Does CRISPR-Cas open new possibilities for patents or present a moral maze?

Philip Webber

CRISPR-Cas systems, which enable the production of new artificial genes, synthetic proteins and new transgenic organisms, will challenge patent practices worldwide.

CRISPR-Cas systems have been heralded as a jaw-dropping breakthrough in the treatment of hereditary diseases because they allow targeted mutations to be introduced into DNA. But CRISPR (an acronym for clustered regularly interspaced short palindromic repeats)-Cas (CRISPR-associated protein) systems also enable the production of artificial genes, synthetic proteins and new transgenic organisms, and patents are likely to be sought for all of these. Here, we review the patentability criteria for gene patents and the approaches that patent offices have taken for the patenting of new microorganisms and transgenic plants and animals. We also raise questions about whether the newfound power to make designer plants and animals should be embraced, particularly in light of the rules many national patent offices have against the patenting of "immoral" inventions.

CRISPR-Cas systems

CRISPR, present in many bacterial genomes, form part of a basic immune system where foreign DNA is incorporated between palindromic sequences to provide the bacteria with a molecular 'memory' of viruses that have previously invaded the bacteria. If the same virus then subsequently invades the bacteria, the bacteria use these CRISPR sequences to recognize the virus; the virus is then cleaved with the bacteria's Cas enzymes.

Systems that recognize and cleave specific DNA sequences have attracted considerable attention. CRISPR-Cas systems—in particular, the type-II CRISPR-Cas9 system of *Streptococcus pyogenes*—can be used with programmable, double-stranded RNA 'guide' molecules to make very specific changes, including substitutions, insertions and deletions, in bacterial genomes[1,2]. More importantly, the type-II CRISPR-Cas9 system has now been shown to alter the genomes of eukaryotes, including humans[3,4]. In contrast to previous mutagenesis systems such as zinc finger nucleases[5], CRISPR-Cas do not require the engineering of new enzymes for each target sequence; they only require the production of a short RNA guide.

CRISPR-Cas systems therefore provide researchers with a simple RNA-programmable method for introducing specific mutations into a target DNA with high levels of accuracy and efficacy. It is hoped that this level of accuracy might make the system adaptable to therapeutic applications, such as treating human diseases and possibly even correcting defective genes in *in vitro*–fertilized embryos before implantation. On the commercial side, CRISPR-Cas systems also offer the agbiotech industry an enhanced method for the production of transgenic plants and animals. Other, more controversial fields to which such systems could be applied include the production of designer pets and designer babies.

Criteria for patentability

Inventions relying on CRISPR-Cas systems may qualify for protection under the patent system. Such inventions could be based on new methods of applying CRISPR-Cas systems or on products such as genes, proteins or transgenic organisms made with such systems. Although the patentability of any inventions will be judged by the various patent offices using the standard criteria that apply to all inventions, such as, novelty, nonobviousness, usefulness or industrial applicability, and enablement, some additional criteria discussed below generally apply only to biotechnological inventions. It must also be remembered that patent practice around the world is not totally harmonized, and that many differences do exist between countries.

What can be patented?

CRISPR-Cas systems open up new opportunities in a number of areas.

Research tools. Although CRISPR-Cas systems were initially used to alter prokaryotic organisms, they have now also been applied to eukaryotic organisms. If further developments in CRISPR techniques are made, particularly if CRISPR is applied in nonobvious fields or if technical hurdles have been overcome in a non-obvious way, then patent claims may be filed for such new methods. Patents may also be based on genetically engineered Cas enzymes or guide RNAs that specify the target sequence to be cleaved by the CRISPR system.

Genes and proteins. The key use for CRISPR is to introduce targeted mutations—substitutions, insertions or deletions—into specific DNA sequences, thus enabling the production of novel gene sequences, RNA and protein sequences.

As far as patent offices are concerned, such sequences are treated like any other chemical entity, and they are generally patentable as long as they meet standard patentability criteria. Novelty will often be assured in this context by virtue of the fact that CRISPR has been used to change a known gene sequence into a new sequence; and such a sequence may be accepted as being nonobvious if the resulting gene, RNA or protein has unexpected properties. For example, the invention might be based on a new protein sequence wherein the sequence differs from a previously known one by a single amino acid. This difference

Philip Webber is at Dehns Patent and Trade Mark Attorneys, Oxford, UK.
e-mail: pwebber@dehns.com

would satisfy the novelty hurdle; and if this change results in a protein having an unexpectedly longer half-life, for example, then such a protein might be considered to be nonobvious.

There is a special requirement that the utility (US) or industrial application (Europe) of any claimed genes must be disclosed in the patent application to prevent the patenting of gene sequences with unknown uses. However, if the inventor is making a specific mutation using CRISPR, then it seems likely that the inventor will have a particular reason for doing that and will be well aware of the use of the gene and/or protein.

The US Supreme Court ruled last year that genomic DNA is not patentable[6] on the grounds that it is a product of nature, but this ruling does not prevent the patenting of artificial DNA sequences such as cDNA or, as here, CRISPR-mutated DNA (unless the mutated DNA corresponds to a genomic sequence). In Europe, the EU Biotech Directive[7] has specifically confirmed the patentability of DNA sequences (genomic or otherwise).

Microorganisms. In a landmark case, in 1980, the US Supreme Court ruled that bacteria that had been genetically modified to degrade oil spills were patentable in the United States, thus opening the door for patents on higher life forms[8]. However, a patent for a new type of yeast had been granted in Finland in 1843 (ref. 9), and hence the groundwork for patents on life forms in Europe had been established well before the modern-day genetic revolution arrived.

Patent offices generally evaluate modified microorganisms in the same way as complex chemical compositions, asking, is the microorganism changed in any way compared to a previously known microorganism (i.e., is it novel)? And does the change produce some surprising or unexpected effect (i.e., is the change nonobvious)? If so, then the microorganism is potentially patentable. For example, the introduction of a new gene from one bacterial species into another bacterial species will produce a novel bacterium; and if such a modification is not obvious, then that modified bacterium will potentially be patentable.

Patenting plants and animals. The same criteria also apply to the patenting of transgenic plants and animals. If a known plant or animal is modified in some way, then a novel entity will be produced that will potentially be patentable if it is also not obvious. For example, if CRISPR is used to introduce a fish gene into a plant (e.g., to produce omega oils in plants) or to introduce a human gene into a cow (e.g., a human insulin gene), then novel plants or animals will have been produced. If such steps are not obvious, then the transgenic plant or animal will potentially be patentable.

Box 1 European rules against patenting transgenic animals

1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to ordre public or morality...
2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable...

   (d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

Source: (Article 6(2)d of Directive 98/44/EC)

The moral maze

Many countries have patent laws that include rules against the patenting of immoral inventions. These include the contracting states of the European Patent Convention. One notable exception, however, is the United States. The general reason for the rule is that patent offices (which are government bodies) should not be seen to be condoning the exploitation of immoral inventions (although this does not fit squarely with the fact that a patent right is merely a right to prevent others from exploiting an invention; it does not give the patent owner any rights to exploit his invention).

Transgenic plants. In Europe, some early transgenic plant patents, including a patent granted to Plant Genetic Systems[10], were challenged by Greenpeace on the grounds that granting a patent to a life form was immoral[11]. Although the European Patent Office (EPO) agreed that inventions whose exploitation was likely to seriously prejudice the environment should be excluded from patentability on moral grounds if the threat to the environment was sufficiently substantiated, this did not mean that there should be a blanket ban on the patenting of transgenic plants. This remains the practice of the EPO today.

Transgenic animals. One of the first European patent applications on a transgenic animal[12], however, had a far rougher ride. This invention related to the Harvard Oncomouse, which was genetically engineered to develop tumors readily if exposed to small amounts of carcinogenic substances. Given that testing for the carcinogenic activity of substances is accepted as being necessary in some fields, the rationale for this invention was that smaller numbers of Oncomice would be needed in such testing compared to the number of standard laboratory mice that would ordinarily be needed; consequently, the overall number of laboratory animals needed would be reduced. During the initial examination of the Oncomouse patent application, the EPO examiner raised objections to the morality of this invention and rejected the patent application on this ground. During an appeal against this rejection, the morality issue was discussed further and one of the EPO's technical boards of appeal put forward a test to determine whether or not such inventions should be considered immoral based on balancing the potential suffering of the transgenic animal against the medical benefit to mankind (**Box 1**). This test was later included in the EU Biotech Directive (Article 6(2)d) and the European Patent Convention (Rule 28(d)). Although the Oncomouse European patent was granted, it was opposed afterwards at the EPO by a record number (17) of parties on various grounds including lack of morality. Although narrow claims to transgenic mice were eventually considered to be acceptable to the EPO, Harvard did not pursue the European patent further and the patent was revoked by the EPO. Overall, it is considered unlikely that many other transgenic animal inventions will fall within this exclusion because most such inventions will not result in suffering to the animal.

Designer pets and babies. It is not difficult to envisage how CRISPR-Cas systems could be exploited in areas beyond the traditional fields of biotech, such as in the production of designer pets and human babies having desirable traits.

Designer pets are unlikely to be patentable if the invention is based merely on a cosmetic difference compared to a previous animal (e.g., a cat having a novel fur pattern or a dog that is smaller than typical for its breed) because the patent system is set up to grant patents for technical innovations as opposed to aesthetic ones. Some designer pets, however, might still be capable of satisfying this technical hurdle (e.g., hypoallergenic pets or species of pets that no longer suffer from inbred genetic defects).

As for designer babies, the patent laws of most countries, including Europe[13] and the United States, ban the patenting of human

beings, so such patents are unlikely to be granted. The question remains, however, as to whether society would allow the production of designer babies or pets or ban them completely, but that is a question for the people and legislature of each country.

The addition of the CRISPR-Cas system to the genetic researcher's toolbox provides the ability to make targeted mutations with a degree of specificity not seen with other techniques. It may open the door to human therapeutic applications, a new generation of artificial genes and synthetic proteins, and new transgenic plants and animals. The patent systems around the world are already well versed in dealing with such new inventions, both from a technical perspective and a moral one.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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