

REVIEW ARTICLE

## The commercialization of genome-editing technologies

Katelyn Brinegar<sup>a,b</sup>, Ali K. Yetisen<sup>a,b,c</sup>, Sun Choi<sup>b</sup>, Emily Vallillo<sup>b</sup>, Guillermo U. Ruiz-Esparza<sup>a,b</sup>, Anand M. Prabhakar<sup>d,e</sup>, Ali Khademhosseini<sup>a,b,f</sup> and Seok-Hyun Yun<sup>a,c</sup>

<sup>a</sup>Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA; <sup>b</sup>Biomaterials Innovation Research Center, Division of Biomedical Engineering, Brigham and Women's Hospital, Harvard Medical School, Cambridge, MA, USA; <sup>c</sup>Harvard Medical School and Wellman Center for Photomedicine, Massachusetts General Hospital, Cambridge, MA, USA; <sup>d</sup>Department of Radiology, Division of Cardiovascular Imaging, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; <sup>e</sup>The Wharton School of the University of Pennsylvania, Philadelphia, PA, USA; <sup>f</sup>Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA, USA

### ABSTRACT

The emergence of new gene-editing technologies is profoundly transforming human therapeutics, agriculture, and industrial biotechnology. Advances in clustered regularly interspaced short palindromic repeats (CRISPR) have created a fertile environment for mass-scale manufacturing of cost-effective products ranging from basic research to translational medicine. In our analyses, we evaluated the patent landscape of gene-editing technologies and found that in comparison to earlier gene-editing techniques, CRISPR has gained significant traction and this has established dominance. Although most of the gene-editing technologies originated from the industry, CRISPR has been pioneered by academic research institutions. The spinout of CRISPR biotechnology companies from academic institutions demonstrates a shift in entrepreneurship strategies that were previously led by the industry. These academic institutions, and their subsequent companies, are competing to generate comprehensive intellectual property portfolios to rapidly commercialize CRISPR products. Our analysis shows that the emergence of CRISPR has resulted in a fivefold increase in genome-editing bioenterprise investment over the last year. This entrepreneurial movement has spurred a global biotechnology revolution in the realization of novel gene-editing technologies. This global shift in bioenterprise will continue to grow as the demand for personalized medicine, genetically modified crops and environmentally sustainable biofuels increases. However, the monopolization of intellectual property, negative public perception of genetic engineering and ambiguous regulatory policies may limit the growth of these market segments.

### ARTICLE HISTORY

Received 6 July 2016  
Revised 23 September 2016  
Accepted 14 November 2016



### KEYWORDS


Biotechnology; CRISPR; gene editing; entrepreneurship; business; investments

### Gene-editing sector

The emergence of disruptive gene-editing techniques is transforming the biotechnology business sector. In 2015, biotechnology companies received a total of \$1.2 billion in venture capital funds, which accounted for 16.3% of corporate venture investment capital, making biotechnology the second highest funded sector in the United States [1]. The biotechnology market has grown rapidly over the last decade. In 2014, the gene-editing market was estimated to be worth \$1.84 billion and is projected to reach to \$3.51 billion by 2019 with a Compound Annual Growth Rate (CAGR) of 13.75% [2]. Traditional gene-editing technologies include zinc finger nucleases (ZFN), transcription activator-like effector nuclease (TALENs) and meganucleases. However, these technologies have had limited use due to design complexity, transfection

inefficiencies and limitations in multiplexed mutations [3]. Conversely, companies using clustered regularly interspaced short palindromic repeats (CRISPR) have played an important role in the recent expansion of the gene-editing market. Since 2013, leading companies utilizing CRISPR have received over \$600 million in venture capital and public market investments [4]. CRISPR can be utilized in a wide range of biotechnology sectors including healthcare, agriculture, veterinary medicine and industrial production processes. Recently, CRISPR has been used in the editing of non-viable human embryos [5], genetic screening of patients [6] and the modification of crops for human consumption [7]. The successful use of CRISPR in a wide array of applications has garnered global interest in the development, investment and commercialization of gene-editing products.

**CONTACT** Ali K. Yetisen  akyetisen@gmail.com  Harvard Medical School, Brigham and Women's Hospital, 65 Landsdowne St., Cambridge, MA, 02139 USA

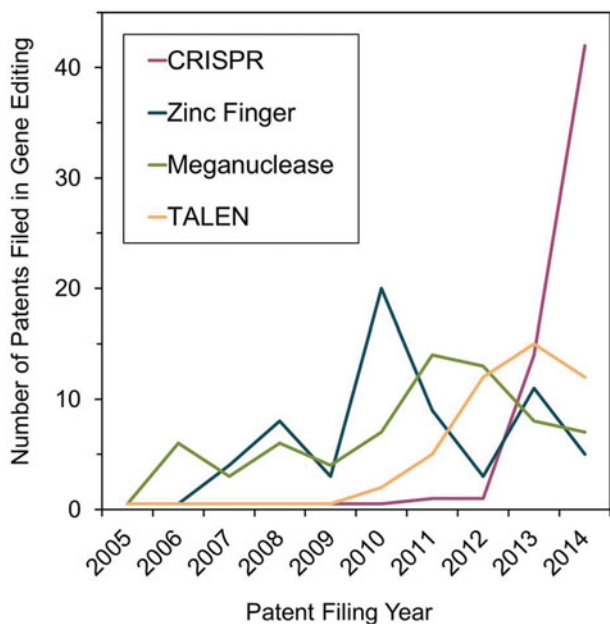
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## Intellectual property protection for gene editing

The number of patent applications filed in gene-editing technologies increased 15 fold since 2005 (Figure 1) [8]. Forty-two US patent applications involving CRISPR were filed in 2014. Intellectual property (IP) ownership of gene-editing technologies is diversified among academia and industry, which have implemented separate licencing strategies. The majority of CRISPR IP ownership belongs to several academic institutions (Figure 2(a)), whereas other gene-editing IPs, such as nuclease-based technologies, have originated from biotechnology firms (Supporting Information Tables S1–4) [8]. The majority of IP in nuclease-based gene-editing technology is owned by industrial organizations (Figure 2(b)). Sangamo Biosciences holds the majority of the patents for ZFN technology, and Cellectis and Precision Biosciences own the majority of the patents for engineered meganucleases, which were cross-licensed in 2014 as part of a patent litigation settlement (Figure 2(c)) [9]. However, a large portfolio of patents does not necessarily translate to a large market presence. In TALENs, both Cellectis and Thermo Fisher own blocking IPs [10]. Their IP portfolio also includes the foundational work conducted at the University of Minnesota and Martin Luther University, which strengthens the capability of both firms to commercialize TALENs (Figure 2(d)) [10].

The US Patent and Trademark Office (USPTO) awarded the Broad Institute the first patent for the use of CRISPR-Cas9 in April 2014 [11]. However, CRISPR IP



**Figure 1.** Number of patent applications filed for gene-editing technologies in the United States.

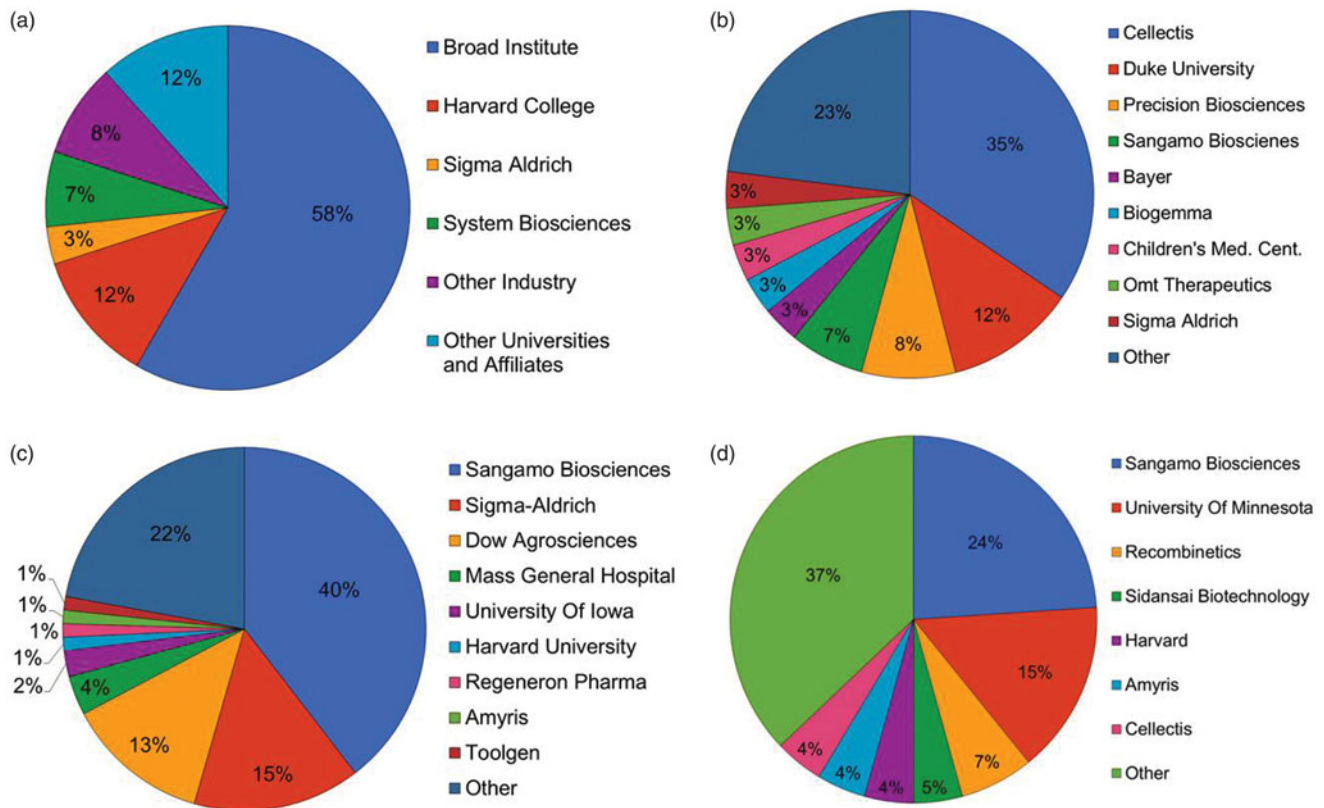
ownership is claimed by at least seven different parties [12]. Despite the uncertainty in patent ownership, major IP owners have licenced out CRISPR technologies to numerous biotechnology companies (Figure 3(a)) [13]. Additionally, academic IP owners of CRISPR have established their own startup companies such as Editas, Caribou Biosciences and CRISPR Therapeutics. These companies have exclusive access to the CRISPR intellectual properties owned by their respective affiliated institutions. At the time of analysis, Broad Institute had issued 13 nonexclusive licensing agreements, while the other five IP holders had approximately three contracts (Figure 3(b)) [13].

The large number of licenses from the Broad Institute, in comparison to other CRISPR IP holders, can be attributed to the Broad Institute holding the key-stone Patent No. 8,697,359 as well as 12 other CRISPR patents. The “359” is a potential blocking patent to the CRISPR-Cas9 system and its applications [14]. The ongoing patent interference dispute filed in April 2015 over the “359” patent may take years to be resolved. In February 2016, Caribou Bioscience was issued Patent No. 9,260,752, which makes claims to using CRISPR to detect and analyze DNA rather than to edit it [15]. The ramifications of this patent are currently unknown. However, it has the potential to be a blocking IP if its claims are deemed to be a key aspect of gene editing and the patent would then affect the CRISPR-Cas9 system outlined in the Broad patents and any alternative CRISPR methods yet to be discovered.

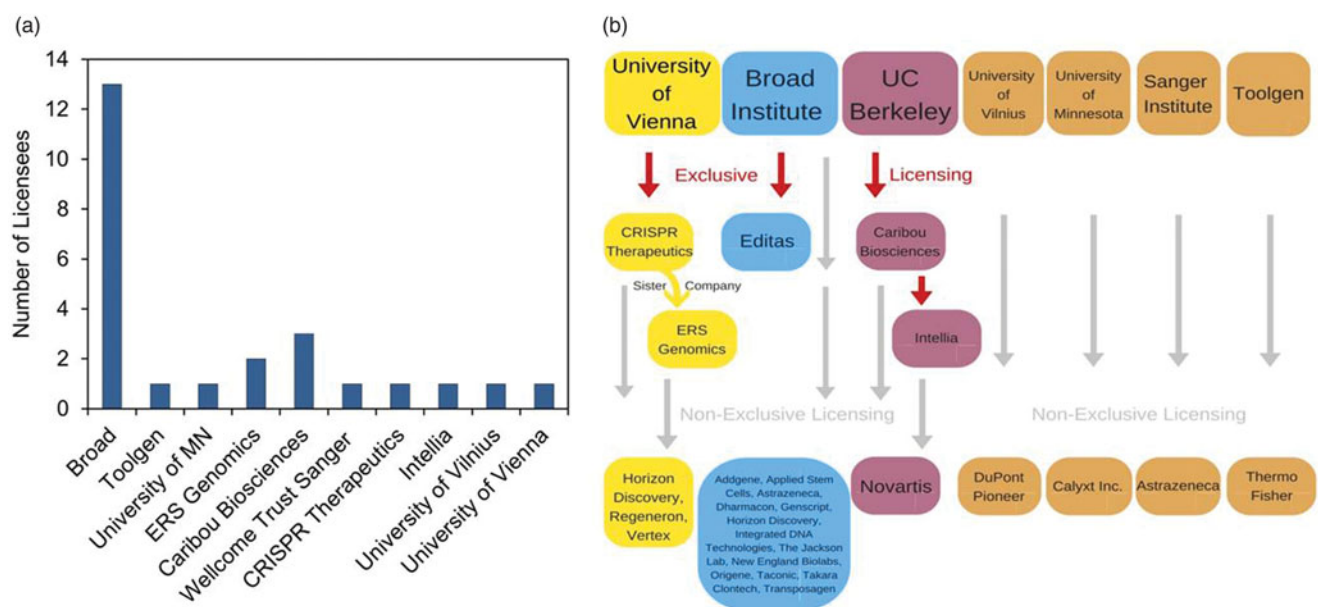
China also has a dynamic gene-editing patent landscape between academia and industry. China’s growing interest in CRISPR technology is reflected by its rapid increase in filing priority patents since 2013 (Figure 4(a)) [16]. China is second only to the United States in CRISPR priority patent applications [16]. Chinese patent assignees are spread across a diverse array of institutions and industry; whereas in the US patent landscape is dominated by a handful of major players (Supporting Information Table S5). Currently, the majority of CRISPR-related patent applications filed in China describe the use of CRISPR to knock out specific genes [17]. In 2013, Nanjing Sync Biotech Co. Ltd. filed a patent application for an improved method of gene knockout in eukaryotes. The following year, Hangzhou Normal University filed a patent application for the microRNA family knockout method, and Nanjing University applied for a patent application to knockout the hepatitis B virus. In 2015, Shenzhen Ke Huirui Biomedicine Co. Ltd. filed a patent application for knockout of the  $\beta$ 2-microglobulin gene in 293T cell lines. Also, South China Agricultural University applied for a patent application for the knockout of the PTMS12–1 gene to create thermo-

sensitive sterility rice [17]. Chinese universities and research institutions have a more robust patent portfolio in comparison to private companies (Figure 4(a)). The majority of the patents are intended to be effective

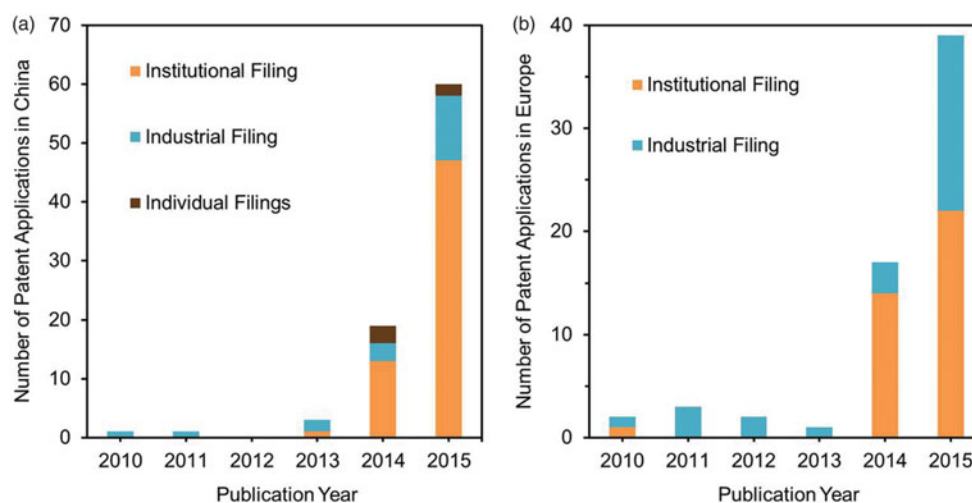
within China since a limited number of patents have been expanded to Patent Corporation Treaty (PCT) applications. Patent applications through local institutions and industry may be narrower in the scope of



**Figure 2.** Patent applications filed in gene-editing technology in the United States (2005–2014). (a) CRISPR, (b) meganuclease, (c) ZFNs, and (d) TALEN technologies categorized by patent filer (Supporting Information Tables S1–4).



**Figure 3.** Distribution of CRISPR licensing. (a) The number of licenses contracted by IP owners. (b) Allocation of IP through exclusive and non-exclusive licensing.



**Figure 4.** Patent applications filed related to CRISPR in (a) China and (b) the European Union based on assignee type (Supporting Information Tables S5 & 6).

protection [16]. Thus, the patent strategy in China fundamentally differs than the IP strategy in the US market. However, the ineffective enforcement of patents in China might limit the patent applications and their scope [18].

Similar to the United States and China, the number of patent applications in Europe has increased significantly since 2010 (Figure 4(b)). However, the patent applications in Europe are dominated by American institutions and companies (Supporting Information Table S7). The fundamental differences between European and US patent law have CRISPR patent applications; while the United States can fast track patent applications through “Track One” prioritized examination, the EU has more stringent regulations that require a clear establishment of the intellectual ownership and the novelty of use. For example, third-party observers are allowed to contest patent ownership and lodge complaints against novelty, which results in the rejection and limitation of patent scope in Europe. This has been the case in the CRISPR patent ownership dispute in Europe as a number of third-party observers disputed the initial filings of Broad Institute [19]. In contrast to the United States, patent exemptions for research exist under the national laws of each European country. While these exemptions will allow institutions, without CRISPR patents, to use CRISPR technology, these research institutions may have limited potential to partner with commercial enterprises [20].

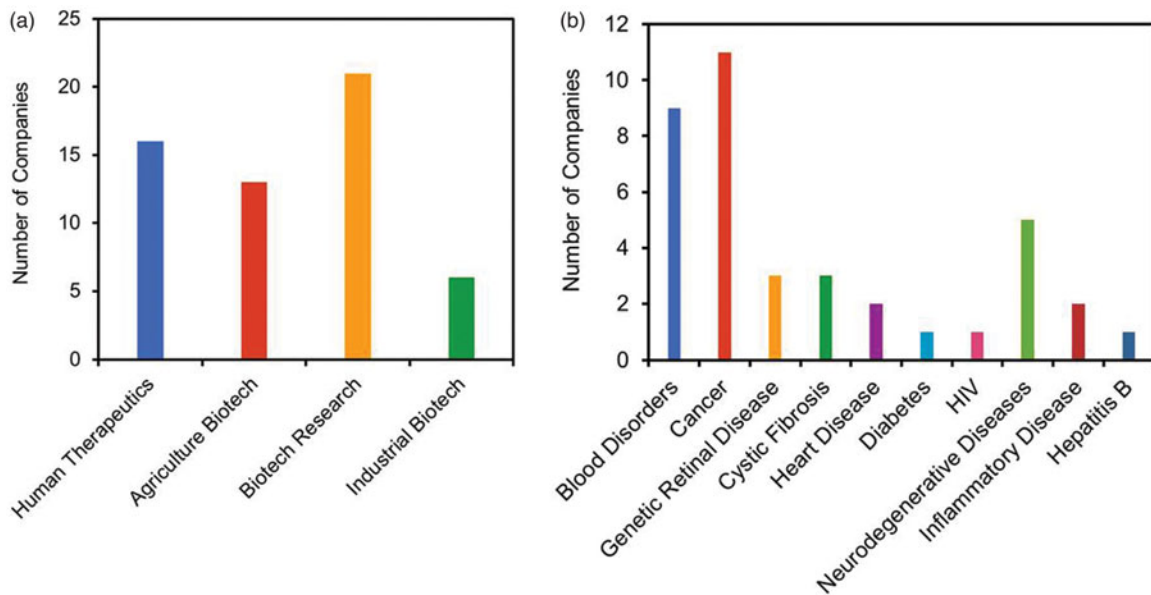
### Geographic distribution of companies involved in gene editing

In the analysis of 46 companies involved in genome-editing research, 36 firms were located in the United States (Supporting Information Table S7). Massachusetts

and California are home to 17 companies that have the largest gene-editing biotech landscape. Moreover, the majority of the companies are startups rather than established biotechnology corporations. Both states have a regions' large aggregation of academic and research institutes as well as preexisting biotechnology firms, thus allowing these areas to be ideal locations for genome editing startups. In contrast, gene-editing companies located outside of the United States are mostly comprised of pre-established biotech companies. Twenty-five percent of the gene-editing companies analyzed are outside of the United States, ten of which are located in the European Union (EU). The established biotechnology companies in the EU that utilize gene-editing technology originate from Switzerland (Novartis, Lonza) and Germany (BASF Plant Sciences and Bayer Crop Sciences). Asia has also seen growth in the genome-editing market with companies such as Toolgen (South Korea), which originated was the Center for Genome Engineering at Seoul National University.

### Segmentation of gene-editing market

The market for gene-editing is divided into research, human therapeutics, agricultural and industrial biotechnologies (Figure 5(a)) [21]. Research is the largest sub-market in the selected companies analyzed and comprised 38.6% of the market share. Companies in biotechnology research typically obtain CRISPR licenses to sell reagents, cell lines, and animal models to gene-editing companies and research institutes. However, the development of CRISPR has led to significant market growth in gene editing since 2012, especially due to the limitations of other preexisting gene-editing technologies [22]. Moreover, approximately another 25% of



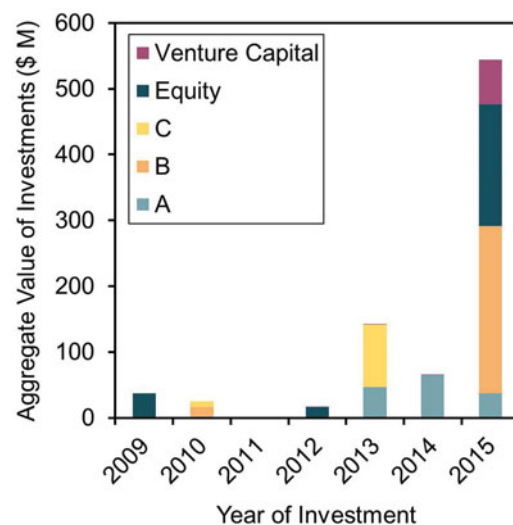
**Figure 5.** Applications of gene-editing technologies. (a) Companies utilizing gene-editing technology ( $n = 47$ ). (b) Gene-editing companies involved in human therapeutics by disease ( $n = 18$ ) (Supporting Information Table S7).

the selected companies focus on agriculture biotechnology and utilize gene-editing techniques in plants and animals, which can be used for sustainable food production. Early adoption of older gene-editing techniques (ZFNs and meganucleases) and less stringent regulatory standards have allowed the commercialization of gene-edited food products [23]. Industrial biotechnology (12.3%) has the smallest market share of the companies analyzed. Companies such as Sigma Aldrich and Precision Biosciences are developing high performance oils for various applications, and Collectis is developing biofuel from photosynthetic algae [24,25]. 26% of the companies analyzed are developing therapeutic products to treat a range of diseases including immunotherapies and hemoglobinopathies (Figure 5(b)) [21].

### Investment in gene editing

In the analysis of 17 gene-editing startup companies, the monetary investments were evaluated between 2009 and 2015 (Supporting Information Table S8). Each of these companies has used one or more of the four major gene-editing technologies: CRISPR, meganucleases, ZFNs and TALENs (Figure 6). In 2015, gene-editing startups received \$550 million in investments, a twofold increase as compared to the aggregate investments in 2013 and 2014. This increase in investment corresponds to the establishments of Editas, CRISPR Therapeutics and Intellia.

Between 2010 and 2015, more than 60 investors funded the 46 gene-editing companies analyzed



**Figure 6.** Investments in gene-editing startups categorized by funding round (Supporting Information Table S8).

(Supporting Information Table S8). These investors included six pharmaceutical companies, six angel investors, three private equity firms, and three investment groups in addition to a small number of government grants. However, the majority of investors in gene editing (~30) are venture capital firms. Twenty-five of these firms have focused on the healthcare or biotechnology sectors; 15 specialize in early-stage funding, 13 participate in all stages of funding and the remaining firms specialize in middle to late-stage funding, including commercialization and buyout. Over the past 5 years, ~\$280 million was invested in seed and series A

funding, and \$420 million was invested in series C funding. Only Origene, a company founded in 1996, has received Series D funding at \$17 million. Aside from typical funding rounds, early-stage companies have also been acquired such as Dharmacon (\$13.6 billion, Thermo Fisher Scientific) [26].

The recent influx in gene-editing startups has drawn major private investments to the US market. Since 2013, over \$1 billion has been invested in US gene-editing startups and the majority of this investment was allocated to CRISPR-based companies. Since its inception through 2015, Caribou Biosciences has raised \$36.6 million, and Editas has received \$180 million from private investors such as Google Ventures (Alphabet Inc.) and partnerships before raising \$109 million in its initial public offering [27,28]. Large pharmaceutical companies have also partnered with venture capital firms to fund startups. In 2014, Novartis and Atlas Ventures invested \$15 million in Intellia Therapeutics [29]. In 2015, Bayer invested \$335 million in CRISPR Therapeutics [30]. The same year, Celgene joined Abingworth, New Enterprise Associates, SR One and Versant Ventures in an investment of \$64 million for CRISPR Therapeutics [31]. In early 2016, Baxalta made a \$105 million deal with Precision Biosciences to develop cancer-treatment therapies [32]. Hence, investments in gene-editing startups remain strong despite the ambiguity in product to market timeline and stringent FDA regulations.

With approximately 435 biotechnology companies, the United Kingdom is a leader in the biotechnology sector. However, with a decline in stock values of almost 37% in 2007, UK companies have limited funding [33]. Because of this downward trend or due to strict regulations, European investors are hesitant to invest in gene-editing companies. However, some European startups have secured funding; CRISPR Therapeutics (2013, Switzerland) has raised \$124 million. Additionally, China is rapidly raising funds for gene-editing technologies. The Chinese government has been actively involved in gene-editing funding. The National Natural Science Foundation of China (NNSF), invested \$3.5 million in over 40 CRISPR projects during 2015. Through the NNSF and the National Basic Research Program, the Chinese government has funded the first use of CRISPR for the modification of human embryos [34]. Additionally, Shenzhen Jinjia Color Printing Group Co., a public company, has pledged \$0.5 million to fund Sun Yat-sen University for studying CRISPR in embryos [35].

### Regulations of gene-editing technologies

A barrier to the commercialization of gene-editing human therapeutic products is the unclear regulations.

The FDA's guidance for the utilization of CRISPR in human clinical trials are ambiguous since the implications of CRISPR use in medical practice are not fully understood [36]. Currently, Sangamo Biosciences is conducting a phase-II clinical trial to determine the safety and tolerability of a drug modified with ZFNs (SB-728) [37]. Thus far, no adverse events have been reported, which could potentially influence the approval of CRISPR for human studies. Despite the unclear regulatory guidelines, investments in human therapeutic gene-editing have not been stalled. Other regulatory agencies such as US Department of Agriculture (USDA) have decided not to regulate some CRISPR-modified organisms. The USDA has declared that at least eight cases of ZFNs and TALENs mutations do not fall under their regulatory jurisdiction [23]. As a result, agricultural corporations including Dow AgroSciences, Cellectis, Agrivida, and Cibus can conduct trials and commercialize products without further review. Moreover, the USDA approved the cultivation and commercialization of CRISPR-Cas9 modified white button mushroom (*Agaricus bisporus*) that resist browning [38]. In contrast, the EU's historically strict regulation against GMO's has limited the use of genome editing in agriculture [23]. Hence, genetically modified agricultural products have a clear path toward commercialization.

### Clinical impact of genome-editing technologies and ethical implications

During the next decades, genome-editing technologies will play an important role in human and animal health. Currently, several genetically engineered therapeutic strategies aside from CRISPR have been utilized in oncology clinical trials and are on the path toward regulatory approval [39]. Nevertheless, it is expected that a new generation of therapeutics will arise from the use of CRISPR technology, as it will enable scientists to target specific genome sequences that other therapeutic modalities are not currently able to target. Genetic diseases will mainly benefit from genome-editing technologies; however, non-hereditary pathologies such as some degenerative disorders can be impacted, as most of these diseases have cumulative genetic mutational components that are the result of epigenetic changes [40].

Before reaching the clinical arena, several challenges remain in the application of CRISPR including: long term safety implications, off-target mutations and deleterious effects [41]. In the case of large mammalian genomes, CRISPR/Cas9 may cleave highly homologous DNA sequences, causing mutations that may result in unwanted effects such as cell apoptosis [42]. Several

efforts to improve off-targeting using CRISPR have been made [43]; however, the technology must be further developed before finding clinical applications.

The ethical debate of genome editing has reached the international stage. In 1997, the Universal Declaration on the Human Genome and Human Rights, a moratorium against the intervention of genetically modified human germlines, was issued by United Nations Education, Scientific and Cultural Organization (UNESCO) [44]. Recently, the US National Institutes of Health (NIH) also called for a moratorium, prohibiting NIH-funded research in embryologic genome editing [45]. The clinical realization of gene-editing technologies, such as CRISPR, has furthered ethical and legal concerns. The misuse and ethical implications of this technology on modified human germlines was recently debated at the International Summit on Human Gene Editing [46]. In the US, concerns regarding the transmission of genetic modifications to future generations, and the uncertainties of the technology are barriers to clinical entry. However, in other countries such as China and the United Kingdom, regulators recently approved the use of CRISPR/Cas9 in human embryos exclusively for research purposes [34,47,48]. Nevertheless, there are concerns about the potential to select specific human genetic characteristics to modify appearance, physical, and intellectual capabilities. To date, these concerns have not affected the exponential growth in patent filings in genome editing technologies for human healthcare. Before the application of genome editing technologies in humans and other species, regulatory discussion and norms should be implemented to prevent the abuse of this technology concerning the social, ethical and legal implications.

### The future of gene-editing commercialization

The commercialization of CRISPR technologies demonstrates the increasing role of academic institutions in the formation of business ventures. This change in the entrepreneurial culture indicates that knowledge-based economies are set to expand the growth of academic-born bioventures. CRISPR-related technologies will continue to rapidly spread in agricultural and healthcare applications. While academic institutions in the US and EU will continue to debate and contest the ownership of CRISPR technology, emerging global players such as China will have a clear path to further the development of CRISPR and create their bioventures, where the US and EU patents are not strictly enforced. Moreover, China, where the regulations are less stringent, may take the lead in developing commercial applications for gene-editing in humans. Although the patent

ownership dispute of CRISPR technologies has caused hesitance among some investors, it has not significantly hindered the growth of investments. A concern in market segmentation is patent ownership-related monopolization of the gene-editing methods, which may limit the scope of commercial products. Additionally, the FDA regulations regarding the CRISPR technology remain unclear. Gene-edited agricultural products will have significant market share in the short term, while gene-edited human therapeutics may take decades to enter to market and revolutionize healthcare.

### Acknowledgements

We thank Amir Manbachi and Joao Ribas for discussions.

### Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

### References

- [1] Boslet M. Corporate VCs Set 15 Year Investment Record with \$7.6 Bln Deployed in 2015. [cited 2016 Apr 12]. Available from: <https://www.pehub.com/2016/01/659007/>
- [2] Genome Editing/Genome Engineering Market by Application (Cell Line Engineering, Animal & Plant Genetic Engineering), Technology (CRISPR, Antisense, TALEN, Zinc Finger Nuclease) & End User (Biotechnology & Pharmaceutical, Cro) - Global Forecast to 2019. [cited 2016 Apr 12]. Available from: <http://www.marketsandmarkets.com/Market-Reports/genome-editing-engineering-market-231037000.html>
- [3] Doudna JA, Charpentier E. The new frontier of genome engineering with CRISPR-Cas9. *Science*. 2014;346:1258096.
- [4] van Erp PB, Bloomer G, Wilkinson R, et al. The history and market impact of CRISPR RNA-guided nucleases. *Curr Opin Virol*. 2015;12:85–90.
- [5] Liang P, Xu Y, Zhang X, et al. CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes. *Protein Cell*. 2015;6:363–372.
- [6] Shalem O, Sanjana NE, Hartenian E, et al. Genome-scale CRISPR-Cas9 knockout screening in human cells. *Science*. 2014;343:84–87.
- [7] Lawrenson T, Shorinola O, Stacey N, et al. Induction of targeted, heritable mutations in Barley and Brassica Oleracea using RNA-Guided Cas9 nuclease. *Genome Biol*. 2015;16:1–13.
- [8] The data was compiled from USPTO patent full-text and image database from 1976 to April 9th, 2016, the search terms were “CRISPR”, “TALEN(s)”, “Zinc Finger Nuclease”, “Meganuclease”, and “Engineered Nuclease” in all fields. The name of the gene-editing method was present in the abstract of the patent application. The results were cross-referenced with Google

- Patents. [cited 2016 Sep 22]. Available from: <http://patft.uspto.gov/netahtml/PTO/search-bool.html>.
- [9] Precision Biosciences and Collectis SA Announce Cross-License and Settlement Agreement for Gene Editing Technology, Press Release, Collectis. [cited 2016 Sep 22]. Available from: <http://www.collectis.com/en/content/precision-biosciences-and-collectis-sa-announce-cross-license-and-settlement-agreement-gen-0>.
- [10] Collectis and Thermo Fisher Scientific Enter into Agreements on Talen™, a Leading Gene Editing Technology, Press Release, Collectis. [cited 2016 Sep 22]. Available from: <http://www.collectis.com/en/content/collectis-and-thermo-fisher-scientific-enter-agreements-talentm-leading-gene-editing-0>
- [11] Ledford H. How the US CRISPR patent probe will play out. *Nature*. 2016;531:149.
- [12] Sherkow JS. CRISPR: pursuit of profit poisons collaboration. *Nature*. 2016;532:172–173.
- [13] The data was compiled from press releases from the company websites, Keywords searched were “company name”, “gene editing technology”, and “license agreements” in Google. [cited 2016 Jan 15]. Available from: <https://www.google.com/#q=Gene+Editing+Technology+License+Agreements>
- [14] Zhang F. CRISPR-Cas systems and methods for altering expression of gene products. US Patent (US 8,697,359). 2014.
- [15] May AP, Haurwitz RE, Doudna JA, et al. Compositions and methods of nucleic acid-targeting nucleic acids. WO2014150624 A1 (Patent application) 2014.
- [16] Le Buhan C. CRISPR Patents – the Raise of China. [cited 2016 May 25]. Available from: <http://www.ipstudies.ch/2015/09/crispr-patents-the-raise-of-china/>
- [17] Peng Y. The morality and ethics governing CRISPR-Cas9 patents in china. *Nat Biotechnol*. 2016;34:616–618.
- [18] Yueh L. Patent laws and innovation in China. *Int Rev Law Econ*. 2009;29:304–313.
- [19] Kupecz A. Who Owns CRISPR-Cas9 in Europe? *Nat Biotechnol*. 2014;32:1194–1196.
- [20] Sherkow JS. Patents in the Time of CRISPR. *Biochemist e-volution*. 2016;38:26–29.
- [21] The data was collected by searching the company websites to determine CRISPR applications. [cited 2016 Sep 22]. Available from: <https://www.google.com/#q=Applications+of+CRISPR>
- [22] Gupta RM, Musunuru K. Expanding the genetic editing tool kit: ZFNs, TALENs, and CRISPR-Cas9. *J Clin Invest*. 2014;124:4154–4161.
- [23] Wolt JD, Wang K, Yang B. The regulatory status of genome-edited crops. *Plant Biotechnol J*. 2016;14:510–518.
- [24] Collectis Has Successfully Engineered the Genome of Photosynthetic Algae with a View to Biofuel Production. [cited 2016 May 25]. Available from: <http://www.collectis.com/en/content/collectis-has-successfully-engineered-genome-photosynthetic-algae-view-biofuel-production-2>
- [25] Glorikian H. Gene Editing Will Change Everything—Just Not All at One Time. [cited 2016 May 25]. Available from: <http://www.genengnews.com/insight-and-intelligence/gene-editing-will-change-everything-just-not-all-at-one-time/77900351/>
- [26] Fisher Scientific Completes Acquisition of Dharmacon; Expands Its Portfolio of Proprietary Products, Press Release, ThermoFisher Scientific, Hampton, Nh. [cited 2016 May 25]. Available from: <http://ir.thermofisher.com/investors/news-and-events/news-releases/news-release-details/2004/Fisher-Scientific-Completes-Acquisition-of-Dharmacon-Expands-Its-Portfolio-of-Proprietary-Products/default.aspx>
- [27] Editas Medicine Raises \$120 Million to Advance Genome Editing, Editas, Cambridge, MA. [cited 2016 May 25]. Available from: <http://ir.editasmedicine.com/phoenix.zhtml?c=254265&p=irol-newsArticle&ID=2125221>
- [28] Herper M. Bill Gates and 13 Other Investors Pour \$120 Million into Revolutionary Gene-Editing Startup, *Forbes*. [cited 2016 May 25]. Available from: <http://www.forbes.com/sites/matthewherper/2015/08/10/bill-gates-and-13-other-investors-pour-120-million-into-revolutionary-gene-editing-startup/#16c7edc3664c>
- [29] Intellia Therapeutics Announces \$15 Million in Funding to Develop Therapeutic Products Utilizing CRISPR-Cas9 Gene Editing Technology, Business Wire, Cambridge, MA. [cited 2016 May 25]. Available from: <http://www.businesswire.com/news/home/20141118005077/en/Intellia-Therapeutics-Announces-15-Million-Funding-Develop>
- [30] Bayer and CRISPR Therapeutics AG Join Forces to Discover, Develop and Commercialize Potential Cures for Serious Genetic Diseases, Press Release, Bayer, Leverkusen, Germany and Basel, Switzerland. [cited 2016 May 25]. Available from: <http://www.bayer.nl/nl/media/nieuws/bayer-and-crispr-therapeutics-ag-join-forces-to-discover-develop-and-commercialize-potential-cures-for-serious-genetic-diseases.php>
- [31] CRISPR Therapeutics Raises Additional \$64 Million to Translate Breakthrough CRISPR-Cas9 Technology into Next Generation Therapies for Patients, Business Wire. [cited 2016 May 25]. Available from: <http://www.businesswire.com/news/home/20150428007057/en/CRISPR-Therapeutics-Raises-Additional-64-Million-Translate>
- [32] Baxalta and Precision Biosciences Form Global Genome Editing Collaboration in Immuno-Oncology, Press Release, Precision Biosciences, Durham, North Carolina. [cited 2016 May 25]. Available from: <http://precisionbiosciences.com/baxalta-and-precision-biosciences-form-global-genome-editing-collaboration-in-immuno-oncology/>
- [33] Smith G, Akram MS, Redpath K, et al. Wasting cash—the decline of the British biotech sector. *Nat Biotechnol*. 2009;27:531–537.
- [34] Callaway E. Second Chinese team reports gene editing in human embryos. *Nature*. 2016. DOI:10.1038/nature.2016.19718
- [35] China Builds a Faster Beagle in Gene-Editing Race with U.S., *Bloomberg Technology*. [cited 2016 May 25]. Available from: <http://www.bloomberg.com/news/articles/2016-02-23/china-bets-big-on-gene-editing-technology-in-race-against-u-s>
- [36] Brennan Z. Fda Authorizes First Human Study to Use in Vivo Genome Editing Application, *Regulatory Affairs*



- Professionals Society. [cited 2016 May 25]. Available from: <http://www.raps.org/Regulatory-Focus/News/2015/12/08/23734/FDA-Authorizes-1st-Human-Study-to-Use-In-Vivo-Genome-Editing-Application/>
- [37] Study of Autologous T-Cells Genetically Modified at the Ccr5 Gene by Zinc Finger Nucleases in HIV-Infected Subjects, Clinical Trial, U.S. National Institutes of Health. [cited 2016 May 25]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01252641>
- [38] Waltz E. Gene-edited CRISPR mushroom escapes us regulation. *Nature*. 2016;532:293.
- [39] Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. *Science*. 2006;314:126–129.
- [40] Go DE, Stottmann RW. The impact of CRISPR/Cas9-based genomic engineering on biomedical research and medicine. *Curr Mol Med*. 2016;16:343–352.
- [41] Cho SW, Kim S, Kim Y, et al. Analysis of off-target effects of CRISPR/Cas-derived RNA-guided endonucleases and nickases. *Genome Res*. 2014;24:132–141.
- [42] Lin Y, Cradick TJ, Brown MT, et al. CRISPR/Cas9 systems have off-target activity with insertions or deletions between target DNA and guide RNA sequences. *Nucleic Acids Res*. 2014;42:7473–7485.
- [43] Shen B, Zhang W, Zhang J, et al. Efficient genome modification by CRISPR-Cas9 Nickase with minimal off-target effects. *Nat Methods*. 2014;11:399–402.
- [44] Mayor F. The Universal Declaration on the Human Genome and Human Rights. *C R Biol*. 2003;326:1121–1125.
- [45] Collins F. Statement on NIH Funding of Research Using Gene-Editing Technologies in Human Embryos, the Nih Director – National Institutes of Health (NIH), 2015.
- [46] LaBarbera AR. Proceedings of the International Summit on Human Gene Editing: a global discussion—Washington, D.C., December 1–3, 2015. *J Assist Reprod Genet*. 2016;33:1123–1127.
- [47] Cyranoski D, Reardon S. Chinese scientists genetically modify human embryos. *Nature*. 2015. DOI:10.1038/nature.2015.17378
- [48] Callaway E. UK scientists gain licence to edit genes in human embryos. *Nature*. 2016;530:18.