PATENTING OF INVENTIONS RELATING TO GENOMIC EDITING TECHNOLOGY: TWO DECISIONS OF THE INTELLECTUAL PROPERTY HIGH COURT OF JAPAN

KLAUS HINKELMANN
German & European Patent Attorney, Munich, Germany

Introduction

The CRISPR-Cas9 system is a breakthrough genetic modification technology that allows for deletions, replacements, or insertions in the genome sequence at the target site. The inventors of the CRISPR-Cas9 system and method, the French microbiologist Emmanuelle Charpentier and the American biochemist Jennifer Doudna, were awarded the Nobel Prize in chemistry for this invention in 2020. The so-called CRISPR-Cas9 genome-editing technology enables the editing and/or cleaving of a DNA sequence in a simple and efficient manner. The CRISPR-Cas9 system includes Cas9 (cleavage enzymes) and guide RNAs (namely, crRNA and tracrRNA) that guide Cas9 to a target site. For this reason, this very important technology has led to a large number of patent applications all over the world. These patent applications and their handling by courts and patent offices attract much attention in the industries and organisations concerned.

In Japan, the Intellectual Property High Court ('the IPHC') handed down two important decisions on CRISPR-Cas9 genome-editing related patent applications on 25 February 2020.[1]

In the course of the examination proceedings before the Japanese Patent Office ('the JPO') both patent applications had been rejected by the Examining Division at first instance and then by the Appeal Board. In both cases, the patent applications were rejected because of lack of novelty over an older patent application which had, however, been published only after the priority date of the subject patent applications (Reason 1, Lack of Novelty, pursuant to Article 29-2 of the Japanese Patent Act) and because of lack of inventive step over a pre-published scientific paper (Reason 2, Lack of Inventive Step, pursuant to Article 29-2 of the Japanese Patent Act). Against the JPO decisions, appeals were raised before the IPHC. The IPHC on 25 February 2020 rescinded one of the decisions and upheld the other JPO decision. Both decisions of the IPHC of 25 February 2020 will be reported and discussed in this article.

The different interpretation of Article 29-2 of the Japanese Patent Act by the IPHC as compared to the JPO was the reason for granting one appeal. In the decisions, the IPHC offers its interpretation of '*invention described in the written description of prior application*' set out in Article 29-2.

1) (1) Intellectual Property High Court, 25 February 2020, Case No 2019 (Gyo-ke) 10011, regarding Japanese Patent Application No 2016-128599: *The BROAD INSTITUTE, INC., et al. v The Japan Patent Office.* (2) Intellectual Property High Court, 25 February 2020, Case No 2019 (Gyo-ke) 10010, regarding Japanese Patent Application No 2016-117740: *The BROAD INSTITUTE, INC., et al v The Japan Patent Office.*

Lack of Novelty (Pursuant to Article 29-2 of the Japanese Patent Act)

Article 29-2 of the Japanese Patent Act essentially prescribes that an invention in a Japanese patent application is not novel when it has been described in an earlier Japanese patent application even when the earlier Japanese patent application was not published before the priority date of the later patent application. However, this provision shall not apply where, at the time of filing of the younger patent application, the applicant of the younger patent application and the applicant of the other application for patent are the same person. The prior art effect is, however, only with regard to novelty, not inventive step.

Also, the level of technical disclosure required in this Article should be determined from a viewpoint that '*the invention is described to such an extent that those skilled in the art consider that the prior invention is explicitly disclosed in the description or the invention can be carried out based on the description of the prior application*'.

The Examination Guidelines of the JPO state that 'an invention described in prior publication should be an invention that is derived not only from what is explicitly described in the prior publication but also from what is considered to be described by those skilled in the art in light of technical common knowledge at the time of filing the application'. The Examination Guidelines state, moreover, that this standard is also applied to 'an invention described in the written description of prior application'.[2]

It is noted in this regard that an examiner of the JPO may assert that a claimed invention is substantially the same as an invention disclosed in a citation even though there is some difference between the present invention and the cited invention. One strategy that the applicant may take in this instance is to argue that the claimed invention provides new advantages over the cited invention. Often, but not always, the new advantages may be demonstrated by submitting experimental data. In some cases, however, the experimental data may not be entered. This decision indicates that, even in those instances, the claimed invention can be patented if it is distinguishable over the cited invention by considering the possible advantages.

Regarding the 'substantially the same standard' in connection with Article 29-2, the JPO's Examination Guidelines say that this standard applies if the difference between the claimed invention and the cited invention is small, that is, if the difference is a mere addition or replacement of well-known technology and therefore the claimed invention does not provide a new and advantageous effect over the cited invention.[3]

IP High Court Case 2019 (Gyo-ke) 10010

Background

The plaintiffs (the Broad Institute, part of the Massachusetts Institute of Technology (MIT), and Harvard University) filed a patent application for 'Engineering of systems, methods and optimized guide compositions for sequence manipulation' on 14 June 2016 (Japanese Patent Application No 2016-117740) claiming a convention priority of 12 December 2012 (US). The examiner rejected the claimed invention under Article 29-2 of the Japanese Patent Act on the ground that the claimed invention was described in a prior application filed previously, but published after the present application. That decision was upheld by the Board of Appeal within the JPO which also denied the existence of an inventive step. The plaintiffs challenged this decision by filing a lawsuit before the IPHC on 29 January 2017.

Claim 1 at issue

Claim 1 at issue (present invention) reads as follows:

> An engineered, non-naturally occurring Clustered Regularly Interspersed Short Palindromic Repeats

2) Part III, Chapter 3: Enlarged Prior Application 4.2 'Determination of Prior Art Invention'.

3) Examination Guidelines, Part III, Chapter 3, Enlarged Concept of Novelty, 3. 'Requirements of Article 29-2'.

(CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) vector-system comprising one or more vectors comprising:

(a) a first regulatory element operably linked to a nucleotide sequence encoding a CRISPR-Cas system polynucleotide sequence including a guide sequence, tracr RNA and a tracr mate sequence, wherein the guide sequence is capable of hybridizing to a target sequence in a locus in a eukaryotic cell;

(b) a second regulatory element operably linked to a nucleotide sequence encoding a Type II Cas9 protein; and

(c) a recombinant template;

wherein components (a), (b) and (c) are located on the same or different vectors of the system, and the vector system comprises nucleotide sequence(s) coding for one or more nuclear localization signals (NLSs) expressed with the nucleotide sequence encoding for the Cas9 protein, by which the guide sequence targets one or more polynucleotide loci in a eukaryotic cell, and Cas9 protein cleaves one or more polynucleotide loci, by which one or more polynucleotide loci are modified.

Decision by the Board of Appeal

The Board of Appeal of JPO held that the present invention is unpatentable under Article 29-2 of the Japanese Patent Act as it is the same as an invention described in the older patent application PCT/US2013/073307, filed on 5 December 2013 with a priority date of 6 December 2012 and published as WO 2014/089290 on 12 June 2014 (Citation 1) and lacks an inventive step over a scientific publication of Jinek, published online on 28 June 2012 (Citation 2). The Board of Appeal found that Citation 1 discloses an invention which is directed to a vector system, comprising:

> a vector including a promoter control sequence, operably linked to a nucleic acid encoding for at least one Type II Cas9 protein comprising at least one nuclear localization signal;
>
> a vector including promoter control sequence operably linked to DNA coding for at least one guide RNA comprising the first region at 5′ terminal that is complementary to a target site in the chromosomal sequence in a eukaryotic cell, the second internal region in stem-loop structure and the third region which is essentially single chain; and
>
> a vector including at least one donor polynucleotide, wherein the guide RNA derives Type II Cas9 protein into the target site in the chromosomal sequence in a eukaryotic cell, Type II Cas9 protein derives the cleavage of the double strand DNA of the chromosomal sequence at the target site, and the cleavage of the double strand DNA is restored in the restoration process as the chromosomal sequence is restored.

Arguments by the Plaintiffs

The plaintiffs argued that Citation 1 does not show any support such as experimental data for the modifications of sequence at the target site and the Board of Appeal erred by failing to provide any rationale for its finding that the CRISPR-Cas9 system could be applied to a eukaryote.

The plaintiffs further argued that Citation 1 fails to disclose the functional limitation of the present invention: '*the guide RNA derives Type II Cas9 protein into the target site in the chromosomal sequence in a eukaryotic cell, Type II Cas9 protein derives the cleavage of the double strand DNA of the chromosomal sequence at the target site and the cleavage of the double strand DNA is restored in the restoration process as the chromosomal sequence is restored*'.

One of the main issues was whether Citation 1 discloses the claimed configuration of 'wherein the guide RNA directs the type II Cas9 protein to a targeted site in the chromosomal sequence in the eukaryotic cell where the type II Cas9 protein introduces a break of double-strand of chromosomal DNA in

the targeted site, and the break of double-strand is repaired by a DNA repair process such that the chromosomal sequence is modified'.

The plaintiffs concluded that the present invention is thus not substantially the same as the cited invention ('the plaintiffs' argument 1'). Moreover, the plaintiffs concluded that the system disclosed in Citation 1 is unable to solve the problem that the present invention wants to solve and, therefore, Citation 1 cannot serve to exclude later filed applications from being patented as set forth in Article 29-2 of the Japanese Patent Act ('the plaintiffs' argument 2').

The plaintiffs argued in particular that Example 4 (FACS testing) of Citation 1 can only be used for screening and Example 5 (PCR testing) of Citation 1 is the more sensitive and accurate test, and that, based on the results of Example 5 (PCR) which did not show results of integration, a person skilled in the art should have concluded that there was no integration into the target site in Citation 1, and, therefore, Citation 1 should not be described as a 'prior application'.

Decision of the IPHC

In its judgment the IPHC offered its interpretation of 'an invention described in the written description of prior application' set forth in Article 29-2 of the Japanese Patent Act and upheld the JPO's Appeal Board decision rejecting the patent application. The IPHC found in particular that Citation 1 substantially discloses in comparison with the present invention that:

> *the guide RNA derives Type II Cas9 protein into the target site in the chromosomal sequence in a eukaryotic cell, Type II Cas9 protein derives the cleavage of the double strand DNA of the chromosomal sequence at the target site and the cleavage of the double strand DNA is restored in the restoration process as the chromosomal sequence is restored.*

The IPHC furthermore found that:

> *Example 4 (FACS) describes a specific test method for confirming that a donor sequence (GFP gene) is integrated into the target sequence. Moreover, from the results of Example 4 (FACS), it can be understood that ... double-strand breaks and repair occur at the target site. Example 5 (PCR) cannot be interpreted as an obstacle to the above understanding.*

The IPHC concluded from this that the vector system can be read from Citation 1 and is thus disclosed as it performs the same function. Based on this understanding, the IPHC rejected the plaintiffs' argument 1.

With regard to an interpretation of Article 29-2 Japanese Patent Act, the IPHC found that:

> *'an invention described in the prior application' set forth in Article 29-2 covers an invention that is derived from not only what is explicitly described but also what is considered to be described in the prior application. What is considered to be described should be interpreted as that derived from the description of the prior application in light of technical common knowledge at the time of filing the application. Accordingly, an invention described in the prior application can be determined to include what is considered to be described in understanding that invention. In contrast, an invention that is abstract or an invention that is considered not to be described even in light of technical common knowledge of those skilled in the art does not exclude later applications from being patented. Therefore, the degree of disclosure of technical contents required in Article 29-2 is sufficient if the prior invention is described to such an extent that those skilled in the art can understand that the prior invention is explicitly disclosed in the description and that the invention can be carried out in light of the description of the prior application.*

The IPHC found that Citation 1 describes a prior invention to such an extent that those skilled in the art would understand the prior invention from the reference and make the prior invention in light of the descriptions of Citation 1. Also, the IPHC found that Citation 1 should be interpreted to disclose technologies that are qualified to exclude later applications

from being patented, including '*the guide RNA derives Type II Cas9 protein into the target site in the chromosomal sequence in a eukaryotic cell, Type II Cas9 protein derives the cleavage of the double strand DNA of the chromosomal sequence at the target site and the cleavage of the double strand DNA is restored in the restoration process as the chromosomal sequence is restored*'. The IPHC thus also rejected the plaintiffs' argument 2.

IP High Court Case 2019 (Gyo-ke) 10011

Background

The plaintiffs (the Broad Institute and MIT) filed a patent application for 'CRISPR-Cas system and method for modifying the expression of gene products' on 29 June 2016 (Japanese Patent Application No 2016-128599) claiming a convention priority 12 December 2012 (US). The examiner rejected the claimed invention under Article 29-2 Japanese Patent Act on the ground that the claimed invention was described in a prior application filed previously but published after the present application. That decision was upheld by the Board of Appeal of JPO which also considered the claims obvious. The plaintiffs filed a lawsuit before the IPHC on 29 January 2017 to have the decision revoked.

The Claim at Issue

Claim 1 at issue reads as follows:

> An engineered, non-naturally occurring Clustered Regularly Interspersed Short Palindromic Repeats (CRISPR)-CRISPR associated (Cas) (CRISPR-Cas) vector-system comprising one or more vectors comprising:
>
> (a) a first regulatory element operably linked to one or more nucleotide sequence(s) encoding one or more CRISPR-Cas system guide RNA(s) which hybridize to a target sequence in a locus in a eukaryotic cell, wherein the guide RNA includes a guide sequence, a tracr sequence and a tracr mate sequence, and
>
> (b) a second regulatory element operably linked to a nucleotide sequence encoding a Type II Cas9 protein, wherein the protein includes a nuclear localization signal (NLS), wherein components (a) and (b) are located on the same or different vectors of the system, and the tracr sequence is 30 or more nucleotides in length, by which the guide sequence targets one or more polynucleotide loci in a eukaryotic cell, and the Cas9 protein cleaves the one or more polynucleotide loci, by which sequence of the one or more polynucleotide loci is modified.

Decision by the Board of Appeal

The Board of Appeal of the JPO held that the invention is unpatentable under Article 29-2 of the Japanese Patent Act for lack of novelty (Reason 1) over an unpublished prior patent application, namely PCT/US2013/073307 (Citation 1), filed on 5 December 2013 with a priority date of 6 December 2012 and published as WO 2014/089290 on 12 June 2014, and for lack of inventive step (Reason 2) over the scientific publication '*Science*, August 2012, vol. 337, pp. 816–821, Supplementary Materials' (Citation 2). The Board of Appeal found that:

> *Citation 1 recites an invention which is directed to a vector system, comprising:*
>
> *vector including a promoter control sequence, operably linked to a nucleic acid encoding for at least one Type II Cas9 protein comprising at least one nuclear localization signal; vector including promoter control sequence operably linked to DNA coding for at least one guide RNA comprising the first region at 5' terminal that is complementary to a target site in the chromosomal sequence in a eukaryotic cell, the second internal region in stem-loop structure and the third region which is essentially single chain, and vector including at least one donor polynucleotide, wherein the guide RNA derives Type II Cas9 protein into the target site in the chromosomal sequence in a eukaryotic cell, the Type II Cas9 protein derives the cleavage of the double strand DNA of the chromosomal sequence at the target site and the cleavage of the double strand DNA is restored in the restoration process as the chromosomal sequence is restored.*

The Board of Appeal also found that:

> *the present invention recites 'the traced sequence is 30 or more nucleotides in length' (the lower limit). In contrast, Citation 1 does not specify the length of the tracr sequence, and it only says that the total length of 'the second and the third regions' including 'tracr and tracr mate sequence' is approximately 30 to 120 nucleotides, which in turn means that the cited invention includes a vector system of which a sequence portion corresponding to the tracr sequence of the present invention is not only less than 30 nucleotides in length but also more than 30 nucleotides in length.*

Decision of the IPHC

Novelty: Interpretation of Article 29-2 of the Patent Act

The IPHC found that:

> *an 'invention' described in the prior application set forth in Article 29-2 covers an invention that is derived from not only what is explicitly described but also what is considered to be described, in the prior application. What is considered to be described should be interpreted as that derived from the description of the prior application in light of technical common knowledge at the time of filing the application.*
>
> *The present invention is characterized in that the tracr sequence is limited to 30 or more nucleotides in length based on the inventor's findings that the length of the tracr sequence is critical to the efficiency of gene modification.*
>
> *In contrast, Citation 1 discloses that*
>
> *– guide RNA includes three domains from the first domain to the third domain;*
>
> *– the length of the stem may be from approximately 6 to 20 base pairs in length;*
>
> *– typically, the third domain is approximately 4 or more nucleotides in length, and for example, the length of the third domain is in the range from approximately 5 to 60 nucleotides in length; and*
>
> *– the total length of the second and third domain of the guide RNA can be in the range from approximately 30 to 120 nucleotides in length.*
>
> *Also, considering the description of the present application that 'a part of the sequence of the 3' side of the loop corresponds to the tracr sequence', the 'tracr sequence' of the present invention is thought to be a combination of the third domain and one side of the stem in the second domain; however, Citation 1 does not have any idea of specifying the length of the tracr sequence (combination of the third domain and one side stem of the second domain) as one element of its patent claim.*
>
> *Further, no evidence shows that there was technical common knowledge at the time of priority date that the length of the tracr sequence should be made to be 30 or more nucleotides in length.*
>
> *Accordingly, Citation 1 fails to teach or suggest that 'the tracr sequence is 30 or more nucleotides in length' or does not seem to disclose this feature even in light of technical common knowledge at the time of the priority date.*

Inventive Step

The IPHC also determined that the invention of the application, which is characterised in that an efficiency of genome modification in eukaryotic cells increases by adopting the configuration that a 'tracr sequence is 30 or more nucleotides in length', would not have been easily conceivable to a person ordinarily skilled in the art on the basis of Cited Invention 2 which is at an *in vitro* level.

Arguments by the Defendant

The defendant asserted that:

> *no difference could be found between guide RNA (+48) having the tracr sequence of 26 nucleotide length and guide RNA (+54) having the tracr sequence of 32 nucleotide length, both targeting proto spacer 2, 4 and 5. Also, the present invention in which the tracr sequence is 30 or more nucleotides in length does not*

have any advantage that improves the gene modification efficiency without depending on the target sequence. Therefore, the present invention does not provide any new advantage over the cited invention.

The IPHC disagreed, finding that the specification shows that chimeric RNA (+54) having a tracr sequence of 32 nucleotides provides an enhanced gene modification efficiency over chimeric RNA (+48) having a tracr sequence of 26 nucleotides, for different targeting sequences such as proto spacer 1 and 3, so that it cannot be said that there is no possibility that the present invention of which the tracr sequence is 30 or more nucleotides in length increases the gene modification efficiency of a eukaryotic cell for other targeting sequences other than proto spacers 1 and 3.