Head: Patent analysis: CRISPR Technology in India

SF: CRISPR technology is an upcoming and most researched gene-editing tool in recent age. It is likely that many patent applications directed to CRISPR technology will be filed in India, says Hemant Singh of Inttl Advocare, who analyses some of the early applications and the rules on patentability.

PQ:

"Rapid commercialisation and industrial uses stemming from use of CRISPR technology will also determine whether any patents on CRISPR/Cas9 technology can be declared as standard-essential patents."

CRISPR is the acronym for 'clustered regularly interspaced short palindromic repeats'. The technology is a targeted tool used to edit genomes with unparalleled precision, efficiency, and flexibility.

While many of us might think that CRISPR was discovered by humankind, this is not the case. CRISPR has in fact long been part of bacterial immune systems as a defence mechanism against invading phages/viruses. Upon invasion by any virus, a bacterium's defence system creates unique repeated sequences of DNA with short sequences of spacers. These spacers are derived from the DNA of viruses after their first bacterial attack.

Acting as a memory bank, the spacers in the bacteria serve as a template for CRISPR RNA (crRNA) and on subsequent attack by the same virus crRNA is activated by identification of the viral DNA sequence and matching the spacer sequence with it. Having done this matching exercise, crRNAs along with trans-activating crRNA (tracrRNA, together referred to as guide RNA) guide the bacterial DNA cutting enzyme, Cas (CRISPR-associated enzyme) to reach the invading viral DNA and cut it, thereby disabling the virus.

A number of Cas enzymes, also known as molecular scissors, have been identified. The most well studied and researched is the Cas9 enzyme, which is an RNA-guided DNA endonuclease associated with the CRISPR defence system in *Streptococcus pyogenes*, among other bacteria. These endonucleases create specific double-stranded breaks at desired locations in the genome, and thereafter the cell's endogenous mechanism repairs the induced break.

The accuracy and precision of cleavage of DNA sequences with minimum off-site target cleavage gives it a distinct advantage over its predecessor restriction enzymes such as Zinc Finger Nucleases and TALEN (Transcription activator-like effector nuclease) and makes it the most sought-after tool in the biotechnology industry. CRISPR technology simply requires one to

alter the sequence of the guide-RNA to match with the target DNA sequence for effecting precise edits on the target DNA using Cas9. This technology is now being researched further for detection and removal of defective genes responsible for genetic disorders and insertion of correct DNA sequences for treatment of these disorders.

Indian patent landscape for CRISPR

Before discussing the Indian patent filing trends with regard to CRISPR, it is important to mention the two pioneer groups associated with discovering this technology. One of the groups is led by Jennifer Doudna, a professor of chemistry and molecular and cell biology at the University of California, Berkeley, who, in collaboration with Emmanuelle Charpentier among other inventors, was the first to file a patent application directed to CRISPR technology at the US Patent and Trademark Office (USPTO) in May 2012. Doudna's application essentially claims the amino acid sequence (structure of Cas9 protein) and function of CRISPR/Cas9 complex, in particular, Cas9 enzyme. The use of the claimed CRISPR/Cas9 complex targets polyribonucleotides, which includes polyribonucleotides in eukaryotic cells.

The second group, headed by Feng Zhang, a member of the Broad Institute of MIT and Harvard, was second to file a patent application with the USPTO in December 2012, almost six months after Doudna's application. Zhang's application, which is the first one to be granted in the US (patent number 8697359), claims the use of the CRISPR/Cas9 complex for altering expression in targeted DNA of eukaryotic cells, particularly human cells. Although Zhang was second in the race to file a patent application, he was granted his patent first by requesting accelerated examination before the USPTO. Doudna and Zhang are presently fighting for their patent rights in interference proceedings pending before the USPTO.

After Doudna's and Zhang's applications were filed at USPTO, numerous applications relating to several uses of the CRISPR/Cas9 technology have been filed in various jurisdictions, including India.

With this background, we have analysed Indian patent filing trends in relation to CRISPR technology (although not exhaustively). As expected Doudna, through Regents of the University of California, is the first to file an application in India as a national phase application 9897/DELNP/2012 arising from PCT/US2011/035775. The claims essentially pertain to the structure (amino acid sequence) of the Cas9 enzyme (referred to as variant Cys4 endoribonuclease). Other claims are directed to use of the CRISPR/Cas9 system for regulating production and detecting specific sequence of target RNAs in eukaryotic cells.

With Doudna's application, 9897/DELNP/2012, being the first filed at the Indian Patent Office (IPO), other applicants such as Fred Hutchinson Cancer Research Center, Vilnius University, Bayer CropScience, and Sigma-Aldrich have also entered India for securing patent rights for

specific uses and modifications of CRISPR/Cas9 technology. A non-exhaustive list of published Indian patent applications is provided below:

1. **Applicant:** The Regents of the University of California
   Indian patent application number: 9897/DELNP/2012
   Use disclosed in the application: The description broadly mentions the use of this technology for various forensic, research, and diagnostic applications. In particular, the technology has been claimed to be used for regulating production, detecting specific sequence of target RNAs in eukaryotic cells. The patent application further specifies that the target RNA to be edited or detected is a non-human embryo and/or non-human stem cell. However, the pending claims are not limited to non-human embryo and/or non-human stem cells.
2. **Applicant:** Fred Hutchinson Cancer Research Center
   Indian patent application number: 7853/DELNP/2014
   Use disclosed in the application: The description broadly mentions the use of this technology for altering the expression of globin (haemoglobin) genes for treatment of thalassaemias, sickle cell disease and other haemoglobinopathies.
3. **Applicant:** Vilnius University
   Indian patent application number: 7846/DELNP/2014
   Use disclosed in the application: The description indicates the use of this technology derived from *Streptococcus thermophilus* for cloning procedures, target DNA modification and DNA cleavage in eukaryotic cells including mammalian cells apart from its use for site-specific nicking of a nucleotide sequence.
4. **Applicant:** Bayer CropScience
   Indian patent application number: 8318/DELNP/2014
   Use disclosed in the application: The description indicates the use of this technology to introduce targeted modification, including insertion, deletion or substitution at a precisely localised nucleotide sequence in the genome of a plant cell/plant via agribacterium-mediated transformation. In particular, targeted gene insertion is disclosed with herbicide tolerance genes, insect resistance genes, abiotic stress tolerance genes resulting in plant varieties with such genetic traits.
5. **Applicant:** Sigma-Aldrich
   Indian patent application number: 1500/KOLNP/2015
   Use disclosed in the application: The description broadly mentions the use of this technology for targeted DNA cleavage, modification and detection. The application discloses use of CRISPR technology with different types of effector domains linked to Cas proteins (combined to form fusion proteins) to generate extended cleavage, altering DNA sequence, increase/activate transcription of genes, decrease/terminate

transcription of genes. The fusion protein/CRISPR technology has been disclosed to modify cells and animals, including human cells but excluding non-human embryos.

Considering the increased filing of patent applications pertaining to the field of biotechnology, the Indian Patent Office (IPO) has published guidelines for examination of biotechnology applications. Since all of the aforementioned applications have yet to be examined, it is still to be seen how the IPO will treat these applications and their claims.

Apart from establishing that the claimed invention is novel, inventive and capable of industrial application, the hurdle which an applicant has to overcome is to establish that the claims do not fall under section 3 of the Indian Patents Act, which specifies categories of inventions which are not patentable.

Jumping the section 3 hurdle

The relevant provisions of section 3 of the act which may get attracted for examination of inventions pertaining to CRISPR technology are as under :

Section 3(b), which covers inventions contrary to morality or which cause serious prejudice to human, animal or plant life, or health or the environment.

An invention, the primary or intended use of which is likely to violate the well accepted and settled social, cultural, legal norms of morality, eg. a method for cloning of humans, has been cited in the Manual of Patent Office Practice and Procedure as one of the examples which is not considered as an invention according to section 3 (b) of the act.

Additionally, the examination guidelines cite a few other non-limiting examples of inventions which may face the patentability bar under section 3(b), such as:

(i) A process for cloning human beings or animals;

(ii) A process for modifying the germ line of human beings;

(iii) A process for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical or other benefit to man or animal, and also animals resulting from such process;

(iv) A process for preparing seeds or other genetic materials comprising elements which might cause adverse environmental impact; and

(v) Uses of human embryos for commercial exploitation.

With regard to the scope of patentability under section 3(c), which concerns scientific principles or abstract theory or discovery of living things or non-living substances, the guidelines clarify that products such as microorganisms, nucleic acid sequences, proteins, enzymes, compounds, etc, which are directly isolated from nature are not patentable subject matter. However, processes of isolation of these products can be considered subject to requirements of section 2(1)(j) of the act.

Regarding the patentability bar under section 3(d), which covers discovery of new forms of known substances which do not result in enhancement of efficacy, any minor modifications in the already existing substances, eg, proteins/enzymes/nucleotide sequences, etc, are not patentable unless the improved property/efficacy of the modified substance is established.

Apart from this, patent applications relating to compositions involving two or more biological products, for instance, should disclose a combinative effect of the components over the sum of their individual effects to overcome an objection based on section 3(e), which relates to mere admixture resulting only in aggregation of the properties or a method of making such mere admixture.

Since CRISPR technology/gene-editing tools may be used to treat genetic disorders, any process or method claim may invite an objection under section 3(i) of the act depending on the structure of the claims. Section 3(i) covers any process for the medicinal, surgical, curative, prophylactic diagnostic, therapeutic or other treatment of human beings or any process for a similar treatment of animals to render them free of disease or to increase their economic value or that of their products.

According to the act and guidelines, microorganisms are patentable under section 3(j), which covers plants and animals in whole or any part other than microorganisms but including seeds, varieties and species and essentially biological processes for production or propagation of plants and animals. However, section 3(c) prohibits obtaining a patent on discovery of living things occurring in nature, meaning only modified microorganisms are patentable.

Apart from the aforementioned possible objections which may have to be overcome, one of the key requirements to be satisfied for grant of inventions in this field is the fulfilment of detailed disclosure with respect to ‘credible utility’, which warrants a specific disclosure of how to use, practical ways of using and specific substantial utility of the invention.

The future of the pending Indian patent applications in this field has yet to be tested within the Indian legal framework.

Future of CRISPR in India

In the event that Doudna's or Vilnius University's applications are granted by IPO, it would be interesting to see the kind of claim protection granted to them. Rapid commercialisation and industrial uses stemming from use of CRISPR technology will also determine whether any patents on CRISPR/Cas9 technology can be declared as standard-essential patents for the purpose of licensing on fair, reasonable and non-discriminatory (FRAND) terms.

Caribou Biosciences, a gene research company founded by Doudna, and Editas, formed by Zhang, have reportedly already entered into cross-licensing and inked multiple deals for exploring and understanding further commercial use of this extremely fascinating molecular scissor technology.

As India is an attractive destination for investment on account of its huge population, many more patent applications in this field are bound to be filed. It will be interesting to see how the Indian legal, political and business framework responds to such technology, as it will require a mature balancing act between ethics, public interest and technological advancement.

Sign off:

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