Third Party Observation for application Number EP20240165204

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Title: COMPOSITION FOR CLEAVING A TARGET DNA COMPRISING A GUIDE RNA SPECIFIC FOR THE TARGET DNA AND CAS PROTEIN-ENCODING NUCLEIC ACID OR CAS PROTEIN, AND USE THEREOF
Publication Number: EP4397760
Applicant: TOOLGEN INC[KR]
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1. Facts and evidence

1.1. Reference is made to the following documents

PL1 US7736886 15.06.2010 Recombination systems and methods for eliminating nucleic acid sequences from the genome of eukaryotic organisms

1.2. Observations concerning the public availability of the non-patent literature

NPL1
Uploaded documents:
1. NPL1_EP-4397760 3POs.pdf

2. Prior Use

2.1. Prior use (1)

When did the prior use occur?

What was made available?

Where was it made available?

How and to whom was it made available?

3. Common General Knowledge

4. Novelty (Article 54 EPC)

4.1. Novelty (1)

5. Inventive step (Article 56 EPC)

5.1. Inventive step (1)

Features known from the prior art:

Novel features not known from the prior art:

The technical effect caused or technical problems solved by the novel features:

Reasons why it would be obvious to the skilled persons to combine the features as set in the independent claim:
The examining division might not be aware that the EPO has already considered the obviousness of delivering a complex of Cas9 and a guide RNA into cells. In particular, the opposition division handling EP 3346003 (in the same family as the present application) has indicated in its preliminary opinion of 24th April 2025 that such delivery would have been obvious.

The opposition division's preliminary opinion is that the patent should be revoked for (among several reasons) lack of inventive step. In particular, on page 30 the opposition division explains that delivery of a Cas9–guide RNA complex would have been obvious.

The opposition division's view is based on US patent 7,736,886 (published 2005). This document relates to the delivery of genome-editing enzymes to eukaryotic cells, and discloses that direct protein delivery specifically avoids the disadvantage of integration of enzyme-encoding sequences into the genome (see column 18, point 7). This is the same technical effect described in the present application for the direct delivery of Cas9–guide RNA complexes, as opposed to using a plasmid encoding Cas9 (see paragraph [328]).

Therefore, the EPO has already indicated that it would have been obvious to use direct delivery of a composition comprising a Cas9 protein and a guide RNA. The present examining division is therefore taking a position that contradicts the position which has already been taken in opposition proceedings. This contradiction is both undesirable for the EPO and harmful for the certainty of the public.

6. Any further Observations, e.g. Articles 52(2), 53, 57, 76, 83, 84, 123(2) EPC, validity of the priority date

6.1. Unallowable amendments (Articles 76 and 123 EPC)

6.2. Sufficiency of disclosure (Article 83 EPC)

6.3. Clarity (Article 84 EPC)

6.4. Further observations

CARPMAELS & RANSFORD

EUROPEAN PATENT APPLICATION 24165204.9
TOOLGEN INCORPORATED
FURTHER OBSERVATIONS UNDER ARTICLE 115 EPC

July 2025

1. EP-24165204.9 is pending with four independent claims, filed on 15th July 2025:

> 1. An *in vitro* or *ex vivo* method for cleaving a target DNA in a mammalian cell, inducing a targeted mutagenesis in a mammalian cell or genome editing in a mammalian cell, the method comprising the steps of
>
> (a) providing a composition comprising a single-chain guide RNA (sgRNA) and a Cas9 protein, and
>
> (b) transferring the composition into the cell,
>
> wherein the Cas9 protein is a *Streptococcus pyogenes* Cas9 protein.

> 2. An *in vitro* or *ex vivo* method of preparing a mammalian cell, the method comprising the steps of
>
> (a) providing a composition comprising a single-chain guide RNA (sgRNA) and a Cas9 protein, and
>
> (b) transferring the composition into the cell,
>
> wherein the Cas9 protein is a *Streptococcus pyogenes* Cas9 protein.

> 4. An *in vitro* or *ex vivo* use of a sgRNA and a Cas9 protein for transfer into a mammalian cell for cleaving a target DNA in said mammalian cell, inducing a targeted mutagenesis in said mammalian cell or genome editing in said mammalian cell, wherein the sgRNA and the Cas9 protein are provided in a composition and the composition is transferred into the cell, and wherein the Cas9 protein is a *Streptococcus pyogenes* Cas9 protein.

> 5. An *in vitro* or *ex vivo* use of a Cas9 protein complexed with a sgRNA for transfer into a mammalian cell for cleaving a target DNA in said mammalian cell, inducing a targeted mutagenesis in said mammalian cell or genome editing in said mammalian cell, wherein the Cas9 protein is a *Streptococcus pyogenes* Cas9 protein.

2. The applicant argued that the examining division acknowledged an inventive step for methods involving direct delivery of a composition comprising sgRNA and Cas9 protein into cells (previous claim 3), and so the new independent claims must also be inventive.

3. However, the examining division might not be aware that the EPO has already considered the obviousness of delivering a complex of Cas9 and a guide RNA into cells. In particular, the opposition division handling EP-3346003 (in the same family as the present application) has indicated in its preliminary opinion of 24th April 2025 that such delivery would have been obvious.

4. Claim 1 of EP-3346003 is as follows:

> **1.** A Type II Clustered Regularly interspaced Short Palindromic Repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) composition for cleaving a target DNA in a plant cell, wherein the target DNA is endogenous DNA, and wherein the composition comprises a complex of:
>
> (a) a CRISPR-associated protein 9 (Cas9) polypeptide; and
> (b) a guide RNA specific to the target DNA,
>
> wherein the guide RNA is:
>
> (i) a dual guide RNA comprising a CRISPR RNA (crRNA) and a trans activating crRNA (tracrRNA); or
> (ii) a single-chain guide RNA comprising a CRISPR RNA (crRNA) fused to a trans activating crRNA (tracrRNA),
>
> wherein the composition further comprises polyethylene glycol (PEG).

5. The opposition division's preliminary opinion is that the patent should be revoked for (among several reasons) lack of inventive step. In particular, on page 30 the opposition division explains that delivery of a Cas9–guide RNA complex would have been obvious:

> There is no evidence on file about a surprising/unexpected effect provided by the composition as claimed. Introduction of a protein, instead of the corresponding nucleic acid construct encoding for the same protein, would be regarded as an obvious design alternative. Document D45 hints at this alternative on page 635, right column, bottom paragraph. Document D55 states on column 18, point 7. that the DSBI (double-strand break inducing) enzyme may be introduced directly into (plant) cells, ... for example via polyethylene glycol transfection. Document D55 discloses several alternatives to introduce the DSBI into the cell and the advantage linked to this approach, which would lead to no DSBI-enzyme-encoding sequences remaining in the genome.
>
> It should therefore be concluded that the person skilled in the art, faced with the problems stated above, would have considered the introduction of a complex as claimed, which comprises Cas9 directly in the form of a polypeptide. This can be carried out with a reasonable expectation of success, following the general knowledge and the teaching in the available state of the art, as summarised for example above.

6. D55 cited to support the opposition division's view is US patent 7,736,886 (published 2005), enclosed as PL1. PL1 relates to the delivery of genome-editing enzymes to eukaryotic cells, and discloses that direct protein delivery specifically avoids the disadvantage of integration of enzyme-encoding sequences into the genome (see column 18, point 7). This is the same technical effect described in the present application for the direct delivery of Cas9–guide RNA complexes, as opposed to using a plasmid encoding Cas9 (see paragraph [328]).

7. Therefore, the EPO has already indicated that it would have been obvious to use direct delivery of a composition comprising a Cas9 protein and a guide RNA. The present examining division is therefore taking a position that contradicts the position which has already been taken in opposition proceedings. This contradiction is both undesirable for the EPO and harmful for the certainty of the public.

8. The pending claims therefore lack an inventive step, and the application is not suitable for allowance.

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