

CRISPR/Cas9 system and gene editing tools – On patent rights, recent disputes and its potential commercial applicability in biotechnology and medicine

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ABSTRACT

The CRISPR/Cas9 discovery has emerged as a powerful technology tool to edit genomes, which allows researchers, innovators and life science entrepreneurs to alter DNA sequences and modify gene function in a range of species. The simplicity, high efficiency and seemingly broad use of the CRISPR/Cas9 system has led to hopes that this disruptive technology may have the potential to transform important sectors of biotechnology and medicine. The technology will enable users to make changes in the sequence or expression of virtually any gene, cell type or organism. The rapid progress in the development of CRISPR/Cas9-based technologies over the past years has been extraordinary. In spite of that, many outstanding questions remain to be addressed, and potentially interesting applications as well as potential risks yet need to be explored. Without doubt, the rapid advances and extensive commercial applicability of the CRISPR technologies is likely to have a societal impact within the decades to come.

In medicine, recent and future advances in the applicability of Cas9-based systems for genome and epigenome editing are likely to advance the technology forward to therapeutic applications, in respect to treatment of a variety of human diseases. In biotechnology, these techniques may be exploited in several respects to the benefit of society at large. In the biosciences, the CRISPR technology may have significant applications to make changes in the genome of various forms of organisms, including cells of domestic animals, cells of plants and various crops, bacteria, viruses and other cells. The technology

may also find a future use in “de-extinction” of various animals such as the woolly mammoth and passenger pigeon.

The recent discoveries and developments have led to extensive patenting efforts, resulting in some major patent disputes. The extensive patenting may risk creating a scenario, which could hamper the further development of this technology and ultimately limit full value creation of this technology for major societal and industrial stakeholders.

1. INTRODUCTION

The CRISPR technology, which allows researchers to easily alter DNA sequences and modify gene function has over the past decade emerged a simple and powerful tool for editing genomes¹ The CRISPR/Cas9 is a system initially found in bacteria as a mechanism involved in immune defence. Bacteria use CRISPR/Cas9 to cut up the DNA of invading viruses to avoid being killed by the virus invasion. From its initial discovery, scientists have adapted this bacterial molecular machinery for entirely different purposes. Molecular engineering has made it possible to use this system to change any chosen nucleotide (or "letter") in the DNA code of an organism. By doing so, CRISPR/Cas9 can be used to correct a disease-causing genetic error that was inherited or occurred later in an individual's DNA when replicated. Alternative uses of the technology may be to change the genetic code in order to enhance or introduce specific functions in e.g. plants to improve crops or to modify genes in domestic animals. There are also on-going efforts to bring back extinct species to life that were previously eradicated by humans.² However, in addition to the wide range of possible favourable applications of the CRISPR/Cas9 technology, the technology also raises a range of ethical concerns.³

¹ Lander, E.S. [2016]. The Heroes of CRISPR, Cell January 14, 2016, Crossley, M. [2018]. What is CRISPR gene editing, and how does it work? The Conversation, January 31, 2018. <https://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591> and Vidyasagar, A. [2018]. What Is CRISPR?

Live Science April 20, <https://www.livescience.com/58790-crispr-explained.html>.

² Crossley, M., [2018]. What is CRISPR gene editing, and how does it work? The Conversation, January 31, 2018. <https://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591>

³ Vidyasagar, A. [2018]. What Is CRISPR? Live Science April 20, <https://www.livescience.com/58790-crispr-explained.html>.

⁴ Ibid.

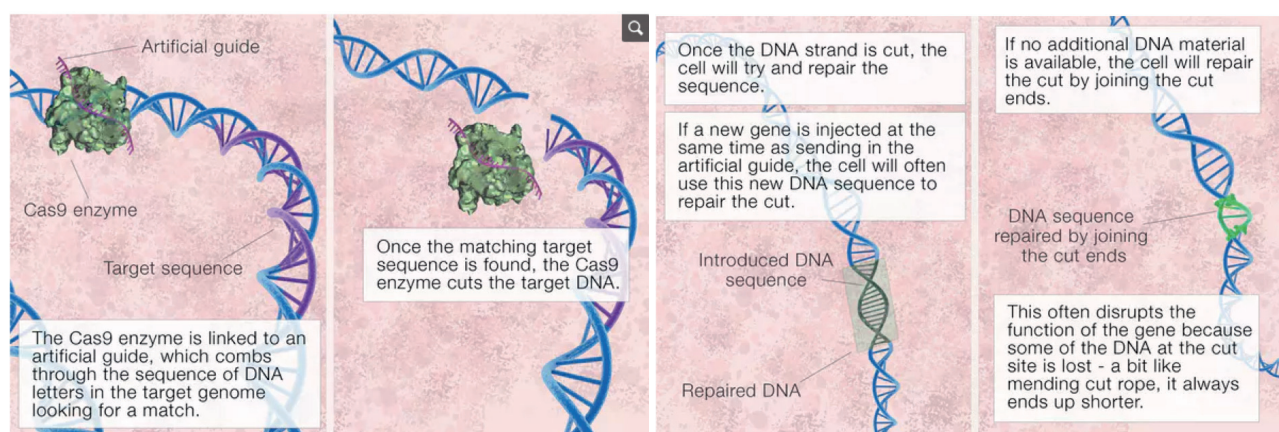


Figure 1: CRISPR/Cas9 technologies may be used as DNA editing tools in medicine and biotechnology. The Cas9 “scissors” is provided with a copy of the DNA to be altered in order to identify where to cut the DNA strand. If a selected new DNA strand is injected, it will take the place of the DNA that was cut out. Creative Commons licence (CC BY-ND)

Cas9 is the technical name for the virus-destroying “scissor” protein that evolved in bacteria. The CRISPR part of the acronym relates to the specific DNA sequences of the complex immune system telling the Cas9 “scissors” where to cut the DNA strand (see Figure 1). CRISPR is an abbreviation for “*Clusters of Regularly Interspaced Short Palindromic Repeats*.” The term refers to a specialized region of DNA, presenting with nucleotide repeats and spacers. Such repeated nucleotide sequences, (DNA building blocks) are distributed throughout a CRISPR region.⁴ Spacers are pieces of DNA, which are found interspersed among the repeated sequences. The CRISPR systems initially identified in bacteria, as adaptable and dynamic immune mechanisms, which the bacteria had developed in order to protect themselves from alien virus or plasmid nucleic acid material.⁵

In order to modify the genetic code (see Figure 1), a unique DNA sequence guide code can be made that will line up with only one specific part of the 3 billion base pair long genome in the cell. By carefully designing the DNA sequence, only one section of the DNA will match it exactly. After administration, the new DNA sequence will then move around in the cell and move into the only place where it fits among the billions of pieces of base pairs in the genome. In practice, the CRISPR/Cas9 components are administered together with the donor DNA to alter the gene. In the laboratory, it can be made by simple injection, or by a range of other molecular biology techniques. Importantly, in real life, it is also possible to administer the essential CRISPR/Cas9 components directly to living humans or animals. Taken together, with the CRISPR/Cas9 technology it is easy to change the genome of any

form of life, by cutting away genes, or inserting new genes.⁶

In this review, we provide an overview of how this CRISPR/Cas9 system works and how it has been applied to perform genome editing across a wide variety of cell types and whole organisms. We also discuss the current extensive patenting efforts from many different actors. Further we describe the recent and on-going patent disputes following the discovery and early exploitation of this system. Finally, we speculate on future challenges related to commercial exploitation that needs to be addressed for efficient use of this emerging genome editing platform in clinical medicine and diverse areas of biotechnology.

2. CRISPR/CAS 9 – A BREAK-THROUGH DISCOVERY

CRISPR/Cas9 is a type of molecular machinery found in some bacteria, including *Streptococcus pyogenes*. The task of this machinery is to destroy intruding DNA chains, originating for example from attacking viruses.⁷ A major leap towards this break-through technology was made by Emmanuelle Charpentier when studying the immune system of bacteria, during a visiting professorship at the University of Umeå in Northern Sweden. It was previously known that bacteria have their own kind of “vaccination program” that protects against attacking viruses, which was known as CRISPR/Cas9. When Emmanuelle Charpentier and her colleague Jennifer Doudna studied this system, they discovered how to control this bacterial defence system, and use it to cut and paste the genome of virtually any cell of interest.⁸

⁵ Sander, J.D. & Joung, J.K. (2014) CRISPR-Cas systems for genome editing, regulation and targeting. *Nat Biotechnol.* 2014 Apr; 32(4): 347–355. doi: 10.1038/nbt.2842.

⁶ Ishino Y., Mart Krupovic, M., Forterre, P. (2018). History of CRISPR/Cas from

encounter with a mysterious repeated sequence to genome editing technology. *J Bacteriology* April ,200 (7): 1-17, e00580-17.

⁷ Crossley, M. (2018). What is CRISPR gene editing, and how does it work? The Conversation, January 31, 2018. <https://theconversation.com/what-is-crispr-gene->

[editing-and-how-does-it-work-84591](https://theconversation.com/what-is-crispr-gene-editing-and-how-does-it-work-84591).

⁸ Doudna, A. & Charpentier, E. (2014). The new frontier of genome engineering with CRISPR/Cas9. *Science* 28 Nov; 346 (6213) doi: 10.1126/science.1258096,



The machinery has two main components. One is a protein, Cas9, which is an enzyme that cuts DNA chains. The other is a collection of DNA fragments, called CRISPRs (Figure 1).

Cas 9: This enzyme extracts a DNA fragment from CRISPR and searches for occurrences of the same sequence in other DNA chains. When Cas9 identifies such a DNA sequence, it cuts off this DNA chain, which then loses its ability to perform its function. In the bacteria, which are under attack, the spacer DNA pieces are taken from viruses that previously attacked the organism. These DNA fragments serve as a memory bank, which enables bacteria to recognize the viruses and defend them from future viral attacks. When the components of this natural defence system are introduced and put to work in more complex organisms, it allows for the manipulation of genes, or "genetic editing" in various mammals or plant species.

CRISPR: The CRISPRs are specific strands of DNA, while the protein Cas9 (or "CRISPR-associated") is an enzyme capable of cutting strands of DNA, acting like a pair of "molecular scissors". The term "CRISPR" sometimes also stands for "CRISPR/Cas9." The CRISPR natural defence mechanisms of bacteria and archaea (the domain of single-celled microorganisms) have developed over evolution to fight off attacks by viruses and other foreign bodies. That system builds on CRISPR-derived RNA and various Cas proteins, including Cas9 (Figure 1), which allows the defending cells to cut and destroy the DNA from a foreign invader. The spacer is incorporated into the

host DNA, and when the virus attacks the host cells again, a portion of the CRISPR DNA will be transcribed and processed into CRISPR RNA, or "crRNA." The nucleotide sequence of the CRISPR can then act as a template to produce a complementary sequence of single-stranded RNA (crRNA), consisting of a nucleotide repeat and a spacer portion.⁹

The Cas9 protein is essentially an enzyme that has the capacity to attack foreign DNA. The Cas9 protein then binds to two RNA molecules, one of which is crRNA and the other tracrRNA (or "trans-activating crRNA"). These two RNA molecules then guide Cas9 enzyme to the target site where it can cut the target DNA, which may be complementary to a 20-nucleotide stretch of the crRNA. The Cas9 can cut cuts both strands of the DNA double helix, and make a "double-stranded break".

The CRISPR/Cas9 system also has a built-in safety mechanism, which prevents Cas9 to just cut anywhere in a genome. This mechanism is made up of short DNA sequences called PAMs ("protospacer adjacent motifs"), which are located adjacent to the target DNA sequence and serve as "tags" for Cas9. If the Cas9 complex does not identify a PAM next to the target DNA sequence, it will not cut the DNA. This safety mechanism may be reason why Cas9 never attacks the CRISPR region in bacteria.¹⁰

Due to these functionalities, it is possible to use the CRISPR systems to do specific genomic sequence changes in living cells and organisms. CRISPR/Cas9 can therefore be used as a powerful tool not only in biological research, and it also has the potential system to be used in the management of specific forms of genetic diseases. Such targeted genome editing will provide a new method to induce targeted deletions, insertions or to make precise sequence changes in a broad range of biological organisms and cell types. For example, specific nucleotide sequence alterations can be made to correct defective genes for therapeutic applications in specific genetic diseases, or to transfer valuable traits to agricultural crops and livestock. Although the early work related to CRISPR/Cas9 gene-editing system began in the 1990s, the full identification and understanding of these mechanisms has stretched over decades.

In 2009 Emmanuelle Charpentier and her research group

⁹ Doudna, A. & Charpentier, E. [2014]. The new frontier of genome engineering with CRISPR/Cas9. *Science* 28 Nov: 346 [6213] doi: 10.1126/science.1258096.

¹⁰ Ibid.

¹¹ Deltcheva, E., Chylinski, K., Sharma, C.M., Gonzales, K., Chao, Y., Pirzada, Z.A., Eckert, M.R., Vogel, J. & Charpentier, E. [2011]. CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III. *Nature* 471; 602–607.

¹² Deltcheva, E., Chylinski, K., Sharma, C.M., Gonzales, K., Chao, Y., Pirzada, Z.A., Eckert, M.R., Vogel, J. & Charpentier, E. [2011]. CRISPR RNA maturation by trans-encoded small RNA and host factor RNase III. *Nature* 471; 602–607 and Jinek, M., Chylinski, K.,

Fonfara, I., Hauer, M., Doudna, J.A., & Charpentier, E. [2012]. A programmable dual-RNA-guided DNA endonuclease in adaptive bacterial immunity. *Science*. Aug 17; 337[6096]: 816–821. doi: 10.1126/science.1225829.

¹³ Charpentier, E. & Doudna, J.A. 2013. *Biotechnology: Rewriting a genome*. *Nature* 495[7439]:50-51 and Doudna, A. & Charpentier, E. [2014]. The new frontier of genome engineering with CRISPR/Cas9. *Science* 28 Nov: 346 [6213] doi: 10.1126/science.1258096.

¹⁴ Cong, L., Ran, F.A., Cox, D., Lin, S., Barretto, R., Habib, N., Hsu, P.D., Wu, X., Jiang, W., Marraffini, L.A. & Zhang, F. [2013]. Multiplex genome engineering using CRISPR/Cas

systems. *Science* Feb 15; 339[6121]: 819–823 doi: 10.1126/science.1231143 and Hsu, P.D., Lander, E.S., Zhang, F. [2014]. Development and Applications of CRISPR/Cas9 for Genome Engineering (Review). *Cell* 157, [6] 5: 1262–1278, June 2014, <https://doi.org/10.1016/j.cell.2014.05.010>.

¹⁵ Qi, L.S., Larson, M.H., Gilbert, L.A., Doudna, J.A., Weissman, J.S., Arkin, A.P., Lim, W.A. [2013]. Repurposing CRISPR as an RNA-Guided Platform for Sequence-Specific Control of Gene Expression. *Cell* 152 [5], 1173–118, 28 February, doi.org/10.1016/j.cell.2013.02.022.

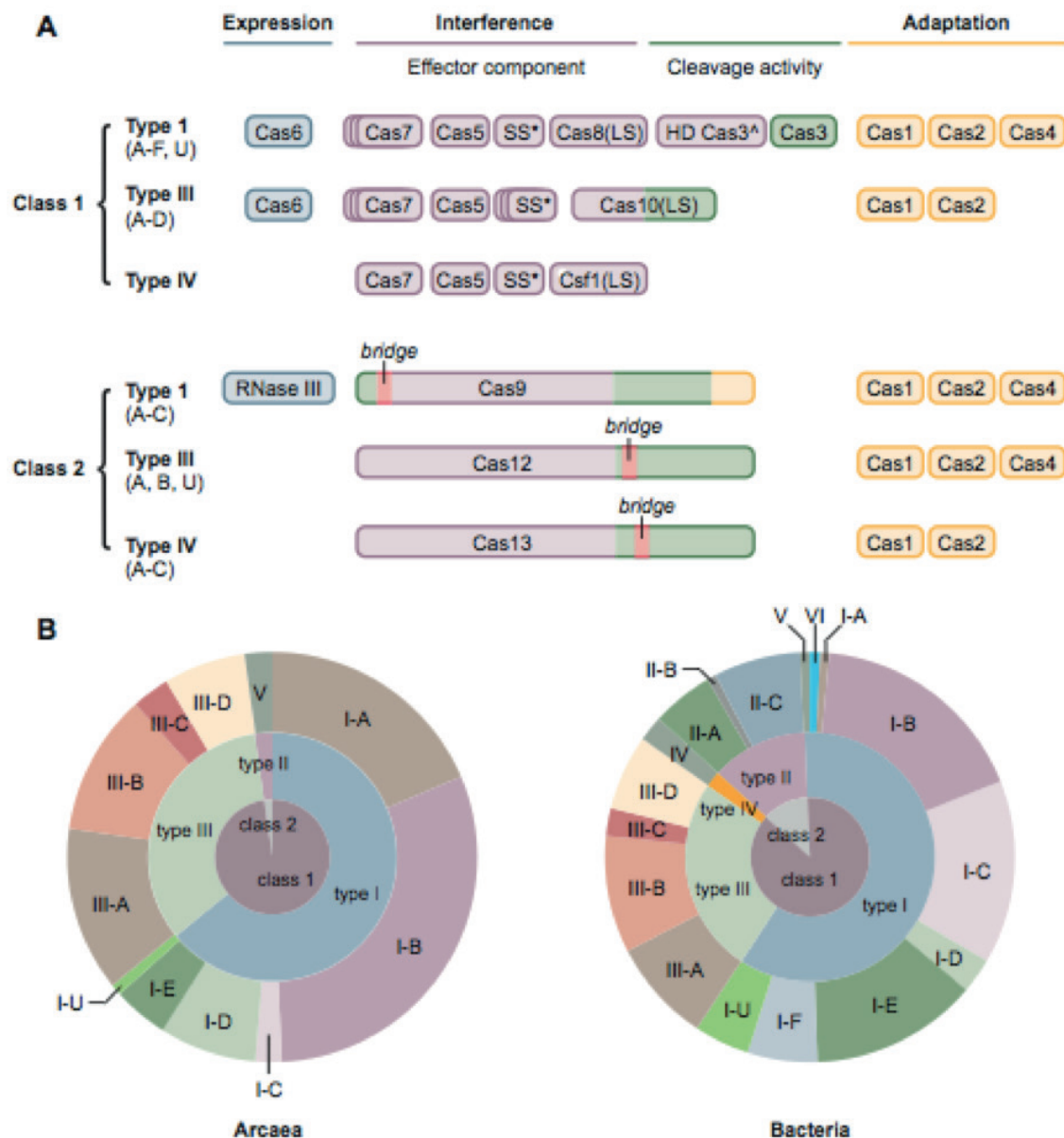


Figure 2: A recent overview and classification of CRISPR/Cas immune systems. Adapted from Ishino Y, Mart Krupovic M, Forterre P. History of CRISPR/Cas from Encounter with a Mysterious Repeated Sequence to Genome Editing Technology. J Bacteriology April 2018 Volume 200 (7), pp 1-17, e00580-17 (see fn. 6)

A - upper panel. CRISPR-Cas classification into two major classes depending on whether the effector is a complex composed of multiple Cas proteins or a single effector. This is based on detailed sequence analyses and gene organization of the Cas proteins. In addition to the conventional types are I, II, and III, and in

addition to that, types IV and V were added to classes 1 and 2, respectively. Types IV and V are those proteins which do not have Cas1 and Cas2, necessary for adaptation process, in the same CRISPR loci. The most recently added to class 2 was Type VI.

B - lower panel. This chart shows the proportions of identified CRISPR/Cas loci in the total genomes of bacteria and archaea from the current literature. Loci that could not be classified unambiguously were not included.

at Molecular Infection Medicine (MIMS) at Umeå University in Sweden had discovered how *Streptococcus pyogenes* used the enzyme Cas9 in its defence against virus attacks.¹¹ Key papers were published in the journals Nature 2011 and in Science 2012 by teams led by Emmanuelle Charpentier and Jennifer Doudna, showing that the natural machinery in a cell could be turned into a “programmable” editing tool, which could cut any DNA strand.¹² The follow-up research by Charpentier and Doudna, also enabled work on a modified and stabilized Cas9, which led to a series of advances in the use of the “genetic scissor” technology which is available today.¹³

The Cas9-based method has since 2012 been refined

into a more precise and reliable technique to modify DNA strands in cell nuclei. The technology is today increasingly used by molecular biologists, to make changes in the genome of various forms of organisms, including mammalian cells, plant cells, and bacteria. During the years following the discovery by Charpentier and Doudna, scientists started to extend the gene editing efforts to the genomes of human cells. In January 2013, researchers from laboratories at Harvard and Broad Institute led by Feng Zhang were first to publish papers showing that this could be done.¹⁴ Doudna also published results confirming this a few weeks later.¹⁵ It then became clear to almost everyone in the field that CRISPR might become a flexible way to thera-

peutically modify DNA, and a tentative method to treat rare metabolic problems and genetic diseases in humans.¹⁶ Such previously difficult to treat diseases ranged from blood disorders such as haemophilia to neurodegenerative diseases such as Huntington's.

The discovery of the CRISPR/Cas microbial adaptive immune system and its development into a gene editing tool represents the work of many scientists from various laboratories around the world. The timeline presented below (Table 1) provides a brief history of some of the major findings of the scientists who contributed to move this field forward. Such discoveries include the initial discovery of CRISPR and its function to the first demonstrations of CRISPR-mediated genome editing. For further details on the history of CRISPR research, see review by Lander.¹⁷

A number of methods to modify bacterial CRISPR/Cas systems have thus been developed into unique and flexible technological platforms. Any efforts to re-program a CRISPR editing system require identification and deletion of a particular piece of DNA. In practical terms, this requires only the synthesis of a custom RNA strand, which today can be done easily and cost-effectively. Researchers can simply order an optional RNA sequence online for delivery the next day or the same day, at a cost from a few to about a hundred USD. With the custom RNA sequence and a basic CRISPR kit, which is also inexpensive, an individual researcher can perform a gene-editing job quite easily.

TABLE 1
CRISPR/Cas9 discoveries and development timeline

Discovery of CRISPR and its function

1993 - 2005 — Francisco Mojica, University of Alicante, Spain

Discovery of Cas9 and PAM

May, 2005 — Alexander Bolotin, French National Institute for Agricultural Research (INRA)

Hypothetical scheme of adaptive immunity

March, 2006 — Eugene Koonin, US National Center for Biotechnology Information, NIH

Experimental demonstration of adaptive immunity

March, 2007 — Philippe Horvath, Danisco France

Spacer sequences can be transcribed into guide RNAs

August, 2008 — John van der Oost, University of Wageningen, Netherlands

CRISPR acts on DNA targets

December, 2008 — Luciano Marraffini and Erik Sontheimer, Northwestern University, Illinois, USA

Cas9 cleaves target DNA

December, 2010 — Sylvain Moineau, University of Laval, Quebec City, Canada

Discovery of tracrRNA for Cas9 system

March, 2011 — Emmanuelle Charpentier, Umea University, Sweden and University of Vienna, Austria. The final piece to the puzzle in the mechanism of natural CRISPR/Cas9-guided interference came from the group of Emmanuelle Charpentier

CRISPR systems can function heterologously in other species

July, 2011 — Virginijus Siksnys, Vilnius University, Lithuania

Biochemical characterization of Cas9-mediated cleavage

September, 2012 — Virginijus Siksnys, Vilnius University, Lithuania and

June, 2012 — Charpentier and Jennifer Doudna, University of California, Berkeley, USA

CRISPR/Cas9 harnessed for genome editing

January, 2013 — Feng Zhang, Broad Institute of MIT and Harvard, McGovern Institute for Brain Research at MIT, Massachusetts, USA

3. A RUSH TO PATENT

The CRISPR/Cas9 technology has been called the greatest discovery of the decade and some even call it the discovery of the century. The cellular CRISPR system, essentially represents a “search and replace function” for DNA, which allows disabled or dysfunctional genes may be replaced by new DNA letters in order to change or normalize their function. If, or rather when the CRISPR technology turns out to be a commercially important way to modify living cells, then the intellectual property and commercial control over the underlying key technological steps could be worth billions of USD in future revenues.

Today, the patent landscape related to CRISPR/Cas9 technology is becoming increasingly complex. For any party successful in claiming IP, there may be opportunities to claim rights to an innovation platform that may turn out be one of the most important genetic engineering techniques in recent biotechnology.¹⁸ The technique has made it much easier to design potential cures to severe genetic diseases, eradicate pests, and to genetically modify plants. There are also attempts to genetically engineer pigs so that they can become suitable organ donors to humans, to name just a few examples. Anyone who holds this patent can engage in applications, which may have significant future value. Feng Zhang, Jennifer Doudna and Emmanuelle Charpentier have founded their own biotech companies, where venture capitalists have already invested several hundred million USD.

When various stakeholders early on became aware of the potential value of the CRISPR technologies, venture capital groups quickly began to recruit the key scientists, aiming to patent key steps in the CRISPR process and form gene-editing startups. Charpentier became associated with CRISPR Therapeutics in Europe. Doudna joined the company Caribou Biosciences, and in 2013 she joined Zhang and Church in the company Editas as a cofounder. Editas attracted a start-up capital of \$43 million from some leading venture funds.¹⁹

Another important event took place in April of 2014, when Zhang and the Broad Institute was awarded the first of a series of US patents covering the use of the CRISPR technology in eukaryotes which essentially includes the use of the technology in any species whose cells contain a nucleus.²⁰ This included the rights to use CRISPR technology in mice, pigs, cattle, humans, or in every creature other than bacteria.

The approval of this patent surprised many of the stakeholders involved in the CRISPR race. To get the patent application reviewed quickly, Broad Institute had paid extra and along with the patent application came more than 1,000 pages of additional support documents. In less than six months, the application was approved by the USPTO, and few of the stakeholders knew it was underway. According to Broad Institute, the work of Doudna and Charpentier had only predicted that the technique could work in humans, and claimed that Zhang had made the discovery proving that the CRISPR technique would work in humans. Therefore, it was argued that Zhang was the first to show it, in a separate and “surprising” act of invention underlying the patent claim. The patent disclosure has caused considerable distress among researchers and start-ups. Several of those scientists claim that they also at an early stage managed to get CRISPR to work in human cells, a claim which also the scientific literature seems to support. This will be an important matter of discussion, since the easy reproducibility in different organisms is the most important hallmark of the CRISPR technology. Thus, many argue that, in patent terms, it was more or less “obvious” that CRISPR would work in human cells as well. If this is correct the invention claimed by Zhang and co-workers might not have the novelty, nor the inventive step/non-obviousness required to meet the requirements of patent protection.²¹

4. THE BROAD INSTITUTE VS BERKLEY CRISPR PATENT DISPUTE

Currently, only the first round has just been settled in the patent dispute for the new genetic CRISPR/Cas9 engineering technology. At stake is, not only potential future revenues of several billion USD, but also a likely Nobel Prize. Emmanuelle Charpentier and Jennifer Doudna are currently some of the hottest Nobel Prize candidates in Chemistry and/or Medicine. They have already received several major awards, including the Breakthrough prize 2015.²² The US patent on CRISPR/Cas9 awarded to Zhang in 2014 could give him and his research centre control over the most important commercial uses of the technology on the US but probably not in all markets. The recent legal developments also imply that the commercial control of CRISPR/Cas9 patents might in fact end up in different hands. If not solved this will lead to a debate over who invented what, and when, and risk to create a legal controversy or a stalemate over actual ownership. Involved in such a battle are several heavily financed start-up companies, a half-dozen universities, and numerous legal advisors and other stake-holders.

Feng Zhang was also one of the first researchers to explore the CRISPR/Cas9 system and his research team was the first to succeed in modifying multicellular organisms with the new technology. Although he managed to receive a US patent for the technology, Charpentier and Doudna appealed the patent. From 2016 and on, the parties were negotiating with the US Patent and Trademark Office (USPTO) who was the rightful owner of the discovery itself. It is big money at stake, and behind Jennifer Doudna stands Berkeley University on the US West Coast and behind Feng Zhang stands the Broad Institute, an academic institution founded by the top universities MIT and Harvard, on the US East coast.

¹⁶ Xu, X., Qi, L.S. (2019). A CRISPR–dCas9 Toolbox for Genetic Engineering and Synthetic Biology (Review) *Journal of Molecular Biology* 431(1): 34–47, 4 January, <https://doi.org/10.1016/j.jmb.2018.06.037>.

¹⁷ Vidyasagar, A. (2018). What Is CRISPR? *Live Science* April 20, <https://www.livescience.com/58790-crispr-explained.html>.

¹⁸ Katz, Y. (2015). Who owns molecular biology? The patent war for DNA-editing technology. *Boston Review*. https://yarden.github.io/pdfs/yk_who_owns_molbio.pdf. and Sanguanini, M. (2018). A Cutting-edge IP Litigation: the European front of CRISPR patent war. *CUSPE Communications*. <https://www.repository.cam.ac.uk/bitstream/handle/1810/278219/Sanguanini-May-2018.pdf?sequence=1>.

¹⁹ Herper, M. (2015). Bill Gates and 13 other investors pour \$120 million into revolutionary gene-editing startup. *Forbes* Aug 10, 2015. <https://www.forbes.com/sites/matthewherper/2015/08/10/bill-gates-and-13-other-investors-pour-120-million-in-to-revolutionary-gene-editing-startup/>.

matthewherper/2015/08/10/bill-gates-and-13-other-investors-pour-120-million-in-to-revolutionary-gene-editing-startup/.

²⁰ Sheridan, C. (2014). First CRISPR–Cas patent opens race to stake out intellectual property. *Nature Biotechnology* 32 (7): 599 – 601 and Egelie, K.J., Graff, G.D., Strand, S.P. & Johansen, B. (2016). The emerging patent landscape of CRISPR–Cas gene editing technology. *Nature Biotechnology* 34: 1025–1031.

²¹ Herper, M. (2015). Bill Gates and 13 other investors pour \$120 million into revolutionary gene-editing startup. *Forbes* Aug 10, 2015. <https://www.forbes.com/sites/matthewherper/2015/08/10/bill-gates-and-13-other-investors-pour-120-million-in-to-revolutionary-gene-editing-startup/>, Sheridan, C. (2014). First CRISPR–Cas patent opens race to stake out intellectual property. *Nature Biotechnology* 32 (7): 599 – 601, Egelie, K.J., Graff, G.D., Strand, S.P. &

Johansen, B. (2016). The emerging patent landscape of CRISPR–Cas gene editing technology. *Nature Biotechnology* 34: 1025–1031, Ledford, H. (2016). Titanic clash over CRISPR patents turns ugly. *Nature* 537, 460–461. 22 September, doi:10.1038/537460a, Ledford, H. (2016). Bitter fight over CRISPR patent heats up. *Nature* 529, 265, doi:10.1038/nature.2015.17961, Grens, K. (2016). That Other CRISPR Patent Dispute. *The Scientist* Aug 31, <https://www.the-scientist.com/daily-news/that-other-crispr-patent-dispute-32952> and Ledford, H. (2017). Broad Institute wins bitter battle over CRISPR patents. *Nature* 542, 401. 23 February. doi:10.1038/nature.2017.21502.

²² Wikipedia Emmanuelle Charpentier. see https://en.wikipedia.org/wiki/Emmanuelle_Charpentier [8 May 2019].

TABLE 2 CRISPR/Cas9 key patent dispute timeline

May 2012

Charpentier and Doudna submit a patent application to the USPTO.

June 2012

The article by Charpentier and Doudna is published in Science: "A programmable dual-RNA guided DNA endonuclease in adaptive bacterial immunity."

December 2012

Zhang and colleagues submits a patent application to the USPTO.

January 2013

Zhang's article "Multiplex genome engineering using CRISPR / Cas systems" is published in Science.

April 2014

Zhang is awarded a patent by the USPTO.

April 2015

Charpentier and Doudna appeal the patent awarded to Zhang.

March 2016

Negotiations begin on who is the rightful holder of the CRISPR/Cas9 patent. Patent judges requested evidence from all parties.

February 2018

The European Patent Office (EPO) revokes the first of several CRISPR patents filed by Zhang and colleagues from the Broad Institute citing a clear lack of novelty.

March 2018

The EPO grants CRISPR co-inventor Emmanuelle Charpentier, together with the University of California and the University of Vienna, a broad patent covering the use of the CRISPR/Cas9 system for a new application beyond gene editing.

5. CLINICAL TRIALS UTILIZING GENE EDITING IN ADULT HUMANS

After the initial discoveries by Charpentier and Doudna, laboratories around the world started to use CRISPR/Cas9 to change genes from in living organisms ranging from bacteria to monkeys. Recently, researchers in the US and China have started the first tests on humans. In principle, the CRISPR/Cas9 technology will make it possible to change human genes in a way that affects future generations.

The speed by which the CRISPR/Cas9 technology entered into clinical trials has been impressive. It is currently estimated that some 2,700 clinical trials using gene therapies are already under way or approved by regulatory authorities around the world.²³ Academia and pharma industry aim to combat diseases as diverse as cancer, muscular dystrophy and sickle cell anaemia.

Some of the indications where clinical trials are planned or on-going are outlined in Table 3.



Figure 3 Brian Madeux, a 44-year-old from Phoenix, Arizona, is suffering from the rare, life-threatening genetic condition Hunter's Syndrome since birth. In Nov 13, 2017 he became the first person in the world to undergo CRISPR/Cas9 treatment that edited the disease related genes inside his body. Image from Annie Keller, Genetic Literacy Project, January 22, 2018

²³ Gray, R. [2018]. Why gene editing could create so many jobs. BBC 15 October 2018. <http://www.bbc.com/capital/story/20181003-why-gene-therapy-will-create-so-many-jobs>.

²⁴ Gray, R. [2018]. Why gene editing could create so many jobs. BBC 15 October 2018. <http://www.bbc.com/capital/story/20181003-why-gene-therapy-will-create-so-many-jobs>.

²⁵ Gray, R. [2018]. Why gene editing could create so many jobs. BBC 15 October 2018. <http://www.bbc.com/capital/story/20181003-why-gene-therapy-will-create-so-many-jobs>.

²⁶ Waltz, E. [2016]. CRISPR-edited crops free to enter market, skip regulation. Nature Biotechnology 34: 582. doi <https://doi.org/10.1038/nbt0616-582>. Yin, K., Gao, C. & Qiu, J. L. [2017]. Progress and prospects in plant genome editing. Nature Plants 3,

17107. <https://doi.org/10.1038/nplants.2017.107> and Gao, C. [2018]. The future of CRISPR technologies in agriculture. Nature Reviews Molecular Cell Biology 19: 275–276, 31 January <https://doi.org/10.1038/nrm.2018.2>.

²⁷ Gao, C. [2018]. The future of CRISPR technologies in agriculture. Nature Reviews Molecular Cell Biology 19: 275–276, 31 January <https://doi.org/10.1038/nrm.2018.2>.

²⁸ Hammond, A., Galizi, R., Kyrou, K., Simoni, A., Siniscalchi, C., Katsanos, D., Gribble, M., Baker, D., Marois, E., Russell, S., Burt, A., Windbichler, N., Crisanti, A. & Nolan, T. [2016]. A CRISPR/Cas9 gene drive system targeting female reproduction in the malaria mosquito vector *Anopheles gambiae*. Nature Biotechnology 34: 78–83 <http://dx.doi.org/10.1038/nbt.3439> [2015], Callaway, E.

[2015]. Mosquitoes engineered to pass down genes that would wipe out their species. Nature 07 December, doi:10.1038/nature.2015.18974 and Kyrou, K., Hammond, A.M., Galizi, R., Kranjc, N., Burt, A., Beaghton, A.K., Nolan, T. & Crisanti, A. [2018]. A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. Nature Biotechnology 36: 1062–1066.

²⁹ Callaway, E. [2015]. Mosquitoes engineered to pass down genes that would wipe out their species. Nature 07 December, doi:10.1038/nature.2015.18974.

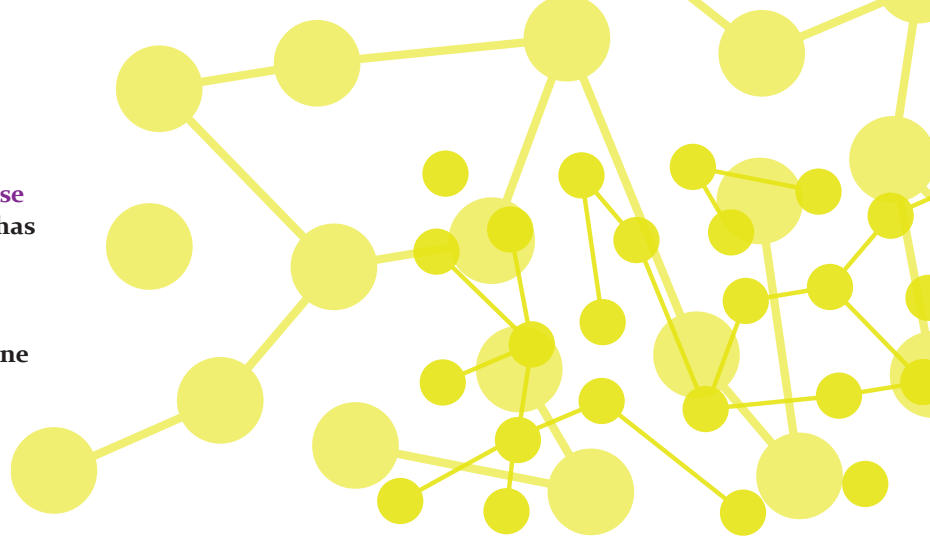


TABLE 3
CRISPR/ Cas9 – Clinical applications and use

- **Disease where CRISPR/Cas9 technology has already been used**
- Hunter syndrome (metabolic disease)

- **Diseases in which which CRISPR/Cas9 gene editing could provide a cure**
- Cancer (selected forms)
- Cystic Fibrosis
- Haemophilia (type A and B)
- Beta-Thalassemia (blood disorder)
- Sickle cell disease
- Leber Congenital Amaurosis (Hereditary form of blindness)
- AIDS
- Muscle Dystrophy (Duchenne's)
- Huntington 's Chorea
- Alpha-1 antitrypsin deficiency
- Amyloidosis (amyloid transthyretin)
- Mucopolysaccharidosis (types I and II)
- Primary hyperoxaluria type 1
- Severe combined immunodeficiency (SCID)
- Usher syndrome type 2a

The CRISPR technology has emerged from a natural defence mechanism, which allows many bacteria fight off viruses. This mechanism built on a function by which the bacteria were inserting fragments of viral DNA into specialized structures in their own genome (the “clustered regularly interspaced short palindromic repeats” that give CRISPR its name). By using this unique system, bacteria would provide their daughter cells with a way to recognize and halt future viral invasions. Once this long-overlooked mechanism was discovered, researchers realised that genome editing could be carried out in any species, including humans, simply by tiling and editing sequences of DNA.

It was also early realised that the research findings could be turned into innovations and numerous potential clinical applications. After the first patient case in 2017, additional patients were enrolled in clinical studies in the US, which were carried out eight patients with Hunter syndrome and three with Hurler syndrome. Preliminary results showed that a few of the Hunter patients experienced a boost in the level of a missing enzyme, although levels did reach the normal level seen in healthy individuals. The preliminary results from the patients with Hurler syndrome showed clinical improvements.

6. MUCH AT STAKE AND A NEW JOB-MARKET EMERGING

Most of the small gene therapy companies behind the various CRISPR/Cas9 clinical trials have partnerships with Big Pharma, including companies such as Bayer, GlaxoSmithKline, Pfizer, Merck and Novartis. Within the Pharma and Biotech sector, several actors remain positive as regards future job opportunities. Several Big Pharma companies are today actively seeking to hire their own in-house gene therapy scientists.²⁴

In addition to the Pharma sector, the demand for skilled genetic engineers in hospitals and laboratories is expected to soar, as more and more treatments relying on gene editing, move from research laboratories into hospitals around the world. Expectations are that there will also be a growing demand for clinicians as well as laboratory genetic engineers, who can interpret genetic information, offer support and advice to medical staff and guide patients. In the UK, the government predicts that by 2030, there may be more than 18,000 new jobs related to gene and cell therapy. In the US, the US Bureau of Labor Statistics estimates that during the next decade, around 17,500 new jobs will be created, with a 7% increase in jobs in the biomedical engineering sector and a 13% increase in the medical practice and sciences sector. In fact the US Bureau of Labor Statistics currently ranks genetic counsellors as one of the top 20 fastest growing jobs.²⁵

7. A NOVEL TRANSFORMATIVE TECHNOLOGY FOR MEDICINE AND BIOTECHNOLOGY?

In addition to its medical use, the CRISPR technology has also successfully been applied in food and agricultural sciences and innovation projects.²⁶ For example, it has been applied to improve probiotic cultures and to engineer and vaccinate microbial functional food cultures (e.g. yogurt) against viruses. The CRISPR technology is also increasingly being used in modification of various crops in order to improve yields, enhance nutritional qualities and to improve tolerance to e.g. drought.²⁷

Other potential applications include the creation of gene drives, which are genetic systems, capable of increasing chances of a particular genetic trait to pass on from parent to offspring. If successful, this could influence specific genetic traits to more easily spread within populations over generations. Such gene drives could influence or control the global spread of specific diseases such as malaria. The CRISPR technology could e.g. be used to enhance spread of sterility among the female *Anopheles* mosquito disease vector.²⁸ Alternative applications of CRISPR gene drives could be to introduce novel mechanisms in order to eradicate invasive vector borne disease or reverse pesticide and herbicide resistance.²⁹

However, there are a number of drawbacks associated with the technology as well as its extended applications. One obvious limitation is that the CRISPR is neither specific³⁰ nor a 100 % efficient technology³¹ and that the genome-editing efficiencies can vary. For example, in an early study conducted by Doudna and Charpentier, in rice, there were signs of gene editing in only approximately 50% of the cells that received the Cas9-RNA complex. Current evidence also indicate, that depending on the target, editing efficiencies may optimally amount to about 80%. In addition to the data showing a limited efficiency of the CRISPR/Cas9 technology, there is also a concern related to "off-target effects," where the host DNA is cut at sites other than the intended precise target. Such unwanted effects may potentially lead to the introduction of new and unintended mutations.³² This effect may risk introduction of potentially random and dangerous genetic errors, an effect termed "genome vandalism".³³

8. THE FIRST HUMAN EMBRYO GENE EDITING CONTROVERSY

In November 2018, before the Second International Summit on Human Genome Editing in Hong Kong, Chinese scientists became the first to report editing the genomes of human embryos. The research group was led by professor He Jiankui from the Southern University of Science and Technology in Shenzhen, PR China. The group under professor He claimed to have used the CRISPR gene editing technology to alter the DNA of human embryos during in-vitro fertilization. The project had resulted in the birth of twin girls. The objective was to remove a gene called CCR5, so the embryos might be resistant to potential infection with HIV/AIDS, since their father was HIV positive.³⁴

The news sparked an immediate global debate about the ethical implications of such work. While some argued that gene editing in embryos could have a bright future

since such technologies could eradicate serious genetic diseases prenatally, others argued that such work crossed an ethical line. There were earlier concerns that the genetic changes introduced to embryos, known as germline modification, could be heritable and thus cause an unpredictable effect on future generations.³⁵ In fact earlier researchers including the team of professor Huang had found a surprising number of 'off-target' mutations, which were assumed related to CRISPR/Cas9 acting on other parts of the genome in a complex way. This was put forward as a major safety concern related to human germline gene editing, since some of these unintended mutations could be harmful. A number of critical researchers and clinicians had previously argued that there was a need to pause further clinical research in order to solve a number of worries and outstanding issues.³⁶

The human embryo editing by professor He aimed to use CRISPR to remove a single gene, so that the twin girls would be born immune to HIV after the CCR5 gene was altered in their genomes. However, the editing efforts did not appear to be fully successful, and in respect to the clinical indication, critical researchers argued that there were alternative and easier ways to prevent HIV infection. Many of the critics also argued that the twins were the un-consenting subjects of a researcher who had the ambition to be a "scientific first," hoping for international scientific recognition.

9. IS THERE A NEED TO SET LIMITATIONS FROM AN ETHICS AND MORAL PERSPECTIVE?

The expanding number of potential applications of the CRISPR technology have increasingly raised questions about the ethical and moral consequences of altering the genome of humans and other living organisms. The variable efficacy, potential off-target effects and imprecise gene edits all represent potential safety concerns.

For example, there are potential yet unknown ecological impacts of the use of gene drives.³⁷ A trait introduced, either by intention or emerging un-intentionally from the use of the CRISPR technology, could spread beyond the target population and into other organisms through cross-breeding. Alternatively, over generations, the use of gene drives could reduce the genetic diversity of target populations. Particular care has to be considered when the intention is to make genetic modifications in human embryos and reproductive cells such as sperm and eggs, known as germline editing. Since such germline changes can be passed on to coming generations, an extended and liberal use of CRISPR technology in humans is currently raising an increasing number of ethical concerns in the scientific community.³⁸

In addition to the concerns yet raised, there is much related to the CRISPR technology that is still unknown to science. Therefore, groups of scientists, ethics and legal experts³⁹ argue that germline editing raises concerns of unintended consequences for future generations since there are fundamental limits in the knowledge of human genetics, gene-environment interactions, and the pathways of disease (including the interplay between one



Figure 3 He Jiankui, announcing the first human CRISPR gene editing live births. Dr He carried out in-vitro fertilization gene editing to alter the DNA of human embryos. The objective, He said, was to remove a gene called CCR5, and the pregnancy resulted in the birth of twin girls. Public domain.

disease and other conditions or diseases in the same patient). Such ethical concerns need to be discussed, since we risk introducing genetic traits that could fundamentally affect the future generations without having their consent. Also, the possibility that germline editing could be used as an enhancement tool for various human characteristics may also raise concerns.⁴⁰

To identify potential and emerging areas of conflict and concerns, governmental and institutional bodies such as US National Academies of Sciences, Engineering and Medicine have issued a comprehensive report with guidelines and recommendations for genome editing. Although several actors urge caution in exploring germline editing, it does not mean prohibition. One recommendation has been that germline editing should first be done on genes leading to serious diseases and only when there are no other known or reasonable treatment alternatives. Also, there will also be a need to closely and carefully monitor potential health risks and benefits associated with trials in humans or any other living organism. This also include following up on families for multiple generations and environmental impact long-term.

10. PRESENT AND EMERGING PATENT LANDSCAPE AND POTENTIAL FUTURE COMMERCIAL APPLICABILITY

Research and innovation related to CRISPR has tended to speed up during recent years. Although the initial patents remain important pieces of intellectual property related

to the CRISPR technology, their full importance and commercial value remains to be seen. The patent landscape is today becoming increasingly complex, with multiple companies, major universities and research institutes, as well as research groups and individuals claiming key parts of CRISPR/Cas9 patent protection. (Figure 4).

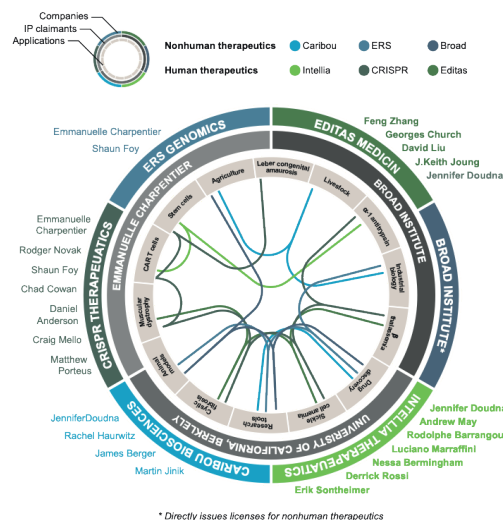


Figure 4. A graphic overview of current CRISPR/Cas9 patenting From reference 41; Rodríguez Fernández C. Doudna and Charpentier Get Second CRISPR Patent in Europe. From <https://labiotech.eu/policy-legal-finance/doudna-charpentier-crispr-patent-europe/> March 01, 2018

³⁰ Oye, K.A., Esvelt, K., Evan Appleton, E., Flaminia Catteruccia, F., Church, G., Kuiken, T., Bar-Yam Lightfoot, S., McNamara, J., Smidler, A., Collins, J.P. (2014). Regulating gene drives. Science Express 17 July, <http://www.sciencemag.org/content/early/recent/> / Page 2 / 10.1126/science.1254287.

³¹ Kosicki, M., Tomberg, K. & Bradley, A. (2018). Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. Nature Biotechnology 2018; 36; 765-771 <https://doi.org/10.1038/nbt.4192>, Guttinger, S. (2018). Trust in Science: CRISPR-Cas9 and the Ban on Human Germline Editing. Sci Eng Ethics. 2018; 24(4): 1077-1096. doi: 10.1007/s11948-017-9931-1 and Schwartz, M. (2018). Target, delete, repair. CRISPR is a revolutionary gene-editing tool, but it's not without risk, Stanford Medicine Winter 2018. <https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html>.

³² Schwartz, M. (2018). Target, delete, repair. CRISPR is a revolutionary gene-editing tool, but it's not without risk, Stanford Medicine Winter 2018. <https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html>.

³³ Kosicki, M., Tomberg, K. & Bradley, A. (2018). Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements.

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³⁴ Cyranoski, D. (2018). CRISPR-baby scientist fails to satisfy critics. Nature November 28, <https://www.nature.com/articles/d41586-018-07573-w>.

³⁵ Cyranoski, D. & Reardon, S. (2015). Rumours of germline modification prove true — and look set to reignite an ethical debate. Nature 22 April 2015 <https://www.nature.com/news/chinese-scientists-genetically-modify-human-embryos-1.17378>.

³⁶ Grant, B. (2015). Credit for CRISPR: A Conversation with George Church. The Scientist Dec 29, 2015. <https://www.the-scientist.com/news-analysis/credit-for-crispr-a-conversation-with-george-church-34306>.

³⁷ Oye, K.A., Esvelt, K., Evan Appleton, E., Flaminia Catteruccia, F., Church, G., Kuiken, T., Bar-Yam Lightfoot, S., McNamara, J., Smidler, A., Collins, J.P. (2014). Regulating

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³⁸ Guttinger, S. (2018). Trust in Science: CRISPR-Cas9 and the Ban on Human Germline Editing. Sci Eng Ethics. 2018; 24(4): 1077-1096. doi: 10.1007/s11948-017-9931-1 and Schwartz, M. (2018). Target, delete, repair. CRISPR is a revolutionary gene-editing tool, but it's not without risk, Stanford Medicine Winter 2018. <https://stanmed.stanford.edu/2018winter/CRISPR-for-gene-editing-is-revolutionary-but-it-comes-with-risks.html>.

³⁹ Baltimore, D., Berg, P., Botchan, M., Carroll, D., Charo, R.A., Church, G., Corn, J.E., Daley, G.Q., Doudna, J.A., Fenner, M., Greely, H.T., Jinek, M., Martin, G.S., Penhoet, E., Puck, J., Sternberg, S.H., Weissman, J.S. & Yamamoto, K.R. (2015). A prudent path forward for genomic engineering and germline gene modification. Science 348(6230): 36-38. 2015 Mar 19. doi: 10.1126/science.aab1028.

⁴⁰ Ibid.

⁴¹ The National Academies of Sciences, Engineering and Medicine (2017). Committee on Human Gene Editing: Scientific, Medical, and Ethical Considerations. <http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=24623>.



Adding further to the complexity of the CRISPR technology platform, the EPO has in 2017 granted a broad patent covering the use of the CRISPR/Cas9 system for new applications beyond gene editing to Emmanuelle Charpentier together with the University of California and the University of Vienna as co-inventors. This new CRISPR patent covers the use of a chimeric Cas9 enzyme, modified to inactivate its DNA-cutting function. Further, in January 2018, the EPO also revoked the first of several CRISPR patents filed by the Broad Institute citing a clear lack of novelty. This decision was a big win for Charpentier and Doudna, in the fight for the ownership of the patent rights against Feng Zhang and the Broad Institute related to ownership of technology behind CRISPR.

In addition, the EPO granted CRISPR co-inventor Emmanuelle Charpentier, together with the University of California and the University of Vienna, a broad patent in 2018 covering the use of the CRISPR/Cas9 system for a new application beyond gene editing. Of importance for claiming priority is that Cas9 enzyme can be combined with a protein domain that either activates or inhibits the expression of the gene targeted by CRISPR without modifying its sequence. This technology is known as CRISPR-a (activating CRISPR) and CRISPR-i (inhibitory CRISPR).⁴² The new patent approved EPO will cover gene regulation using CRISPR/Cas9 in multiple settings, such as in bacteria, plants, animals, as well as human cells. This specific CRISPR patent covers the use of what is called chimeric Cas9 enzyme, which is modified to inactivate its DNA-cutting function. The most important application of this form of CRISPR/Cas9 is in gene regulation. Thus, Zhang seems to be on the winning side so far in the US, but the decisions of the EPO are so far benefitting the Doudna-Charpentier team.

11. PATENTING RELATED TO CRISPR TECHNOLOGIES WILL REMAIN A DYNAMIC AREA FOR MANY YEARS TO COME

It is becoming increasingly clear that there will be major and important life sciences applications emerging from the CRISPR/Cas9 and related technologies in gene regulation. In addition to its wide application in research,

emerging CRISPR technologies are likely to be increasingly used in drug discovery and therapeutics as well as in plant and animal breeding.⁴³ Novel tools based on these findings are becoming widely used in research, particularly for drug discovery. Using libraries of CRISPR targets, such tools may be used to find genes that e.g. enhance the effect of available cancer drugs when specific genes are activated or inactivated. While there are possible therapeutic applications of this form of CRISPR, the biggest potential seems to be in research for now.

The different positions taken by the US and European patent offices are clearly polarizing the CRISPR field. If such trends continue, it may imply, that depending on where you use CRISPR in the world, there will be a need to obtain licenses from the other party. This is likely to increase transaction costs and make it more difficult and expensive for commercial actors to initiate international product development programs within the CRISPR/Cas9 area.⁴⁴

12. CONCLUSIONS AND VISIONS

The discovery of the CRISPR/Cas9 system and realisation of its fundamental biological role and mode of action is likely to change medicine and biotechnology in many respects.

In this review, we have described some of the recent discoveries from the fundamental basics of the system as well as some of the potential uses of CRISPR/Cas9 and related systems, as tools to perform genome editing in medicine and various fields of biotechnology and medicine. In particular, we have addressed the patent aspects related to its discovery and some aspects of the recent legal disputes.

The various CRISPR technologies evolving from the initial CRISPR/Cas9 discovery provide opportunities for developing a “search and replace function” for a variety of DNA strands. Simply put, the technologies evolving from this research may allow for replacement of disabled or dysfunctional genes by new DNA letters in order to change or normalize biological function. At the present early stage of development of the various technology applications, we do not exactly know what novel treatments or benefits this technology will offer clinical medicine in the end.

In an optimistic scenario, the technique may provide radical treatment options for a range of severe genetic diseases, where treatments are currently lacking or are suboptimal. Further, in e.g. transplantation medicine there are hopes that the CRISPR/Cas9 technology could enable us to genetically engineer pigs or other animals so that they can become suitable organ donors to humans. Within vector borne diseases, such as malaria, there is ongoing research to modify the vectors, so that they may not be able to transmit human diseases. In laboratory and diagnostic medicine, there are reasons to believe that CRISPR technologies may realize a number of potential applications and improved techniques.

Further, within plant breeding, there are research and innovation efforts to use the CRISPR technology to eradicate various pests by genetically modifying plants to withstand attacks.

An interesting area, currently under serious exploration, is the CRISPR technologies may provide a new tool for biodiversity conservation and de-extinction, i.e. the possibility to conserve endangered species and even bring back extinct animal species, such as the passenger pigeon and the woolly mammoth. Although this may sound like science fiction, there are hopes (and fears) that the resurrection of extinct species may soon be reality.

However, within all medical or biological areas of application, there are a number of ethical problems that needs to be addressed and clarified. While the CRISPR/Cas9 discoveries are offering a number of potential game-changing opportunities within Life Sciences, the perceived risks and potential rewards may vary greatly between applications. Also estimated and perceived long-term values may vary significantly between stake-holders, such as the individuals, regulators, companies involved as well as society at large. Since numerous potential applications of the CRISPR/Cas9 technology are already underway, we may expect an increased public awareness and debate related to the CRISPR/Cas9 technology area within the near future.

Today, the patent landscape related to CRISPR/Cas9 technology is becoming increasingly complex. For any party successful in claiming IP, there may be opportunities to claim rights to an innovation platform that may turn out be one of the most important genetic engineering techniques in recent biotechnology. Thus, anyone who can claim key patents in one or several areas, may look forward to significant rewards if or when such applications start to become commercial. In 2018 we saw major legal conflicts evolving from disputes between the some of the early actors and their host institutions claiming patent rights. Since major work and funding are focussed on patenting the key technologies and applications related to the biological CRISPR/Cas9 platforms, there are reasons to believe that there may be additional disputes coming in order to gain a monopoly position which may allow for future benefits and profits from the technology. However the road to future profits from the CRISPR in any technology field or area is difficult and expensive. Extensive funding and major commitment to development will be required to reach the various commercial applications.



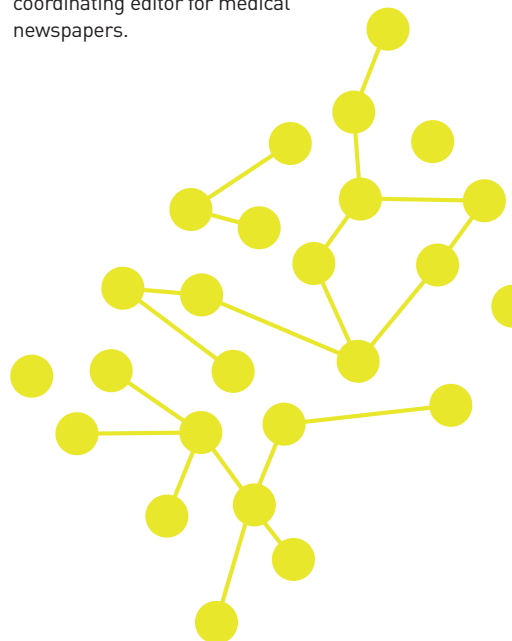
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⁴² Baltimore, D., Berg, P., Botchan, M., Carroll, D., Charo, R.A., Church, G., Corn, J.E., Daley, G.Q., Doudna, J.A., Fenner, M., Greely, H.T., Jinek, M., Martin, G.S., Penhoet, E., Puck, J., Sternberg, S.H., Weissman, J.S. & Yamamoto, K.R. (2015). A prudent path forward for genomic engineering and germline gene modification. *Science* 348(6230): 36–38. 2015 Mar 19. doi: 10.1126/science.aab1028.

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⁴⁴ Rodríguez Fernández, C., Doudna and Charpentier Get Second CRISPR Patent in Europe. From <https://labiotech.eu/policy-legal-finance/doudna-charpentier-crispr-patent-europe/> March 01, 2018.