected that the largest animal subcategory also relates to breeding (50 patents), with pigs being dominant (22 patents), followed by sheep (12 patents), mammals in general (5 patents), fish (4 patents), birds (3 patents), goats (2 patents), cows and rabbits (1 patent each). Applications concern fertility, meat production, milk quality, resistance to various diseases including viruses, and sheep wool color.

The geographical origins of these patents are shown in Fig. 2e. Upon analysis up to the priority date of 31 May 2017 (215 'plants' patents and 64 'farm animal' patents), China leads the plant category (60.5%), followed by the United States (26%), while patents of European origin represent only 8% (17 patents, of which Germany and the Netherlands contributed 6 and 5 patents, respectively). Japan and the Republic of Korea represent 2.3% each (5 patents). For farm animals, China leads with 87.5%, with 8% for the United States and a single patent each for Australia, Israel, Japan and the United Kingdom. Three patents for 'plants' were co-deposited respectively by inventors from China and the United Kingdom, from Denmark and Canada, and the United States and the Netherlands. One was co-deposited for 'farm animals' by inventors from the United Kingdom and United States. Private companies filed 27% and 5% of these 'plant' and 'farm animal' patents, respectively. Private companies with the most deposits are DuPont-Pioneer (United States; 12 patents), KWS Saat (Germany; 5 patents), Keygene (the Netherlands; 4 patents), Dow Agrosciences (the United States; 3 patents) and Beijing DBN Technology (China; 3 patents). Public depositors are mostly represented by Chinese public organizations: China Agricultural University and the Institute of Genetics and Development Biology/Chinese Academy of Sciences (14 patents each), Anhui Academy of Agricultural Sciences (11 patents) and the Institute of Crop Science/Chinese Academy of Agricultural Sciences (10 patents). The University of California is the most important US depositor for agricultural sector, with 9 patents filed.

Discussion

The CRISPR system is at the center of a growing influx of patented inventions. Compiling all CRISPR-related patents is of obvious importance for industrial strategical planning and other reasons discussed below, but has proven excessively difficult. The method described here for CRISPR patent compilation highlights the challenges of reaching 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.[8] up to 2015, and extended the list up to the 31 December 2017 priority date (as publicly available on 30 November 2018). A second challenge, of a 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, although the technology itself is not central to the described invention. Therefore, our detailed analysis focused on what we considered bona fide CRISPR patents: namely, ones whose claims specifically focus on a CRISPR-type system to implement the invention (see our criteria in the Supplementary Note).

A more detailed analysis of these patents revealed a rush to improve the technology itself (942 patent families out of a total of 2,072), 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 directly related to medical purposes, to industrial (including pharmaceutical) applications,

or to agricultural purposes, following the criteria explained above. Such a separation is inevitably a matter of interpretation, but a classification into categories and then into subcategories appeared useful to highlight the diverse applications of CRISPR gene editing. Note that Supplementary Table 1 contains specific color codes which help the visualization of related patents despite the fact they were classed in different categories (for example, for health, medical and pharmaceutical patents share the same color code; farm animal and 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 United States, while 'industrial' patents are dominated by China, as are pharmaceutical patents, which we chose to add to this 'industrial' category).

In our opinion, these inventions are also revolutionizing the plant and animal breeding sectors. Note, 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. Our study shows that, to date, the modifications concern primarily single-gene characters, which are often inactivated (by knockout of the responsible gene). However, some patents do describe gene insertion or gene overexpression (for example, by insertion of a particularly strong promoter or intervention on regulators or 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 quantitative effects), and, as such, the CRISPR system cannot effectively act on the character given the present state of art, as a better knowledge of the relevant genes is required. In this context, we note that while the keywords "knockout" or "knock-out" appear 28 times in the 'plants' category (Supplementary Table 1; titles and abstract alone), "multiplexing" or "multi-target" (i.e., the simultaneous modification of several loci of the same genome) appear only 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[12] 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 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[15]. The same author also discussed the ethical implications of CRISPR patenting[16] and "lessons about science and society"[17]. The present compilation and further updates will allow documented discussions about these ethical issues.

Obviously, the regulatory status of gene-edited organisms will influence 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[18]. Their marketing as GMOs will be very costly and be subject to political opposition. This will limit public laboratory research, which resulted in most CRISPR patents to date (1,344 patent families out of 2,072; 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[13]. 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 those of the United States 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 showed that "Europe lags far behind the USA in the production of important, highly cited research."[19] 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[20]. It would be a delusion not to consider the GMO bans in Europe as having had a strong negative impact on the future of biotechnology on the continent (including in relation to health aspects). The definition of what is patentable (which includes "ethical" considerations) in Europe versus in other parts of the world may also add to European cultural naivety in the current economic competition. The cost of EU patent protection was estimated to be 18–20 times more than in the United States. Although this may no longer be the case with the new European unitary patent system[21], a reluctance to file patents may persist for all the above-mentioned factors. Whatever their relative contributions, an overall consequence is a long-term trend of patent numbers for all types of patents granted by the European Patent Office to trail far behind the number granted by the USPTO (http://www.wipo.int/edocs/pubdocs/en/wipo_pub_941_2017.pdf). Thus, the differential trend in the US versus Europe in the case of CRISPR was not unexpected.

Regarding China, its patent office surpassed the European Patent Office in 2005 and the USPTO in 2011 in terms of patents granted per year. In addition, Chinese patent owners are overwhelmingly Chinese, while the ratios between 'resident' and 'non-resident' are about equal for the European Patent Office and USPTO (see link above). However, it was unexpected that this general trend would reflect in CRISPR patents so soon: previous CRISPR patent landscapes have considered geographical aspects[8,12,22], but to our knowledge none have pointed out that China has taken the lead over the United States in terms of patents per year. This can be explained by China's massive investment in biotechnology. One 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 China's 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 patent system that can be considered an economic protectionist tool[23]. The essentially domestic purpose of their patents is corroborated by the fact that Chinese CRISPR patents are rarely extended to other countries. In a dense patent 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 to regain

its footing in this new biotech battlefield. The information provided here makes it possible to identify key inventors, to identify 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 the actors in the field and the strategic trajectories of those who 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 lead to litigation, especially in the context of the legal battle surrounding the original inventions. Regulation should ideally be particularly responsive to adapt to the fast evolution of such innovative domains, although this is not always the case, and we believe that such a patent landscape can contribute to the adaptation of regulation in many regions of the world. ❐

Jacqueline Martin-Laffon[1], Marcel Kuntz[1] and Agnès E. Ricroch[2*]

[1]*Laboratory of Plant and Cell Physiology, University of Grenoble Alpes, CNRS, CEA, INRA, Grenoble, France.* [2]*IDEST, Paris-Sud University, Sceaux, France.*
**e-mail: agnes.ricroch@u-psud.fr*

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Competing interests

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Additional information

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