lspn connect

The Membership Programme for the Life Sciences

In association with:

lsipr

ABE & PARTNERS

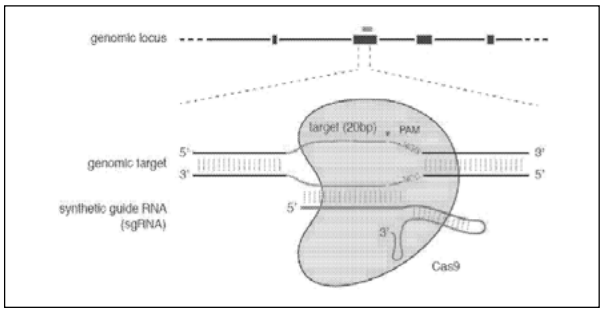
阿部国際総合法律事務所

CASE STUDY

The Broad Institute's CRISPR-Cas9 patents

The Broad Institute's CRISPR-Cas9 patents

There is fierce competition among researchers when it comes to patenting applications for genome editing technology. One legal case, in particular, highlights the issues, writes Takanori Abe of Abe & Partners.



Genome editing technology, which was the reason for awarding the Nobel Prize in Chemistry in 2020, generates fierce competition among researchers when it comes to patenting. This is a case in which the Broad Institute in the US and the Japan Patent Office (JPO) disputed over a patent application by the Broad Institute and others who accomplished genome editing technology with eukaryotes such as animals.

2019 (Gyo-Ke) 10010

Summary of the case

The present case is a lawsuit to revoke the JPO's trial decision in which the examiner made a refusal with regard to the patent application of the Broad Institute, the Massachusetts Institute of Technology and the President and Fellows of Harvard College (the Broad Institute) concerning an invention titled "ENGINEERING OF SYSTEMS, METHODS AND OPTIMIZED GUIDE COMPOSITIONS FOR SEQUENCE MANIPULATION".

The Broad Institute filed a request for a trial against the examiner's decision of refusal, the JPO dismissed that request, and thus the Broad Institute sought to revoke the JPO's trial decision.

Reasons for revocation are [i] Erroneous determination of Article 29-2 of the Patent Act based on the cited invention 1 (Reason 1); and [ii] Erroneous determination of an inventive step based on the cited invention 2 (Reason 2).

Judgment of February 25, 2020, the IP High Court

The IP High Court (Presiding Judge Takabe) held with regard to Reason 1 as follows and dismissed the Broad Institute's claim.

(1) It is found that the invention of the present application is identical to the cited invention 1.

It should be deemed that the cited document 1 discloses not only formally but also substantially that "a guide RNA directs a Type II-Cas9 protein to a target site in chromosomal sequence in eukaryotic cells where the Type II-Cas9 protein introduces a double-stranded break of chromosomal DNA in the target site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified".

It can be understood that the vector system of the cited invention 1 is also disclosed as a vector system which includes the above function.

(2) A. An object of Article 29-2 of the Patent Act is as follows. An invention stated in the description, etc, of an earlier application—even if that invention is not stated in the claim—is laid open to the public in a publication, etc, of the earlier application. Thus, even if a later application is filed before the publication, etc, of the earlier application, when the invention of the later application is identical with the invention of the earlier application, no new technology is laid open to the public in the publication, etc, of the later application.

Therefore, granting a patent to such an invention is improper from the viewpoint of the patent system, which intends to protect an invention as the reward for laying it open to the public.

The "invention" stated in the description, etc, of the earlier application in Article 29-2 is construed as an invention which is understood from a matter stated in the description, etc, of the earlier application and from a matter equivalent to that stated in the description, etc, of the earlier application. The "matter equivalent to that stated" means a matter which can be derived from the stated matter by taking common general technical knowledge of filing into consideration. Thus, even if there is no statement in the description, etc, of the earlier application, the invention can be found by taking the common general technical knowledge of a person ordinarily skilled in the art into consideration.

"Granting a patent to such an invention is improper from the viewpoint of the patent system."

On the other hand, in a case where an invention is abstract or where the technical content of an invention is insufficiently disclosed (even when the common general technical knowledge of a person ordinarily skilled in the art is taken into consideration), such an invention does not fall under the "invention" mentioned above and does not have the effect of excluding the later application stipulated in Article 29-2.

In addition, it should be deemed that the degree of disclosure of technical content required here should be sufficient if the technical content is disclosed to the extent that a person ordinarily skilled in the art can understand that the invention of the earlier application is shown in the description, etc, of the earlier application and the person ordinarily skilled in the art is enabled to work the invention shown in the earlier application.

B. Regarding the above, Examples 1 to 3 in the cited invention 1 disclose in detail a method for producing each vector of (i) to (iii) in the cited invention 1, and Example 4 discloses a concrete test for confirming whether a donor sequence—green fluorescent protein (GFP) gene—is incorporated in or near the target sequence. In addition, from the experimental results of Example 4, it can be understood that a combination of RNA-guided endonuclease comprising a nuclear localisation signal, guide RNA and donor polynucleotides is incorporated into the eukaryotic cells and that a double-stranded break and repair occur in the target site.

The experimental results of Example 5 are not to be interpreted as a bar to understanding the above. Further, a vector system comprising the above vectors (i) to (iii) has the technical means necessary for appropriate transcription, translation, nuclear translocation, etc, in eukaryotic cells, and the technical means necessary for appropriate modification of the target sequence in eukaryotic cells. Thus, it can be understood that even if the vector system is used, such a system shows the cleavage of target sequences and the modification of target sequences in eukaryotic cells.

From the above, it can be deemed that there is a disclosure in the cited document 1 to the extent that a person ordinarily skilled in the art can understand that the invention of the earlier application is shown in the description, etc, of the earlier application and a person ordinarily skilled in the art is enabled to work the invention shown in the earlier application.

Therefore, it is proper to find that in the cited document 1, a technology was laid open to the public to the extent that the technology was sufficient to exclude the later application, in which the technology includes a portion of the function such that "a guide RNA directs a Type II-Cas9 protein to a target site in chromosomal sequence in eukaryotic cells where the Type II-Cas9 protein introduces a double-stranded break of chromosomal DNA in the target site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified".

2019 (Gyo-Ke) 10011

Summary of the case

The present case is a lawsuit to revoke the JPO's trial decision in which the examiner made a refusal regarding the patent application of the Broad Institute Incorporated and the Massachusetts Institute of Technology (the Broad Institute) concerning an invention titled "CRISPR-Cas SYSTEMS AND METHODS FOR ALTERING EXPRESSION OF GENE PRODUCTS". The Broad Institute filed a request for a trial against the examiner's decision of refusal, the JPO dismissed the request, and thus the Broad Institute sought to revoke the JPO's trial decision.

Reasons for revocation are [i] Erroneous determination of Article 29-2 of the Patent Act based on the cited invention 1 (Reason 1); and [ii] Erroneous determination of an inventive step based on the cited invention 2 (Reason 2).

Judgment of February 25, 2020, the IP High Court

The IP High Court (Presiding Judge Takabe) held as follows and revoked the JPO trial decision for reasons of erroneous determination of Article 29-2 of the Patent Act and erroneous determination of an inventive step.

Reason 1 for Revocation (Erroneous determination of Article 29-2 of the Patent Act based on the cited invention 1)

A. An object of Article 29-2 of the Patent Act is as follows. An invention stated in the description, etc, of an earlier application, even if the invention is not stated in the claims, is laid open to the public in a publication, etc, of

"The cited document 1 merely discloses that a guide RNA comprises three regions."

the earlier application. Thus, even if a later application is filed before the publication, etc, of the earlier application, when the invention of the later application is identical with the invention of the earlier application, no new technology is laid open to the public in the publication, etc, of the later application. Therefore, granting a patent to such invention is inappropriate from the viewpoint of the patent system, which intends to protect an invention as the reward for laying it open to the public.

The "invention" stated in the description, etc, of the earlier application in Article 29-2 is construed as an invention which is understood from a matter stated in the description, etc, of the earlier application and from a matter equivalent to that stated in the description, etc, of the earlier application. The "matter equivalent to that stated" means a matter which can be derived from the stated matter by taking common general technical knowledge at the time of filing into consideration.

B. The invention of the present application states that the efficiency of genome modification increases by focusing on "a length of a tracr sequence" and adopting the configuration that the "tracr sequence is 30 or more nucleotides in length". On the other hand, the cited document 1 merely discloses that a guide RNA comprises three regions. In general, the length of the stem can range from about six to about 20 base pairs in length, the length of the third region is about four or more nucleotides in length and the length of the third region ranges from about five to about 60 nucleotides in length. The combined length of the second and third regions of the guide RNA can range from about 30 to about 120 nucleotides in length.

C. According to the description of the present application, namely that "the portion of the sequence 3' of the loop corresponds to the tracr sequence", it is found that the tracr sequence of the present invention is equivalent to the combination of one side of the stem of the second region with the third region in the cited invention 1. However, the cited document 1 does not define the exact length of the tracr sequence (the combination of one side of the stem of the second region with the third region).

Further, there is not sufficient evidence to find that there was common general technical knowledge of a person ordinarily skilled in the art such that the length of the tracr sequence was deemed to be 30 or more nucleotides in length at the time of the priority date of the present application.

D. Therefore, it cannot be deemed that the cited document 1 discloses that the configuration (a tracr sequence is "30 or more nucleotides in length") was adopted. Further, even by taking common general technical knowledge into consideration, it cannot be also deemed that the matter disclosed in the cited document 1 is equivalent to the statement that such configuration was adopted.

Reason 2 for Revocation (Erroneous determination of an inventive step based on the cited invention 2)

A. To a person ordinarily skilled in the art who has read the experimental results in the cited Example 2 (with regard to a length of a tracr sequence), it can be understood that a tracr sequence having a length of 26 nucleotides is preferable to a tracr sequence which is shorter than 26 nucleotides, when tracr sequences shorter than 26 nucleotides are compared.

However, it is not found in the cited Example 2 that when tracr sequences longer than 26 nucleotides are compared, the longer tracr sequence is preferable. In addition, taking all evidence of the present case into consideration, it is not sufficient to find that at the time of the priority date of the present application, there was common general technical knowledge which shows that the greater the length of a tracr sequence is preferable.

B. On the other hand, according to the description of the present application, there is a general explanation regarding a relationship between the length of a tracr sequence and the efficiency of genome modification. From Figure 16 and Figure 17 in the present application, it can be understood that in a case where protospacer 1 and protospacer 3 are targeted, a chimeric RNA having a tracr sequence length of 32 nucleotides is superior to a chimeric RNA having a tracr sequence length of 26 in terms of efficiency of genome modification.

Thus, even if the description of the cited document 2 and common general technical knowledge regarding the priority date of the present application are taken into consideration, with regard to a length of tracr RNA of the cited invention 2, it cannot be deemed that a person ordinarily skilled in the art was motivated to change from a length of 26 nucleotides—which is concretely

"The issue is how much the disclosure of the description of the earlier application can be complemented with other literature."

disclosed in the cited document 2—to 30 or more, with a view to improving the efficiency of genome modification.

C. Further, at the time of the priority date of the present application, there were neither technical papers nor any patent literature which reported that a CRISPR/Cas system derived from the acquired immunity of bacteria and archaea, as disclosed in the abstract of the cited document 2, could be applied to eukaryotic cells rather than a mixture in a buffer solution (*in vitro*). It can be evaluated that improving the efficiency of genome modification in eukaryotic cells, which is achieved by adopting the technical means of setting the length of a tracr sequence to 30 or more, is beyond expectation and prediction by a person ordinarily skilled in the art.

D. Therefore, even if the description of the cited document 2 and common general technical knowledge as to the priority date of the present application is taken into consideration, it cannot be deemed that the matter specifying the present invention, ie, "tracr sequence is 30 or more nucleotides in length" which was listed as the difference 4, would have been easily conceivable to a person ordinarily skilled in the art.

Practical tips

Regarding the application of Article 29-2 of the Patent Act, the issue is how much the disclosure of the description of the earlier application can be complemented with other literature. The Examination Guidelines say that the "secret prior art" covers inventions sharing substantial identity and stipulate that the earlier application can exclude the later application "in cases where a difference between the invention claimed in the application concerned and the cited invention is a very minor difference (an addition, deletion, conversion, etc, of common general knowledge or commonly used art, which does not yield any new effect) in embodying means for resolving a problem".

Judgments differ from case to case. In cases where the patentees won, judgments denied the identity by limitedly adopting the decisive factor of the Examination Guidelines. By contrast, in cases where the patentees lost, the "secret prior art" was judged adopting the decisive factor and applying the factor to the cases almost in the same way as in the inventive step as described by Shingo Kuwashiro *et al* in "Analysis of Trends in Court Rulings on Secret Prior Art", (72[1] Patent 97, 100 [2019]).

This judgment established the criterion that the "matter equivalent to that stated in the description, etc, of the earlier application meant a matter which could be derived from the stated matter by taking common general technical knowledge at the time of filing into consideration". The judgment may have held on the premise that the evaluation criterion of the identity of the earlier application is different from that of the inventive step, although it is not explicitly stated. The court let the patentees win in one case, while letting them lose in another case—based not on the double standard, as in the above analysis, but on the single standard.

It was the presence or absence of substantial differences with the cited inventions that separated the judgments where the Broad Institute won or lost. In the judgment where the Broad Institute won, the difference was adopted that the "tracr sequence is 30 or more nucleotides in length".

The invention detailed in the present application is characterised by the fact that efficient genome modification increases by focusing on "a length of a tracr sequence" and adopting the configuration relating to the above difference. It was determined that since such character is not described in the cited invention 1, and that the cited document 1 does not express a technical idea that defines the length of the tracr sequence, it is a substantial difference. On the contrary, in the judgment where the Broad Institute lost, it was determined that the invention of the present application and the cited invention 1 were the same.

The Broad Institute argued that the cited document 1 does not disclose the configuration of the invention of "the guide sequence targets the one or more polynucleotide locus in a eukaryotic cell, and the Cas9 protein cleaves the locus, thereby the sequence of locus is modified".

A person ordinarily skilled in the art referring to the cited document 1 should have reviewed the contradictory results of the FACS and PCR experiments in the cited document 1 and have concluded that it is unresolved whether the CRISPR-Cas9 system can work in eukaryotic cells, and that the cited

"In the judgment where the Broad Institute won, the difference was adopted that the 'tracr sequence is 30 or more nucleotides in length'."

document 1 only describes a system in which the sequence of genomic DNA in eukaryotic cells could not be edited in the target site. Therefore it cannot be decided that the cited invention 1 is substantially identical to the present invention in which the sequence can be edited.

However, the judgment held that it should be deemed that cited document 1 discloses not only formally but also substantially that "a guide RNA directs a Type II-Cas9 protein to a targeted site in a chromosomal sequence in eukaryotic cells where the Type II-Cas9 protein introduces a double-stranded break of chromosomal DNA in the target site, and the double-stranded break is repaired by a DNA repair process such that the chromosomal sequence is modified". It can also be understood that the vector system of cited invention 1 is disclosed as a vector system which includes the above function.

While genome-editing technology has the potential to revolutionise the medical arena and be a salvation for patients with intractable diseases, it has the downside of triggering the birth of twin genome-edited babies who are resistant to HIV by modifying the genetic information of the fertilised egg. In the Nobel lecture at the Nobel Prize in Literature 2017, Kazuo Ishiguro said: "New genetic technologies—such as the gene-editing technique CRISPR—and advances in Artificial Intelligence and robotics will bring us amazing, life-saving benefits, but may also create savage meritocracies resembling apartheid, and massive unemployment, including to those in the current professional elites."

Professor Jennifer A Doudna has confessed that she had a nightmare in which Adolf Hitler with a pig face said he wanted to understand the uses and implications of the amazing technology she had invented. On the other hand, there is a view that not editing the germline to relieve human suffering may be regarded as inhumane. Consider the case of the mother who lost her child due to a serious genetic disease and shouted at the scientists: "I don't care about difficult theories, just do research on genome editing."

The Nobel Prize in Chemistry 2020 was awarded to Doudna and Emmanuelle Charpentier who developed methods for genome editing. Professor Feng Zhang, the inventor of the present invention, missed the award. ●

Takanori Abe is the founder of Abe & Partners. He can be contacted at: abe@abe-law.com

Case study: The Broad Institute's CRISPR-Cas9 patents

***Life Sciences Intellectual Property Review* is published by Newton Media Limited**
Kingfisher House, 21-23 Elmfield Road, BR1 1LT, United Kingdom
Email: info@newtonmedia.co.uk
Website: www.lifesciencesipreview.com/

Director
Nicholas Lipinski

Group publisher and editor-in-chief
Peter Scott
Telephone: +44 (0)203 301 8217
Email: pscott@newtonmedia.co.uk

Editor
Tom Phillips

Senior editor
Muireann Bolger

Senior writer
Sarah Morgan

Sub-editor
Ros Bromwich

Journalist
Rory O'Neill

Head of content
Sarah Gooding
Telephone: +44 (0)795 767 2202
Email: sgooding@newtonmedia.co.uk

Head of commercial partnerships
Kirsty Pocock
Telephone: +44 (0)203 301 8211
Email: kpocock@newtonmedia.co.uk

Commercial partnerships Lead
Amy Samra
Telephone: +44 (0)203 301 8223
Email: asamra@newtonmedia.co.uk

Commercial partnerships manager
Paul Clifton
Email: pclifton@newtonmedia.co.uk

Production manager
Melissa Warner
Email: production@newtonmedia.co.uk

Project manager
Louise McMillan
Email: lmcmillan@newtonmedia.co.uk

Subscriptions
Adrian Tapping
Telephone: +44 (0)203 301 8203
Email: atapping@newtonmedia.co.uk

Production and design
Fisherman Creative

Cover photo: Shutterstock / ktsdesign