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Datasheet for the decision of 6 May 2024

Case Number: T 2838/19 - 3.3.08

Application Number: 13814364.9

Publication Number: 2898075

IPC: C12N15/63

Language of the proceedings: EN

Title of invention:
Engineering and optimization of improved systems, methods and enzyme compositions for sequence manipulation

Patent Proprietor:
The Broad Institute, Inc.
Massachusetts Institute of Technology
President and Fellows of Harvard College

Opponents:
Boxall Intellectual Property Management Limited
CRISPR Therapeutics AG
Wilding, James Roger
Schlich, George
COHAUSZ & FLORACK
Grund, Martin, Dr.

Headword:
CRISPR complex/THE BROAD INSTITUTE
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
PRESIDENT AND FELLOWS OF HARVARD COLLEGE

Relevant legal provisions:
EPC Art. 100(c), 123(2)
RPBA 2020 Art. 13(2)

Keyword:
Claims as granted (main request) and auxiliary requests 2 to 37 - added subject-matter - (yes)
Admittance of auxiliary requests 1 and 38 to 45 - exceptional circumstances (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 2838/19 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 6 May 2024

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 October 2019 concerning maintenance of the European Patent No. 2898075 in amended form**

Composition of the Board:

Chair	T. Sommerfeld
Members:	M. Montrone
	D. Rogers

Summary of Facts and Submissions

I. Appeals were lodged by the patent proprietors, opponents 02 and 03 ("appellants I to III", respectively) against an interlocutory decision of the opposition division according to which the European patent no. 2 898 075 could be maintained in amended form. Likewise opponent 04 filed an appeal which was, however, later withdrawn. Opponents 01, 04 and 06 are thus parties as of right; opponent 05 has withdrawn its opposition and is thus no longer a party to the proceedings. The patent in suit is based upon European patent application No. 13 814 364.9 which was filed as International patent application published as WO 2014/ 093635 ("patent application").

II. The oppositions against the patent in suit were based on all grounds for opposition under Article 100 (a) to (c) EPC. The opposition division held that the patent could be maintained in amended form on the basis of the claims of the second auxiliary request filed at the oral proceedings on 4 July 2019.

III. Appellant I filed with their statement of grounds of appeal (hereinafter "SGA"), *inter alia* 35 auxiliary requests.

IV. Appellants II and III submitted with their SGA *inter alia* arguments under added subject-matter against the claims considered allowable by the opposition division.

V. Opponents 01 and 04 filed submissions *inter alia* under added subject-matter in reply to appellant I's SGA.

VI. In reply to the other appellants' SGAs, appellant I re-submitted auxiliary requests 1 to 7, 9 to 11, 13 to 15, 17 to 22 and 25 to 36 (corresponding to auxiliary requests 1 to 10, 12 to 14, 16 to 21 and 24 to 35 filed with their SGA) and submitted new auxiliary requests 8, 12, 16, 23 and 24.

VII. The appellants filed various further replies including *inter alia* counter-arguments to each others submissions.

VIII. In a communication pursuant to Article 15(1) RPBA, the parties were informed of the board's preliminary opinion.

IX. In reply, appellant I *inter alia* resubmitted auxiliary requests 1 to 36 and submitted new auxiliary requests 37 to 44.

X. Oral proceedings were held in the presence of appellants I, II and opponent 06. As announced, appellant III and opponents 01 and 04 were not present at the oral proceedings. During the oral proceedings, appellant I filed a new auxiliary request 1, while auxiliary requests 1 to 44 on file were renumbered as auxiliary requests 2 to 45.

XI. Claim 1 as granted (main request) reads:

"1. A composition comprising:

CRISPR complex components comprising:

I. CRISPR-Cas system polynucleotide sequence(s) which comprise(s):

(a) an engineered guide sequence comprised of RNA and capable of hybridizing to a target sequence in a polynucleotide locus,
(b) a tracr mate sequence comprised of RNA, and
(c) a tracrRNA sequence comprised of RNA, and
wherein (a), (b) and (c) are arranged in a 5' to 3' orientation,

II. a Type II Cas9 protein,

wherein the tracr mate sequence hybridizes to the tracrRNA sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to a target sequence,
wherein the CRISPR complex comprises the Type II Cas9 protein complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracrRNA sequence, and
wherein the Type II Cas9 protein is or comprises a *Staphylococcus aureus* Cas9 (SaCas9)".

Claim 1 of the new auxiliary request 1 differs from claim 1 of the main request in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*". Further the features "*in a eukaryotic cell*", "*polynucleotide encoding*" Type II Cas9 protein, "*and comprises one or more nuclear localization signals*" have been added to item (a), item II and at the end of the claim, respectively. Lastly, the alternative "*or comprises*" as regards *Staphylococcus aureus* Cas9 has been deleted.

In the following, the auxiliary requests that were filed as auxiliary requests 1 to 44 in the submission

dated 3 April 2024 are referred to with their new numbering as auxiliary requests 2 to 45 respectively.

Claim 1 of auxiliary requests 2 and 6 differs from claim 1 of the main request in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*".

Claim 1 of auxiliary request 3 differs from claim 1 of the main request in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*" and in that the term "*polynucleotide encoding*" Type II Cas9 protein in item II has been added.

Claim 1 of auxiliary request 4 differs from claim 1 of the main request in that the term "*non-naturally occurring or engineered*" has been added to the preamble and in that "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*".

Claim 1 of auxiliary request 5 differs from claim 1 of the main request in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*" and in that the alternative "*or comprises*" as regards *Staphylococcus aureus* Cas9 has been deleted.

Claim 1 of auxiliary request 7 reads:

"1. A composition comprising:

a vector system comprising one or more vectors comprising polynucleotide sequences encoding CRISPR

complex components, said one or more vectors comprising:

I. a first regulatory element operably linked to a polynucleotide sequence encoding a CRISPR-Cas system chimeric RNA polynucleotide sequence which comprises:
(a) an engineered guide sequence comprised of RNA and capable of hybridizing to a target sequence in a polynucleotide locus,
(b) a tracr mate sequence comprised of RNA, and
(c) a tracrRNA sequence comprised of RNA, and
wherein (a), (b) and (c) are arranged in a 5’ to 3' orientation,

II. a second regulatory element operably linked to a polynucleotide sequence encoding a Type II Cas9 protein,
wherein the tracr mate sequence hybridizes to the tracrRNA sequence and the guide sequence directs sequence-specific binding of a CRISPR complex to a target sequence,
wherein the CRISPR complex comprises the Type II Cas9 protein complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracrRNA sequence,
wherein the Type II Cas9 protein is or comprises a *Staphylococcus aureus* Cas9 (SaCas9) and
wherein said components I and II are located on the same or different vectors of the system".

Claim 1 of auxiliary requests 8 and 9 differs from claim 1 of the main request in that the term "*chimeric RNA*" has been added to item I.

Claim 1 of auxiliary request 10 differs from claim 1 of the main request in that the feature "*and wherein the tracrRNA is 50 or more nucleotides in length*" has been added at the end of the claim.

Claim 1 of auxiliary request 11 differs from claim 1 of the main request in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*" and in that the feature "*and wherein the tracrRNA is 50 or more nucleotides in length*" has been added to the end of the claim.

Claim 1 of auxiliary request 12 differs from claim 1 of auxiliary request 7 in that the feature "*and wherein the tracrRNA is 50 or more nucleotides in length*" has been added at the end of the claim.

Claim 1 of auxiliary request 13 differs from claim 1 of auxiliary request 8 in that the feature "*and wherein the tracrRNA is 50 or more nucleotides in length*" has been added at the end of the claim.

Claim 1 of auxiliary request 14 differs from claim 1 of the main request in that the features "*in a eukaryotic cell*" and "*wherein the Type II Cas9 protein comprises one or more NLS at the amino-terminus and one or more NLS at the carboxy-terminus*" have been added to item (a) and at the end of the claim, respectively.

Claim 1 of auxiliary request 15 differs from claim 1 of auxiliary request 14 in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*".

Claim 1 of auxiliary request 16 differs from claim 1 of auxiliary request 7 in that the features "*in a eukaryotic cell*" and "*wherein the Type II Cas9 protein comprises one or more NLS at the amino-terminus and one or more NLS at the carboxy-terminus*" have been added to item (a) and at the end of the claim, respectively.

Claim 1 of auxiliary request 17 differs from claim 1 of Claim 1 of auxiliary request 14 in that the feature "*chimeric RNA*" has been added to item I.

Claim 1 of auxiliary request 18 differs from claim 1 of the main request in that the features "*in a eukaryotic cell*" and "*comprises one or more nuclear localization signals*" have been added to item (a) and at the end of the claim, respectively.

Claim 1 of auxiliary request 19 differs from claim 1 of the main request in that the features "*in a eukaryotic cell*", "*comprising one or more nuclear localization signals*", "*and wherein the tracrRNA is 50 or more nucleotides in length*" have been added to item (a), item II and at the end of the claim, respectively.

Claim 1 of auxiliary request 20 differs from claim 1 of auxiliary request 18 in that the term "*CRISPR-Cas system polynucleotide sequence(s)*" has been replaced in item I by "*a CRISPR-Cas system chimeric RNA polynucleotide sequence*".

Claim 1 of auxiliary request 21 differs from claim 1 of auxiliary request 20 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 22 differs from claim 1 of auxiliary request 16 in that the feature "*wherein the Type II Cas9 protein comprises one or more NLS at the amino-terminus and one or more NLS at the carboxy-terminus*" has been replaced by "*and comprises one or more nuclear localization signals*".

Claim 1 of auxiliary request 23 differs from claim 1 of auxiliary request 22 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 24 differs from claim 1 of auxiliary request 18 in that the feature "*chimeric RNA*" has been added to item I.

Claim 1 of auxiliary request 25 differs from claim 1 of auxiliary request 24 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 26 differs from claim 1 of auxiliary request 7 in that the features "*a vector system comprising one or more vectors comprising polynucleotide sequences encoding CRISPR complex components, said one or more vectors comprising*" were replaced by "*a single vector comprising polynucleotide sequences encoding CRISPR complex components, said vector comprising*" and in that the feature "*wherein said components I and II are located on the same or different vectors of the system*" has been deleted.

Claim 1 of auxiliary request 27 differs from claim 1 of auxiliary request 26 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 28 differs from claim 1 of auxiliary request 26 in that the features "*in a eukaryotic cell*" and "*wherein the Type II Cas9 protein comprises one or more NLS at the amino-terminus and one or more NLS at the carboxy-terminus*" have been added to item (a) and the end of the claim respectively.

Claim 1 of auxiliary request 29 differs from claim 1 of auxiliary request 22 in that the feature "*wherein the one or more vectors are viral vectors*" has been added.

Claim 1 of auxiliary request 30 differs from claim 1 of auxiliary request 29 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 31 differs from claim 1 of auxiliary request 29 in that the feature "*and comprises one or more nuclear localization signals*" has been replaced by "*and comprises one or more NLS at the amino-terminus and one or more NLS at the carboxy-terminus*".

Claim 1 of auxiliary request 32 differs from claim 1 of auxiliary request 26 in that the features "*in a eukaryotic cell*", "*and comprises one or more nuclear localization signals*" and "*wherein the vector is a viral vector*" have been added.

Claim 1 of auxiliary request 33 differs from claim 1 of auxiliary request 32 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 34 differs from claim 1 of auxiliary request 28 in that the feature "*wherein the vector is a viral vector*" has been added.

Claim 1 of auxiliary request 35 differs from claim 1 of auxiliary request 32 in that the feature "*wherein the vector is a viral vector*" has been replaced by "*wherein the vector is an adeno-associated virus vector*".

Claim 1 of auxiliary request 36 differs from claim 1 of auxiliary request 35 in that the feature "*wherein the tracrRNA is 50 or more nucleotides in length*" has been added to item (c).

Claim 1 of auxiliary request 37 differs from claim 1 of auxiliary request 34 in that the feature "*wherein the vector is a viral vector*" has been replaced by "*wherein the vector is an adeno-associated virus vector*".

Claim 1 of auxiliary request 38 differs from claim 1 of auxiliary request 8 in that the feature "*of a eukaryotic or prokaryotic cell*" has been added to item (a).

Claim 1 of auxiliary request 39 differs from claim 1 of auxiliary request 38 in that the alternative "*or comprises*" as regards Staphylococcus aureus Cas9 has been deleted.

Claim 1 of auxiliary request 40 differs from claim 1 of auxiliary request 39 in that the alternative "*or prokaryotic cell*" has been deleted and in that the feature "*and comprises one or more nuclear localization signals*" has been added.

Claim 1 of auxiliary request 41 differs from claim 1 of auxiliary request 40 in that the feature "*and comprises one or more nuclear localization signals*" has been replaced by "*and wherein the Type II Cas9 protein comprises one or more NLS at the amino-terminus and one or more NLS at the carboxy-terminus*".

Claim 1 of auxiliary requests 42 to 45 differs from claim 1 of auxiliary requests 38 to 41, respectively, in that the feature "*subspecies Aureus*" has been added.

XII. Appellant I's submissions, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Added subject-matter - claim 1

The composition as defined in items I and II of claim 1 defined the minimal components of the complex, while the remainder of claim 1, i.e. the "*wherein*" clauses (see section XI, above), solely defined each of these components further without having an impact on the components' number. This construction was supported throughout the application as filed. The structural characterisation in claim 1 that "*wherein the CRISPR complex comprises the Type II Cas9 protein complexed with (1) the guide sequence that is hybridized to the target sequence, and (2) the tracr mate sequence that is hybridized to the tracrRNA sequence*" at most meant that once the complex was guided to the target sequence through hybridisation of the guide sequence, the target sequence became part of the complex. Thus claim 1 did not require the presence of the target sequence as component of the CRISPR complex.

The composition of claim 1 was in essence based on the disclosure of paragraph [0015] of the application as filed. Although this paragraph disclosed "*a polynucleotide sequence encoding a CRISPR enzyme*" and not "*a Type II Cas9 protein*" as such ("feature 3") as indicated in item II of claim 1, the disclosure of the application as filed as a whole provided a basis for this amendment (see paragraphs [0008], [0009], [00011], [00014], [00061], [0066], [00101], [00133], [00140], [00147], [00156], [00166], [00190], [00191], [00194], [00195], [00203] and [00304]). Even more so since the term "*Type II Cas9 protein*" in claim 1 encompassed not only the protein but also indirectly a polynucleotide sequence encoding this protein. This was evident from the wording of dependent claim 5 which indicated that "*a vector system*" comprised "*polynucleotide sequences comprising or encoding said components I and II are located on the same or different vectors of the system*".

The feature "*the Type II Cas9 protein [...] comprises a Staphylococcus aureus Cas9 (SaCas9)*" in claim 1 ("feature 7"), although being open ended due to the use of the term "*comprises*", excluded the presence of more than one Cas9 protein. This was the logical consequence of the term "*a*" in "*a Type II Cas9 protein*" in item II of claim 1 when read in conjunction with the term "*the*" in "*the Type II Cas9 protein [...] comprises a Staphylococcus aureus Cas9 (SaCas9)*". The comprising language in claim 1 referred thus to a single mutated SaCas9 or a fusion protein that comprised a single SaCas9. This construction was consistent with the subject-matter of claims 2 and 52 as filed too. That a single Cas9 protein was used for all aspects of the invention was also derivable from the disclosure in paragraphs [0008] to [0010], [0012] to [0015], [0018]

to [0021], [0023], [0025], [0068], [0154], [0164] and Examples 3 and 8 of the application as filed.

Auxiliary requests 1 and 38 to 45

Admittance/consideration of auxiliary requests 1 and 38 to 45 in the appeal proceedings

Auxiliary request 1 filed at the oral proceedings combined in claim 1 amendments from claim 1 of auxiliary requests 3 and 20 which were previously filed as auxiliary requests 2 and 19. An intention to file additional auxiliary requests if necessary was already announced in the SGA. Although auxiliary request 1 addressed objections under added matter from the other parties that were on file since the opposition proceedings, procedural economy required that a large number of claim requests taking all those objections into account were not submitted at that stage. Furthermore, none of the other parties was taken by surprise since auxiliary request 1 comprised a combination of known amendments and was hence only formally new. The amendments had been on file for a long time and did not represent a fresh case. The admittance of this set of claims was an issue of equity. Auxiliary request 1 was also not *prima facie* unallowable under the requirements of Article 123(3) EPC since the Type II Cas9 protein of claim 1 as granted already covered a polynucleotide sequence encoding said protein too. This was derivable from claim 5 as granted. The deletion of one alternative from claim 1 compared to claim 1 as granted in fact limited the scope of protection.

Auxiliary requests 38 to 41 were filed with the submission dated 3 April 2024 as auxiliary requests 37

to 40. These auxiliary requests addressed in claim 1 issues linked to claim interpretation that were raised by the board in their preliminary opinion and comprised new combinations of amendments that were already on file for other auxiliary requests. These sets of claims were thus only formally new.

Auxiliary requests 42 to 45 were filed with the submission dated 3 April 2024 as auxiliary requests 41 to 44. While these requests likewise addressed in claim 1 objections under added subject-matter raised by the other parties, these objections were not found convincing by the opposition division in their preliminary opinion annexed to the summons and in the decision under dispute. Furthermore, theses sets of claims were submitted in direct response to the board's preliminary opinion in point 24.10.1 and represented a straightforward amendment that was fully supported by the application as filed. The amendments to claim 1 in these auxiliary requests did not take the other parties by surprise.

XIII. The submissions of appellants II, III and of the parties as of right, insofar as relevant to the present decision, may be summarised as follows:

Main request (claims as granted)

Added subject-matter - claim 1

Inter alia the features "*a Type II Cas9 protein*" and wherein "*the Type II Cas9 protein [...] comprises a Staphylococcus aureus Cas9 (SaCas9)*" (i.e. features 3 and 7, respectively) in claim 1 had no basis in the application as filed and thus comprised added subject-matter.

As regards "feature 3", the application as filed did not disclose a composition as defined in claim 1 which comprised "*a Type II Cas9 protein*". Contrary to the opposition division's finding, none of paragraphs [0008], [0009], [0127], [0132], [0166] and [0203] of the application as filed disclosed a CRISPR protein as such. None of these paragraphs had a functional or structural link to the composition as defined in claim 1. Whenever the application as filed referred to a composition, CRISPR systems were disclosed that comprised a "*sequence encoding a CRISPR enzyme*" (see e.g. paragraphs [0015] or [0016]), or an enzyme composition (see e.g. paragraphs [0014] or [0066]). These compositions were different from that defined in claim 1. Paragraph [0015] disclosed solely a polynucleotide that encoded Cas9 protein. This was not identical to the protein mentioned in claim 1. The subject-matter of dependent claim 5 did not change this fact. Furthermore, none of the paragraphs cited by appellant I in support of feature 3 were linked to the disclosure of paragraph [0015] of the application as filed.

As regards "feature 7", the application as filed did not disclose a CRISPR complex which comprised SaCas9. The opposition division found that paragraphs [0009] and [0068] provided a basis for said feature. While paragraph [0009] solely disclosed the more general term "*Staphylococcus*", paragraph [0068] did not disclose the Cas9 from "*Staphylococcus aureus*" without a specific PAM sequence. Feature 7 was an unallowable intermediate generalisation from the application as filed.

Auxiliary requests 1 and 38 to 45

Admittance/consideration of auxiliary requests 1 and 38 to 45 in the appeal proceedings

Auxiliary request 1 was new and late filed. Its admittance/consideration in appeal was not allowable under Article 13(2) RPBA since exceptional circumstances were missing.

XIV. As regards the requests being relevant for this decision (for the complete list of requests submitted by the parties: see the minutes of the oral proceedings before the board), the parties had the following requests:

XV. Appellant I requested:

- that the decision under appeal be set aside and that the patent be maintained as granted;

- alternatively, that the patent be maintained in amended form on the basis of any of the 45 auxiliary requests on file (AR1 filed at the oral proceedings; AR2 to AR37 filed as AR1 to AR36 with the reply dated 10 July 2020, and AR38 to AR45 filed as AR37 to AR44 with letter of 3 April 2024);

- that auxiliary request 1 filed at the oral proceedings be admitted/considered.

XVI. Appellants II and III requested:

- that appellant I's appeal be dismissed, the decision under appeal be set aside, and the patent be revoked.

Appellant II further requested:

- that auxiliary request 1 filed at the oral proceedings not be admitted/considered.

XVII. Opponents 01 and 04 requested:

- that appellant I's appeal be dismissed;

- that auxiliary requests AR10, AR14, AR18, AR19, AR28, AR31, AR34 and AR37 (corresponding to AR8, AR12, AR16, AR17, AR26, AR29, AR32 and AR35 submitted with the SGA) not be admitted/considered.

(a) Opponent 01 further requested:

- that the decision under appeal be set aside, that the appeals of appellants II and III be upheld, and

- that auxiliary requests 2 and 3 (corresponding to AR1 and AR2 submitted with the SGA) not be admitted/considered.

(b) Opponent 04 further requested:

- that auxiliary requests AR13, AR17, AR24 and AR25 (corresponding to AR11, AR15, AR22 and AR23 submitted with the SGA) not be admitted/considered.

XVIII. Opponent 06 requested:

- that auxiliary request 1 filed at the oral proceedings not be admitted/considered.

Reasons for the Decision

Main request (claims as granted)

Claim construction

1. Claim 1 is directed to a composition, i.e. a product claim.

1.1 This composition comprises "*CRISPR complex components*" which are structurally defined in items I and II.

1.2 Item I specifies that the complex components comprise "*CRISPR-Cas system polynucleotide sequence(s)*" which comprise the three following sequences:
"*(a) an engineered guide sequence comprised of RNA and capable of hybridizing to a target sequence in a polynucleotide locus,*
(b) a tracr mate sequence comprised of RNA, and
(c) a tracrRNA sequence comprised of RNA"
all arranged in a certain order ("*in a 5' to 3' orientation*").

1.3 Item II mentions a "*Type II Cas9 protein*" which is further specified in that it "*is or comprises a Staphylococcus aureus Cas9 (SaCas9)*". The composition of claim 1 thus encompasses at least one *S. aureus*-derived SaCas9 but also other unknown compounds, including for example, further CRISPR enzymes.

1.3.1 Appellant I submitted that the feature "*Type II Cas9 protein*" (hereinafter "feature 3") in claim 1 was not limited to a protein as such but likewise comprised indirectly a polynucleotide that encoded this protein. Reference in this context was made to dependent claim 5

and the skilled person's common understanding of the application as filed as a whole.

1.3.2 The board does not agree. A protein as referred to in claim 1 is a product that differs fundamentally from a polynucleotide sequence encoding a protein. While the former consists of amino acids, the latter consists of nucleotides. This fact does not change by the subject-matter of dependent claim 5 which refers to "*A composition according to any one of the preceding claims, comprising a vector system*". In accordance with ordinary claim construction, claim 5 is thus directed to subject-matter combining the subject-matter of claims 1 and 5. In other words, the subject-matter of claim 5 is directed to a composition which comprises as components of the CRISPR complex *inter alia* a Cas9 protein and a vector system which comprises a polynucleotide sequence that encodes this protein. The combined subject-matter of claims 1 and 5 is clear, since it is devoid of inherent inconsistencies and makes technical sense. There are neither reasons apparent that the skilled person cannot produce such a composition nor are indications available that such a composition may be non-functional. While certain components of the composition might have a redundant functionality, this does not render the claim unclear. Nor does this construction change in the light of the description as a whole, since the skilled person knows that a protein is structurally different from a polynucleotide for the reasons set out above.

1.3.3 Appellant I further submitted that the skilled person in the art based on the application as filed as a whole would construe the term "*or comprises*" in the context of SaCas9 in claim 1 to relate to a mutated enzyme or to a fusion protein that comprised a SaCas9 protein. In

any case, claim 1 was limited to the use of a single SaCas9 protein.

1.3.4 The board does not agree. The term "*or comprises a Staphylococcus aureus Cas9 (SaCas9)*" (hereinafter "feature 7") in claim 1 according to its ordinary meaning is open for the presence of any further compound in the composition of claim 1. While this is not contested by appellant I, it is contested that this includes the presence of further Cas9 proteins, in particular, in view of the use of "*a*" and "*the*" in the context of a Type II Cas9 protein in claim 1 and the description as a whole. It is established case law that clear terms in a claim (here "*comprises*") should be given their broadest technically sensible meaning without reading limitations into a claim that are found in the description only (see Case Law of the Boards of Appeal of the EPO, 10th edition 2022, ("Case Law"), II.A.6.2 and II.A.6.3.4). Furthermore since the number to which the term "*a*" refers is undefined, the use of "*a*" and "*the*" in the context of Type II Cas9 protein in claim 1 does not exclude that besides SaCas9 another Cas9 protein is present as well. Appellant I's reference to various paragraphs, Examples 3 and 8 and claims of the application as filed is thus irrelevant.

1.4 Claim 1 further functionally and structurally defines the three RNA components and the Cas9 protein of sections I and II in that:

- the "*tracr mate sequence hybridizes to the tracrRNA sequence*" and
- the "*guide sequence directs sequence-specific binding of a CRISPR complex to a target sequence*
- *wherein the CRISPR complex comprises the Type II Cas9 protein complexed with (1) the guide sequence that is hybridized to the target sequence, and (2)*

the tracr mate sequence that is hybridized to the tracrRNA sequence" (emphasis added).

1.4.1 This part of claim 1 defines that the tracr mate RNA hybridises to tracrRNA and that the RNA guide sequence directs the "*CRISPR complex*" to a respective target sequence. Further this part specifies that the "*CRISPR complex*" contains a Cas9 protein which is "*complexed with*" *inter alia* the guide sequence that is "*hybridized*" to the target sequence. The terms "*complexed*" and "*hybridized*" as used in this context define a state of the CRISPR complex which includes the target sequence. Thus the target sequence forms part of the CRISPR complex and, is hence, a technical feature of the claimed composition.

1.4.2 Appellant I disagreed with this construction and submitted that the skilled person when reading the application as filed would have understood that the target sequence did not form part of the "*CRISPR complex*". Rather this term referred to "*the combination of the different CRISPR-Cas components*" or "*the use of components capable of forming a complex*".

1.4.3 However, since the wording of claim 1 as such is clear and technically sensible, appellant I's interpretation of claim 1 stands against the wording of claim 1 and is thus not convincing (see Case Law, II.A.6.1).

1.4.4 The composition as defined in claim 1 comprises therefore a CRISPR complex of at least five components, i.e. the RNA sequences defined in items (a) to (c), a SaCas9 protein and a target sequence. The term "*comprises*" does not exclude the presence of further components.

Added subject-matter - claim 1

2. In the following reference to the application as filed/ claims as filed is to the patent application, WO 2014/093635.

3. It is contested whether features 3 and 7 of claim 1 (i.e."*a Type II Cas9 protein*" and "*the Type II Cas9 protein [...] comprises a Staphylococcus aureus Cas9 (SaCas9)*", respectively) have a basis in the application as filed.

4. It is established case law that any amendment to the parts of a European patent application or of a European patent relating to the disclosure (the description, claims and drawings) is subject to the mandatory prohibition on extension laid down in Article 123(2) EPC and can therefore, irrespective of the context of the amendment made, only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of the application as filed (see Case Law, II.E.1.3.1).

5. It is uncontested that paragraph [0015] of the application as filed provides in essence the basis for the composition of claim 1. It is further uncontested that this paragraph is silent on features 3 and 7 of claim 1 but mentions instead "*a polynucleotide sequence encoding a CRISPR enzyme*" and that "*the CRISPR enzyme is a Cas9 ortholog*" selected from a group of microorganisms that includes "*Staphylococcus*".

6. As regards feature 3, appellant I submitted that the term "*a Type II Cas9 protein*" in claim 1 was construed

by the skilled person in view of the application as filed a whole and, in particular, the subject-matter of dependent claim 5 to refer not only to a protein as such but, as an alternative, indirectly also to a polynucleotide sequence encoding a Type II Cas9 protein.

7. For the reasons set out above under claim construction (see point 1.3.2), appellant I's argument that the protein in claim 1 comprises a protein and indirectly a polynucleotide encoding a protein is not convincing.

8. Appellant I further referred to paragraphs [0008], [0009], [00011], [00014], [00061], [0066], [00101], [00133], [00140], [00147], [00156], [00166], [00190], [00191], [00194], [00195], [00203] and [00304] of the application as filed as a basis for a composition comprising a Type II Cas9 protein as such. The opposition division held that in particular the disclosure of paragraph [0009] of the application as filed formed the basis for feature 3 in the claimed composition (see decision under appeal, point 29.5).

9. The board does not agree for the following reasons.

9.1 Paragraph [0008] of the application as filed describes an "*exemplary CRISPR complex*", comprising a "*Cas9 ortholog*", which is "*complexed with a guide sequence hybridized to a target sequence within the target polynucleotide*", wherein the "*guide sequence is linked to a tracr mate sequence, which in turn hybridizes to a tracr sequence*". A similar wording is found in paragraph [00194]. Paragraph [0009] of the application as filed discloses that the "*CRISPR complex of the invention has a wide variety of utilities*", including a use in a "*multiplicity of cell types*" for various

applications. The term "*CRISPR complex of the invention*" in paragraph [0009] seems to refer back to the complex described in paragraph [0008]. These paragraphs, however, mention no composition, let alone the composition of claim 1, which comprises *inter alia* feature 3 as one of its components including other components due to the use of the comprising language (see point 1.4.4 above). Nor is the claimed composition as a product limited to any uses.

9.2 Paragraph [0011] of the application as filed discloses first and second medical uses of "*the present sequences, vectors, enzymes or systems*". Also paragraph [0014] of the application as filed discloses a therapeutic use "*of the present composition or the enzyme*". A similar wording is also used in paragraph [0066]. Claim 1 is not limited to a medical use, or a composition that comprises solely enzymes. A composition as defined in claim 1 is thus not disclosed in paragraphs [0011], [0014] and [0066].

9.3 Paragraph [0061] of the application as filed reads: "*Also envisaged is a method of preparing an vector for delivery of the compositions or the present CRISPR enzymes of the invention and for use in the present methods*". This paragraph relates thus to the preparation of a vector and its use in delivering a composition or CRISPR enzymes. The composition of claim 1 is silent on any vectors, including methods for producing vectors. Paragraphs [00133] and [00147] of the application as filed also relate to vectors.

9.4 Paragraph [00101] of the application as filed teaches that the invention "*relates to the engineering and optimization of systems, methods and compositions used for the control of gene expression involving sequence*

targeting". While the term "*compositions*" is mentioned in this paragraph, this mentioning does not provide a basis for feature 3, since it is not directly and unambiguously derivable therefrom whether or not feature 3 is present. This paragraph further discloses that "*In advantageous embodiments, the CRISPR enzyme is a Cas enzyme, e.g. a Cas9 ortholog*". It is not directly and unambiguously derivable from this sentence whether or not the enzyme is present in the composition or a polynucleotide sequence encoding the enzyme.

9.5 Paragraph [00140] of the application as filed sets out a general definition of the term "*CRISPR system*" as used in the application as filed, namely in that this term "*refers collectively to transcripts and other elements involved in the expression of or directing the activity of CRISPR-associated ("Cas") genes, including sequences encoding a Cas gene, a tracr (trans-activating CRISPR) sequence (e.g. tracrRNA or an active partial tracrRNA), a tracr-mate sequence (encompassing a "direct repeat" and a tracrRNA-processed partial direct repeat in the context of an endogenous CRISPR system), a guide sequence (also referred to as a "spacer" in the context of an endogenous CRISPR system), or other sequences and transcripts from a CRISPR locus*" (emphasis added). The underlined terms in this passage unambiguously mean that the "*CRISPR system*" as disclosed in paragraph [0140] of the application as filed relates to a polynucleotide-based system and not to a complex as specified in claim 1 which comprises a Type II Cas9 protein as such.

9.6 Paragraph [00156] of the application as filed defines the "*guide sequence*" as "*any polynucleotide sequence having sufficient complementarity with a target polynucleotide sequence to hybridize with the target*

sequence and direct sequence-specific binding of a CRISPR complex to the target sequence". Furthermore this paragraph states that "*cleavage of a target polynucleotide sequence may be evaluated in a test tube by providing the target sequence, components of a CRISPR complex, including the guide sequence to be tested and a control guide sequence different from the test guide sequence, and comparing binding or rate of cleavage at the target sequence between the test and control guide sequence reactions*". None of these passages mention a composition comprising feature 3.

9.7 Paragraph [00166] of the application as filed discloses "*methods comprising delivering one or more polynucleotides, such as or one or more vectors as described herein, one or more transcripts thereof, and/ or one or proteins transcribed therefrom, to a host cell*". Furthermore this paragraph mentions that "*In some embodiments, a CRISPR enzyme in combination with (and optionally complexed with) a guide sequence is delivered to a cell*". However, the composition of claim 1 is not limited to a delivery of "*one or more proteins*", or a CRISPR enzyme complexed with a guide sequence to a cell.

9.8 Paragraphs [00190], [00191], [00195] and [00203] of the application as filed disclose methods "*allowing a CRISPR complex to bind to the target polynucleotide to effect cleavage of said target polynucleotide thereby modifying the target polynucleotide*", "*modifying expression of a polynucleotide in a eukaryotic cell*", or for "*cleaving a target polynucleotide*". The composition of claim 1 does not relate to a method.

9.9 Paragraph [00304] of the application as filed states in its last sentence that: "*Therefore, Applicants decided*

to clone the full two-component system: cas9 and the chimeric guide RNA, into an AAV vector to test its functionality in living organisms". In other words this paragraph discloses a vector-based CRISPR system which is different from using a Type II Cas9 protein as such.

9.10 For the considerations indicated above, none of the paragraphs in the application as filed relied on by appellant I provide a basis for feature 3 in the composition of claim 1.

10. As regards feature 7, appellant I in essence submitted that the alternative "*or comprises*" in the context of SaCas9 was limited to the presence of one such Cas9 protein only wherein this SaCas9 was either mutated or part of a fusion protein. However, for the reasons indicated above under claim construction (see point 1.3.4), appellant I's argument is not convincing. Moreover, it is undisputed that the application as filed does not disclose a composition comprising as components of the CRISPR complex more than one SaCas9 protein.

11. For the reasons set out above, at least features 3 and 7 of claim 1 comprise added subject-matter. Claim 1 and hence the main request do not meet the requirements of Article 100(c) EPC.

Auxiliary request 1

Admittance/consideration of auxiliary request 1 in the appeal proceedings

12. Pursuant to Article 13(2) RPBA 2020 (hereinafter, Article 13(2) RPBA), which applies in this case (Article 25(1) and (3) RPBA 2020), any amendment to a

party's appeal case after notification of a summons to oral proceedings is, as a rule, not to be taken into account unless there are exceptional circumstances justified with cogent reasons by the party concerned. Article 13(2) RPBA implements the third level of the convergent approach applicable in appeal proceedings and imposes the most stringent limitations on a party wishing to amend its appeal case at an advanced stage of the proceedings (see document CA/3/19, section VI, Explanatory remarks on Article 13(2) RPBA, in Supplementary publication 2 to OJ EPO 2020). Exceptional circumstances are new or unforeseen developments in the appeal proceedings which lie outside the sphere of influence of the party affected by them, such as new objections raised by the board or another party (see Case Law, V.A.4.5.1).

13. New auxiliary request 1 was filed for the first time at the oral proceedings. Appellant I argued in support of the request's admittance that the amendments in claim 1 were derived from two other auxiliary requests that were already on file. This set of claims was thus only formally new and did not represent a fresh case. Moreover since the amendments were known, none of the other parties was taken by surprise, its submission at the oral proceedings was a matter of procedural economy and its admittance an issue of equity.

14. The board fails to see how the submission of auxiliary request 1 only at the oral proceedings as a reaction to objections that are on file since the first instance proceedings represent exceptional circumstances that could justify this late reaction. Rather the question arises why this auxiliary request has not been filed earlier. In the board's opinion, procedural economy can not justify the late filing of this set of claims since

this provides no reason why as a direct result thereof appellant I was prevented from filing auxiliary request 1 at an earlier stage. The issue of whether or not the other parties are taken by surprise does not relate to the question whether exceptional circumstances have prevented appellant I from filing auxiliary request 1 earlier and is thus irrelevant.

15. The board therefore does not find any exceptional circumstances, justified by cogent reasons, that would support the admittance of new auxiliary request 1 into the proceedings. Accordingly, new auxiliary request 1 was not admitted into the proceedings under Article 13(2) RPBA.

Auxiliary requests 2 to 37

16. Since auxiliary requests 2 to 37 do not comply with the requirements of Article 123(2) EPC (see below), no reasoning for admitting AR2, AR3, AR10, AR14, AR18, AR19, AR28, AR31, AR34 and AR37 into the proceedings is provided.

17. As regards the differences between the subject-matter of claim 1 of auxiliary requests 2 to 6 and 8 to 37 and that of the main request or auxiliary request 7, see section XI, above.

Added subject-matter

18. The subject-matter of claim 1 of auxiliary requests 2 to 37 comprises features 3 and 7, either alone or in combination (see section XI, above).

19. Thus the objections under added subject-matter raised against features 3 and 7 of claim 1 of the main request

apply against claim 1 of auxiliary requests 2 to 37 as well.

20. Auxiliary requests 2 to 37 do not comply with the requirements of Article 123(2) EPC.

Auxiliary requests 38 to 45

Admittance/consideration of auxiliary requests 38 to 45 in the appeal proceedings

21. The board did not take auxiliary requests 38 to 45 into account under Article 13(2) RPBA. The board notes that the minutes of oral proceedings mistakenly refer to auxiliary requests 37 to 45, probably due to the confusion caused by the submission of a new auxiliary request 1 at the oral proceedings, without the withdrawal of any other auxiliary requests.

22. Auxiliary requests 38 to 45 have been submitted in response to the board's preliminary opinion. Appellant I justified the late submission of auxiliary requests 38 to 41 by the board's new interpretation of the complex composition in claim 1 (see point 1.4.1, above) and by arguing that these auxiliary requests contained combinations of amendments (see section XI, above) that were derived from auxiliary requests that were already on file. As regards auxiliary requests 42 to 45, appellant I submitted that the amendments (see section XI, above) in claim 1 addressed objections that were not found convincing by the opposition division, directly responded to the board's preliminary opinion and were straightforward.

23. The board notes that although its approach to claim construction as regards the complex composition in

claim 1 as granted (see point 1.4.1, above) differs from that of appellant I, this construction has no impact on the relevant issue to be decided in the present case, i.e. added subject-matter. Accordingly, the board's claim construction does not result in exceptional circumstances that might justify the late filing of auxiliary requests 38 to 41. Nor has the board invited the parties to file new submissions in reaction to this claim interpretation. Furthermore the combination of amendments introduced in claim 1 of these auxiliary requests address objections under added subject-matter that are on file since the opposition proceedings. This is undisputed. As regards auxiliary requests 42 to 45, appellant I has not submitted any exceptional circumstances that prevented them from filing these requests at an earlier stage. All amendments in claim 1 of these sets of claims address objections under added subject-matter that are on file since the onset of the opposition proceedings. The board therefore fails to see exceptional circumstances justified by cogent reasons why auxiliary requests 38 to 45 could not have been filed earlier.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chair:

L. Malécot-Grob T. Sommerfeld

Decision electronically authenticated