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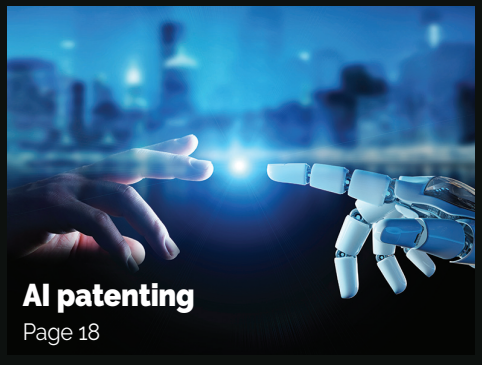

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# A Nobel Prize, a Global Pandemic, and a Patent Dispute walk into a bar... stop me if you've heard this one before

**Richard Gaugeler, Patent Attorney at Cedar White Bradley, explains how a Noble Prize, the Pandemic and a Patent Dispute are all inextricably linked to the CRISPR-*Cas9* Technology.**

Just as the three individuals who walk into a bar seemingly appear independent from one another, they nevertheless always turn out to be inextricably linked through some common thread. And our Nobel Prize, Pandemic, and Dispute are no different. The thread? Of course, I must be talking about CRISPR-*Cas9* Technology. The revolutionary gene editing tool that can be used to make precise incisions in genetic material to edit or even delete unwanted genetic code.

The story of CRISPR-*Cas9* Technology began in 2002, when Emmanuelle Charpentier began her research into pathogenic bacteria. A later meeting between herself and fellow scientist Jennifer Doudna in 2011 at a café in Puerto Rico, led to a discovery previously only imagined in movies and sci-fi novels. It is from this date that their discovery changes all our lives forever.

## CRISPR-*Cas9*

CRISPR-*Cas9* allows us, for the first time, to accurately alter the genetic sequence of human cells. The alteration may be the deletion of a certain portion of DNA, effectively neutralizing a particular gene, or editing a portion of DNA, with the effect of changing the gene altogether.

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) refers to naturally occurring nucleotide sequences found in the genome of certain bacteria. These nucleotide sequences play a role in the bacteria's anti-viral defence mechanisms. The sequences are separated by spacer sequences which correspond to sequences found in various viral genomes.

*Cas9* is a DNA cutting protein and makes up the other half of the technology and, when coupled with guideRNA, is guided to the DNA sequence to be cut. RNA is similar to DNA but comprises a single ribbon of molecules, unlike DNA's double helix ribbon.

Richard Gaugeler

> ***CRISPR-Cas9* allows us, for the first time, to accurately alter the genetic sequence of human cells.**

The functioning of the CRISPR-Cas9 technology is as follows: First, the faulty sequence in the DNA is identified by a scientist. In this case the faulty sequence refers to a defective gene which codes for Sickle-Cell anaemia. Second, CRISPR uses guideRNA to identify, and bind to the sequence. The guideRNA binds to and unravels the faulty sequence in the DNA molecule. Third, *Cas9* cuts the faulty sequence to either deactivate the gene or replace the faulty sequence with a new correct one. In editing the sequence, the gene is repaired and the resulting disease, sickle-cell anaemia, is removed from the genome altogether.

The CRISPR-*Cas9* Technology has near endless possibilities for use and, has been deemed a platform technology providing the springboard for further advancements in gene editing.

Gene editing techniques tend to raise questions around the ethical use of technology.

One such ethical debate began in November 2018 when He Jiankui used CRISPR to produce the world's first "designer-baby" which was edited to remove a gene which produces a HIV receptor effectively making the baby immune to HIV.

While the debate surrounding the ethics of a gene editing tool continues, so too will its use. Good or bad, so revolutionary was this invention, that its inventors were awarded one of the highest accolades in the world.

## The Nobel Prize in Chemistry 2020

On 7 October 2020, Emmanuelle Charpentier and Jennifer Doudna were awarded the Nobel Prize in Chemistry for their invention "a method for genome editing" (CRISPR-*Cas9* Technology).

The Nobel Prize in Chemistry has been awarded 112 times to 186 Nobel Laureates, starting in 1901. Until 2020 only five women, including Marie Curie who won the Nobel Prize in both chemistry

and physics, had won or shared the win of the Nobel Prize for Chemistry.

The origin of the CRISPR-*Cas9* technology dates back to 2002 when Emmanuelle Charpentier began her research into pathogenic bacteria, specifically *Streptococcus Pyogenes*. The seemingly innocuous bacteria responsible for Strep throat and the more severe necrotizing fasciitis also known as *flesh-eating* bacteria.

Emmanuelle's work focused on understanding what made this bacterium so aggressive and resistant to antibiotics.

In 2006 at the University of California, Jennifer Doudna was studying RNA. Jennifer's experience led her to focus specifically on RNA *interference.*

During her studies into RNA Jennifer heard of research into repeated sequences found in the bacteria, appearing to match genetic sequences found in the DNA of different viruses.

The idea was that once the bacteria had successfully fended off a viral attack, a portion of the viral DNA is coded into the bacteria's owns DNA sequence. The coding provided a memory on how to identify and destroy similar viruses should further infections take place in the future.

The repeated sequences are dubbed Clustered Regularly Interspaced Short Palindromic Repeats, or CRISPR for short.

As the research continued, an association between CRISPR and proteins called *Cas* was discovered. The *Cas*-genes are similar to other genes which code for proteins whose job it is to unravel and cut DNA strands in an organism's genome.

In 2009 Emmanuelle, while working at Umeå University in Sweden, studied small, gene regulating RNA molecules. During her research Emmanuelle discovers that the small RNAs found in *S. Pyogenes* are very similar to the CRISPR sequence in the bacterium's genome.

Continued research shows that is the CRISPR system in *S. Pyogenes* requires just one protein to cleave DNA, that protein is *Cas9.*

In 2011, Emmanuelle and Jennifer combine their intellect to understand Cas9's function in *S. Pyogenes.*

After continued testing and experimentation they discover that *Cas9* can cut DNA into two parts.

Prior to publishing their findings in 2012, in the *Jinek et al.* paper[1], they combine the *tracr*RNA and CRISPR-RNA to form 'guide-RNA', to cut DNA at a location of their choosing.

## A patent dispute

With great patent, comes great litigation, and CRISPR-*Cas9* Technology is no exception with disputes taking place in both the US and Europe.

Back in 2012 when Emmanuelle and Jennifer first publish their findings in the Jinek paper, their respective institutions, namely; the University of California, the University of Vienna and the University of Umeå (collectively referred to as "UC") looked to secure their rights in the invention by filing multiple U.S patent applications. The applications are directed to the CRISPR-*Cas9* technology and its use in gene editing.

> **Jiankui used CRISPR to produce the world's first "designer-baby".**

No sooner had UC filed their patent applications that the Broad Institute, which represents a collaboration between MIT and Harvard, filed their patent applications to the same technology.

UC's applications, although filed first, claim the CRISPR-*Cas9* technology for gene editing in *cells,* i.e. without any specificity to bacterial (prokaryotic) or mammalian (eukaryotic) cells. The Broad Institute however, claim their invention to the gene editing capabilities of CRISPR-*Cas9* in mammalian (eukaryotic) cells. According to Broad, this invention is a more specific and more challenging use of the technology. The Broad Institute also decided to fast-track their applications and receive granted patents before the earlier filed applications of UC.

UC argued that their technology creates the platform for gene editing in *any* cell, while the Broad Institute argue that eukaryotic cells are far more complex than prokaryotic cells and that editing genes in eukaryotic cells as claimed in their patent applications is far more complex. Additionally, that their ability to successfully edit eukaryotic cells where others had previously failed, entitles them to the patent and the accompanying rights.

Most of, if not all of, the patents in dispute have been filed pre-March 16, 2013 where the patent system switched from a *First-to-Invent* system to a *First-to-File* system.

A First-to-File system relates to the actual filing date on when an application is presented



1 M. Jinek, K. Chylinski, I. Fonfara, M. Hauer, J.A. Doudna, and E. Charpentier, A Programmable Dual-RNA-Guided DNA Endonuclease in Adapted Bacterial Immunity, 337(6096) Science 816-21 (Aug. 17, 2012).

## Résumé

**Richard Gaugeler, Patent Attorney**

Richard joined CWB as a Patent Attorney in 2016. In this role, Richard works with inventors, entrepreneurs, and start-ups in creating IP to provide registrable IP rights throughout the MENA region and beyond. He also assists R&D teams at large oil & gas organizations in the evaluation and development of new inventions and potential new patents. Richard works closely with UAE inventors through his work on the Takamul Program and innovation programs. As part of these programs, he provides patent and commercialization support to local inventors, entrepreneurs, academic institutions, private sector, and government bodies. Richard routinely advises clients on patent and design preparation, registration, prosecution, and maintenance. He prepares and prosecutes patents in various jurisdictions, including the European Patent Office, The United States Patent and Trademark Office, and the World Intellectual Property Office. Richard performs novelty and patents searches, as well as patentability and Freedom-to-Operate opinions.

**With great patent, comes great litigation.**

for filing at the patent office. Provided all the formal requirements are met the application will receive the filing date on the date at which the application has been filed. This is the date from which you may claim priority hence "First in time equals first in right".

However, the First-to-Invent system in the US worked differently.

The first-to-invent system had two requirements for establishing a filing date. The first requirement was 'conception', which related to the inventor's innovative capacity, and was used to identify the inventor. The second requirement was 'reduction to practice', was obtained either, by developing a prototype or filing the application. Showing that you 'reduced your invention to practice' before the filing date, you could move the effective filing date of an invention. Therefore, a later filed application could potentially predate an earlier filed one.

Thus, UC had to object to Broad's earlier granted patents before the Patent Trial and Appeal Board (PTAB), through a process called interference proceedings. If Broad could show they reduced their invention to practice before UC did, irrespective of their filing dates, Broad could be the rightful owners of the CRISPR-*Cas9* technology.

In interference proceedings, UC showed the Jinek Paper rendered Broad's applications obvious as it clearly showed the technology working in *cells*, prokaryote and eukaryote alike. The allegation was refuted by Broad, who countered that no such teaching was present in the Jinek Paper (or the UC applications for that matter), and therefore their applications are not obvious.

Broad did manage to convince the USPTO that as CRISPR-*Cas9* was only found in prokaryotic cells it was not unreasonable to conclude that the technology would only be applicable to prokaryote cells, despite UC's allegations of working in cells.

The PTAB agreed with Broad and concluded that their applications were non-obvious when read in light of the Jinek paper and UC's applications.

A 2018 appeal by UC to the US Court of Appeals upheld this decision. However, in 2019, a new interference proceeding was launched to decide the fate of the CRISPR patents between the two.

The latest in the interference proceedings occurred on 10 September 2020 when the PTAB ruled in favour of the Broad Institute stating that it had priority in its patents to the CRISPR system in eukaryotic cells.

UC has since filed new claims to their applications based on determining who invented the CRISPR system to function in eukaryotic cells. The application turning on UC's system which requires a single RNA-strand guide, whereas Broad teaches a double RNA-strand.

Interestingly, UC's fresh proceedings have identified that most current applications of the CRIPSR system function using the single RNA-strand.

**What about Europe...**

Unlike the US, the proceedings before the European Patent Office revolve around priority and whether the Broad Institute is entitled to it.

Although previously granting Broad several patents to CRISPR-*Cas9*, a request lodged with the Opposition Department to revoke the patents was granted. In the appeal the decision was upheld by the EPO Board of Appeal (the decision being handed down early in 2020).

In the application UC objected to Broad's patent on the basis that they were not entitled to an earlier priority claim of one of their key European Patents, namely; EP 2 771 468 B1 (the '468' patent).

Accordingly, the 468 patent claims priority, through a PCT application, to a US provisional application filed on 12 December 2012. This provisional application listed 8 applicants, one of which was Professor Luciano Marraffini of Rockefeller University in New York, as owners of the invention.

Prof. Marraffini was not named as an applicant on the European application, nor did his name appear on the PCT application, when it was filed on 12 December 2013. An allegation which could be easily discharged by providing an assignment from Marraffini. However, it is precisely that assignment which is not available, thus there is no record of the transfer of right.

The outcome of the failed assignment is the application of Article 87 of the EPO regulations, which requires a clear chain of priority. Without such a chain the application cannot claim priority to the original US provisional. Losing the earlier priority date, meant that other documents now became relevant as prior art. This prior art effectively destroyed the novelty for Board's application. The European patent was accordingly rejected.

Not surprisingly Broad has appealed this decision, claiming that US priority should be determined under US and not European law, but the Board of Appeal rejected this argument.

With 9 out of 21 of Broad's European patents being affected by the Board of Appeals decision, it is unlikely these proceedings will end anytime soon.

A first attempt was made when Broad looked to correct the minutes from a hearing before the Board of Appeal where they claimed a procedural defect had been noted. The type of defect which would allow Broad to institute a Petition for Review.

However, without the minutes showing the procedural defect, and without a request in the minutes showing that a request to correct the defect at the time it was made, Broad had to

rely on discussions outside of the official court record to prove their case. The outcome was that Broad was unable show such defect ever occurred.

In April 2020, the Board of Appeal rejected Broad's request to amend the minutes shutting the door on their ability to seek a Petition for Review.

## A global pandemic

The importance of a molecular tool capable of reshaping DNA in stopping the spread of a virus or fighting infections related to a global pandemic is very clear.

Severe Acute Respiratory Syndrome CoronaVirus 2 or SARS-CoV-2, the virus which causes COVID-19 or simply the Coronavirus has affected our lives in unprecedented ways.

Could CRIPSR technology be the key in winning the battle against the spread of this Virus and if so, how?

So far CRISPR technology has been used in diagnosing patients with the Virus. The technology uses *Cas12* proteins, as opposed to *Cas9*. In fact, a subsidiary of the Broad Institute recently received Emergency Use Authorization from the US Food and Drug Administration to use the CRISPR SARS-CoV-2 kit, dubbed SHERLOCK, which they had developed for detecting the virus.

The process involves programming CRISPR machinery, to detect short genetic sequences of the virus, collected from the nose, throat, or fluid from the lungs. If the Virus is detected, the CRIPSR enzyme emits a fluorescent glow in under an hour. Researchers in California[2] claim they can achieve similar results in just 40 minutes.

Likewise, UC has also developed a quick testing kit based on CRISPR technology for detecting the Virus called DETECTR. Unlike Broad's SHERLOCK, it is yet to receive FDA approval.

Jenifer Doudna[3] was part of a team that recently reported the development of a CRISPR diagnostic test capable of detecting the Virus in just five minutes.

Unlike other diagnostic tests using CRISPR technology, this test does not require amplification of any viral RNA in order to detect a positive result. The test is less accurate than others and can only detect 100,000 viruses per a microliter of solution compared to the above tests where 1 virus per a microliter can be detected. An added benefit of this "Doudna test" is that it does not require the expensive lab equipment of the other tests.

Additionally, the Doudna test can detect the amount of Virus present in a sample as measuring the intensity of the fluorescent glow when the Virus is detected becomes proportional to the amount of Virus present. This information may be used to tailor treatments for each patient.

**What about more than just detection...**

CRISPR may have additional roles when it comes to defeating the Virus. Including, development of a vaccine and, whether a targeted antibiotic specifically designed for killing the virus could be developed.

Developing vaccines takes time as the viral DNA strands must be incubated. However, with CRISPR the incubator can actually be modified to increase the viral products. By increasing the production rate of vaccine type viral DNA strands per an incubation, the time required in developing the vaccine can be reduced.

Another approach would be to use CRISPR technology to engineer B cells aka white blood cells, which produce antibodies to target and destroy viruses. Using CRIPSR, B cells can be pre-programmed with COVID fighting genes and injected straight into the body to fight the virus or even injected into patient before infection occurs.

The targeted B cells are introduced into the bloodstream, thus skipping the immune manufacturing process and move straight to fighting the virus head-on.

This type of pre-emptive vaccine is referred to as mRNA vaccines. Unfortunately, and until now, these types of vaccines have a very short life span. Meaning that regular 'top-ups' would be required.

## What's next?

What effect CRISPR technology and its associated patents will have on this and future pandemics remains to be seen. The value of such technology may be difficult to quantify with any degree of accuracy.

Most, if not all, countries include compulsory licensing provisions in their Patent laws to allow for use of patented products without the permission of the owners. Such provisions being applicable only when the needs of the public outweigh the rights of the owners.

Countries such as France, Germany, and Italy, which have been severely impacted by the COVID-19 pandemic, have already taken to updating their Patent acts when it comes to compulsory licenses. The changes have the intention of making unilateral confiscation of patent rights less stringent.

While these provisions may appear to focus on medicines, the French Patent Laws allow for compulsory licenses covering either, a drug, medical device, or in vitro diagnostic device; the process for obtaining such products; or a process of *ex vivo* diagnosis.

CRISPR technology appears to fall into all three of these categories for the issuance of a compulsory license in France and, is not limited to a pharmaceutical product.

Italy recently enacted Law Decree No. 18/2020, which included specific provisions under Article

> **"Could CRIPSR technology be the key in winning the battle against the spread of this Virus and if so, how?"**

[2] Broughton, J. P. *et al.* CRISPR-*Cas12*-based detection of SARS-CoV-2 Nature Biotechnol. 2020 Jul;38(7):870-874. doi: 10.1038/s41587-020-0513-4. Epub 2020 Apr 16.

[3] Fozouni, P. *et al.* Direct detection of SARS-CoV-2 using CRISPR-*Cas13a* and a mobile phone medRxiv 2020.09.28.20201947; doi: https://doi.org/10.1101/2020.09.28.20201947

> **The question to be asked may be how high up the patent chain countries can grant compulsory licenses.**

6 for dealing with the COVID-19 outbreak. The Article allows for the requisition of medical products and movable goods from private and public entities by the Civil Protection Department.

Germany included similar provisions in its Patent Laws under Section 13, while Japan provides for non-exclusive licenses to patented products in the case of special necessity based on the welfare of its public under Article 93 of their Patent Laws.

As CRISPR spreads its wings and moves from virus detection to virus destruction you can expect the rights of its patent holders to be limited, or even lost, now that compulsory license requirements are being relaxed worldwide in preparation for future pandemics.

The question to be asked may be how high up the patent chain countries can grant compulsory licenses. Given the recent changes in compulsory license laws in European countries, will the license stop at the product (vaccines) or the manufacturing process itself (platform).

Of course, before the licensing question is answered, we first need to determine whether CRISPR technology can be classified as life-saving. Under the current pandemic it probably won't be so hard to do so.

## Conclusion

What effect has the patent dispute, potential compulsory licensing and a global pandemic had on our laureate winners? Well, seemingly none, as the Royal Swedish Academy found themselves *immune* to all of it when awarding Emmanuelle and Jennifer with their highest accolade. In a world chaotically spinning out of control their Nobel Prize really became the eye of the storm.

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