Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 10 April 2024

Case Number: T 2168/21 - 3.3.04

Application Number: 12723117.3

Publication Number: 2714071

IPC: A61K39/00, C12Q1/68

Language of the proceedings: EN

Title of invention:
Individualized vaccines for cancer

Patent Proprietors:
BioNTech SE
TRON - Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gemeinnützige GmbH

Opponents:
IPrime Rentsch Kaelin AG (Opposition withdrawn)
Strawman Limited
Withers & Rogers LLP

Headword:
RNA cancer vaccines/BIONTECH

Relevant legal provisions:
EPC Art. 100(a), 100(b), 100(c), 54(2), 54(3), 56
RPBA 2020 Art. 12(4)

Keyword:
Grounds for opposition - subject-matter extends beyond content of earlier application (no) - insufficiency of disclosure (no)
Novelty - (yes)
Inventive step - (yes)
Amendment to case - admissibly raised and maintained (no)

Decisions cited:
G 0001/12, G 0002/21

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2168/21 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 April 2024

Appellant: (Opponent 2)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Appellant: (Opponent 3)	Withers & Rogers LLP 4 More London Riverside London SE1 2AU (GB)
Representative:	Graf von Stosch, Andreas Graf von Stosch Patentanwaltsgesellschaft mbH Prinzregentenstraße 22 80538 München (DE)
Respondent: (Patent Proprietor 1)	BioNTech SE An der Goldgrube 12 55131 Mainz (DE)
Respondent: (Patent Proprietor 2)	TRON - Translationale Onkologie an der Universitätsmedizin der Johannes Gutenberg-Universität Mainz gemeinnützige GmbH Freiligrathstrasse 12 55131 Mainz (DE)
Representative:	Schnappauf, Georg ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Former Opponent 1:	IPrime Rentsch Kaelin AG Hirschengraben 1 8001 Zürich (CH)

Representative: IPrime Rentsch Kaelin AG
Hirschengraben 1
8001 Zürich (CH)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 10 November 2021 rejecting the opposition filed against European patent No. 2714071 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman M. Pregetter
Members: B. Rutz
R. Romandini

Summary of Facts and Submissions

I. The appeals by opponents 2 and 3 (appellants) lie from the decision of the opposition division to reject the oppositions to European patent No. 2 714 071 entitled "*Individualized vaccines for cancer*" which is based on European application No. 12723117.3 published under the PCT as international application WO 2012/159754.

II. The opposition proceedings were based on the grounds of Article 100(a) EPC, in relation to novelty (Article 54 EPC) and inventive step (Article 56 EPC), and Article 100(b) and (c) EPC. During the opposition proceedings, opponent 1 withdrew its opposition.

III. With the reply to the appellants' statements of grounds of appeal, the patent proprietors (respondents) requested that the appeal be dismissed, i.e. the patent be maintained as granted, or, alternatively, that the patent be maintained based on one of the sets of claims of auxiliary requests 1 to 9, identical to the requests filed during the opposition proceedings.

IV. Claim 1 of the main request (patent as granted) is reproduced in point 8. of the Reasons below.

V. The board summoned the parties to oral proceedings, as requested, and informed them of its preliminary opinion in a communication under Article 15(1) RPBA.

VI. In this communication, the board indicated that it preliminarily agreed with the findings of the opposition division on added subject-matter, novelty and sufficiency of disclosure. It also made

observations on inventive step starting from document D5 as the closest prior art.

VII. With the letters dated 21 March 2024 and 25 March 2024, the appellants informed the board that they would not be attending or represented at the oral proceedings.

VIII. Oral proceedings were held in the absence of the appellants. In accordance with Rule 115(2) EPC and Article 15(3) RPBA, they were treated as relying on their written cases. During the oral proceedings, the respondents withdrew their request for the appeal of appellant II (opponent 3) to be rejected as inadmissible. At the end of the oral proceedings, the chairwoman announced the board's decision.

IX. The following documents are referred to in this decision:

D2 WO 2011/143656 A2

D3 EP 2569633 B1

D4 J. C. Castle et al., "*Exploiting the Mutanome for Tumor Vaccination*", Cancer Research 72(5), 2012, 1081-91

D5 H. G. Rammensee et al., "*Cancer Vaccines: Some Basic Considerations*", Genomic and Personalized Medicine Volumes I and II, 2009, Chapter 50, 573-89

D8 EP 2100620

D9 WO 03/059381 A2

D10 WO 02/098443

D11 US 2006/0204523

D12 US 2006/0188490

D13 L. Li et al., "*Cancer Genome Sequencing and Its Implications for Personalized Cancer Vaccines*", Cancers 3, 2011, 4191-211

D18 U. Sahin and Ö. Tureci, "*Personalized vaccines for cancer immunotherapy*", Science 359 (6382), 2018, 1355-60

D20 H. G. Rammensee, "*Some considerations on the use of peptides and mRNA for therapeutic vaccination against cancer*", Immunology and Cell Biology 84, 2006, 290-4

D24 A. Suhrbier, "*Multi-epitope DNA vaccines*", Immunology and Cell Biology 75, 1997, 402-8

D25 A. Suhrbier, "*Polytope vaccines for the codelivery of multiple CD8 T-cell epitopes*", Expert Review Vaccines 1(2), 2002, 207-13

D26 J.H. Kessler and C.J.M. Melief, "*Identification of T-cell epitopes for cancer immunotherapy*", Leukemia 21, 2007, 1859-74

D27 J. P. Carralot et al., "*Production and characterization of amplified tumor-derived cRNA libraries to be used as vaccines against metastatic melanomas*", Genetic Vaccines and Therapy 3(6), 2005, 1-10

D28 Experimental Data, 2 pages

D34 U. Sahin et al., 2017, "*Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer*", Nature 547, 2017, 222-6, Supplementary Information (14 pages)

D35 S. Kreiter et al., "*Tumor vaccination using messenger RNA: prospects of a future therapy*" Current Opinion in Immunology 23, 2011, 399-406

D36 Anonymous (Editorial), "*The problem with neoantigen prediction*", Nature Biotechnology 35(2), 2017, 97

D37 M. Günder, "*Charakterisierung des HLA-Ligandoms und des Exoms von Hepato- und Cholangiozellularen Karzinomen im Hinblick auf eine patientenindividualisierte Peptidvakzinierung*", Doctoral thesis, 2012, 1-216

D38 WO 2005/028505 A2

X. The appellants' submissions are summarised as follows.

Claim interpretation

Claims which defined a product in terms of a process were to be construed as claims to the product as such, and a claim was not to be rendered novel merely because it was produced by a new process (Guidelines for examination in the EPO, F-IV 4.12). Similar conditions were also to be applied in the assessment of use claims (Case Law of the Boards of Appeal, II.A 7.4).

Accordingly, both for product and use claims, the principles of product-by-process claims applied.

The features referred to above in the method steps (aa) and (ab) could not be used to distinguish the claimed subject-matter from the prior art.

The language of claim 1 did not define the nature of RNA, i.e. as a single RNA type or as an ensemble of distinct types of RNA molecules. Thus, both embodiments fell under the scope of claim 1.

A single RNA type or an ensemble of distinct types of RNA might encode "a recombinant polyepitopic peptide". The undefined article "a" covered one or more polypeptides. The claim therefore did not exclusively define one single type of RNA coding for one single polyepitopic polypeptide. Embodiments with distinct RNA molecules encoding distinct polypeptides were encompassed by claim 1, where each polypeptide might comprise a single (or more) "mutation based epitopes".

Any "polypeptide" by its very nature was "polyepitopic" as it contained a multitude of epitopes. Since claim 1 did not define a "poly(neo)epitopic" polypeptide but merely a polyepitopic polypeptide, the claim did not require the RNA to code for a polypeptide containing two or more neo-epitopes.

Amendments (Article 100(c) EPC)

The application as filed exclusively referred to "neo-epitopes identified according to the invention" (i.e. according to claim 1 as filed) and not to known neo-epitopes (as defined by paragraph [0038] of the opposed patent). Yet, claim 1 of the patent was not restricted to neo-epitopes identified according to the invention but covered any neo-epitope (including other known neo-epitopes). Any neo-epitope could be a cancer neo-epitope of the "cancer mutation signature" as identified according to the method of the invention or another (known) neo-epitope (which was not identified by the method of the invention and/or not identified for the patient to be treated).

For that reason alone, the subject-matter of claim 1 of the opposed patent extended beyond the content of the application as filed.

The term "cancer mutation signature" as such did not match "neo-epitopes" or "neo-epitopes as identified according to the invention" (see paragraph [0029] of the patent). A "cancer mutation" was not sufficient to render a "mutated peptide (stretch)" a "neo-epitope". For a "mutation" or, rather, a "mutated peptide" (or the group of mutations forming the "cancer mutation signature") to represent "neo-epitopes", the "mutated peptide" had to allow MHC presentation to the immune

system. This property was not exhibited by all peptide structures exhibiting a cancer mutation. In other words, a "cancer-specific mutation" was a necessary but not sufficient prerequisite on its own to render a peptide with a cancer mutation a "neo-epitope".

Novelty (Article 100(a) EPC and Article 54 EPC)

In view of the non-limiting nature of steps (aa) and (ab) in the claim, the subject-matter lacked novelty over the disclosure of documents D2/D3 and D5.

Document D5 disclosed a personalised vaccine based on cancer-specific mutations identified in a tumour specimen (see Figure 50.1). It also disclosed mRNA-based vaccines (see legend to Figure 50.1). "[T]umor specific mutations" were defined as a highly relevant factor (see page 576, right-hand column, first full paragraph).

Document D5 also referred to a "multi-epitope" vaccine approach based on RNA vaccines (see page 584, right-hand column). Figure 50.1 referred to "tumor-specific mutations". Thus, document D5 made it perfectly clear that a plurality of tumour mutations (resulting from a list of patient-specific tumour mutations corresponding to a "cancer mutation signature") were to be combined to establish a multi(=poly)neo-epitopic RNA-based cancer vaccine.

All the features of claim 1 were anticipated by document D5 (see Figure 50.1 and its legend).

Sufficiency of disclosure (Article 100(b) EPC)

Only one embodiment of an RNA vaccine encoding a poly-neo-epitopic polypeptide falling under the scope of the claims was made and tested in the patent. In view of the breadth of claim 1 and the complexity of the technology required to arrive at functional individualised cancer vaccines, the patent's disclosure could not establish sufficiency of disclosure over the entire scope.

Documents D36, D37 and D18 raised serious doubts supported by verifiable facts that the claimed method and in particular the multi-step procedure required for identifying MHC binding neo-epitopes could not be carried out by the skilled person without undue burden.

The patent did not provide sufficient details for a skilled person to carry out the invention. The method relied on a selection method for the identification of suitable neo-epitopes in which only a minor fraction of the identified mutations, namely 0.25%, allowed for successful vaccination.

The algorithms and bioinformatics tools used in the patent for mutation prioritisation had not been further defined or disclosed in the patent. Accordingly, it would be an undue burden for the skilled person to invent these algorithms and methods from scratch.

The next step, i.e. to determine which of the prioritised mutations were both neo-epitopic and immunogenic was performed using a mouse melanoma model.

Only 6 out of 44 sequences were found to be immunogenic neo-epitopes. A polyepitopic polypeptide consisting of the other 38 neo-epitopes was thus not expected to result in a suitable vaccine. While this step might be easily applied in a mouse setting, this was much more difficult in a clinical setting, especially on a personalised basis. The patent was also completely silent on how to select neo-epitopes.

The post-published evidence D34 relied on by the opposition division and the respondents was not relevant because it disclosed methods for neo-epitope selection based on HLA class I and II binding which were not disclosed in the patent and relied on scientific evidence not available at the time of filing of the patent.

The claimed subject-matter could also not be carried out over the entire scope without defining the presence of a linker sequence and, additionally, the length and sequence requirements for a linker allowing the epitopes to be presented to the immune system. These features were characterised by the patent as prerequisites of the disclosed cancer-vaccine technology (see paragraph [0311] of the patent).

Inventive step (Article 100(a) EPC and Article 56 EPC)

Document D5 taught the provision of personalised RNA vaccines and their *in vivo* application. Document D5 provided an incentive for a skilled person to use multi-epitopic constructs (see concluding words: "*RNA or DNA-vaccines, not dependent on HLA typing, similarly have the potential to be used for multi-epitope vaccines in the near future, again, if their immunogenicity can be improved*"). The use of multi-

epitopic constructs was common at the relevant date in vaccine formulations, even for RNA vaccines, as evidenced in documents D8 to D12, which disclosed the successful therapeutic use of nucleic acid constructs encoding polyepitopic polypeptides.

Document D28 compared mutant-based neo-epitopes on a single polypeptide (encoded by a single RNA) and the same mutant-based neo-epitopes (in equivalent amounts) on distinct polypeptides (encoded by distinct mRNAs) and found no difference in immune response. The objective technical problem was therefore the provision of an alternative cancer vaccine.

The opposition division considered the technical effect associated with the distinguishing feature to be the therapeutic efficacy of the vaccination strategy *in vivo*. It thus considered the problem solved by the invention to reside in providing personalised cancer vaccines with therapeutic efficacy *in vivo*.

Only two alternative approaches existed for implementing a multi(neo)epitopic individualised cancer vaccine. The first option was based on distinct mRNAs, each mRNA encoding a single neo-epitope. The second option was based on at least one mRNA encoding a polypeptide containing two or more neo-epitopes. Both alternatives were obvious implementations of the teaching of document D5.

The disclosure of document D5 would also have been combined by the skilled person with that of documents D20, D24 to D26 and D38, which all disclosed polyepitopic vaccines.

The claimed subject-matter also lacked inventive step when starting from document D27 and combining its teaching with that of documents D24 to D26.

Document D38 and D24 were further promising starting points for inventive-step analysis.

XI. The respondents' submissions are summarised as follows.

Claim interpretation

The subject-matter of claim 1 encompassed RNA vaccines featuring the cancer mutation signature of the patient, which were cancer-specific somatic mutations of the patient (identified according to the invention). The RNA of the vaccine thus had to encode neo-epitopes that were a part of the cancer mutation signature of the patient. However, other epitopes could be included in the polyepitopic polypeptide in addition to the neo-epitopes identified according to the invention, as explained on page 11, bottom paragraph of the application as filed and in claim 11 as filed. Thus, the vaccine might contain other epitopes "not identified according to the invention", but the vaccine had to contain neo-epitopes "identified according to the invention".

The fourth full paragraph on page 7 of the application as filed clearly stated that MHC-presented epitopes with the identified sequence changes were also termed "neo-epitopes". The subject-matter of granted claim 1 was already directed to epitopes which were MHC-presented epitopes.

The definitions in claim 1 were clear in requiring that the polypeptide encoded by the RNA of the vaccine

comprised a plurality of mutations based neo-epitopes. The term "a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes" excluded any RNA which encoded a polypeptide with a single mutation-based neo-epitope only. The definitions of claim 1 excluded RNA vaccines comprising a library of RNAs, each RNA of the library encoding a different polypeptide with a single mutation-based neo-epitope.

Claim 1 is a purpose-limited product claim. Thus, pursuant to Article 54(5) EPC, any feature of the treatment - if claimed as such - infringing Article 53(c) EPC was decisive for novelty.

Amendments (Article 100(c) EPC)

Claims 1, 9, 16 and 21, which were all linked, disclosed most features of claim 1 as granted. The term "polyepitopic" was disclosed on page 9, third paragraph of the application as filed and in the paragraph bridging pages 10 and 11.

All features of the subject-matter of claim 1 were explicitly disclosed in the application as filed and in a manner such that the features were clearly combinable with each other. None of the features was disclosed in isolation from the other features or in a manner that indicated that the features could not be combined.

Novelty (Article 100(a) EPC and Article 54 EPC)

The disclosure of document D5 was not enabling for an individualised RNA cancer vaccine as claimed. The argument that it was enabling was purely speculative and not supported by facts, let alone experimental data. Document D5 also did not disclose polyepitopic

polypeptides comprising mutation-based neo-epitopes, much less an RNA encoding such a polyepitopic polypeptide and its use as a vaccine for treating a cancer patient.

The Guidelines for Examination in the EPO (F-IV, 4.12.1) stated that a product defined by product features and process features can establish novelty if the claimed product had different properties from the products known from the prior art. The claimed product is an RNA vaccine required to comprise an RNA encoding "a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes".

There was no direct and unambiguous disclosure in document D2 that the mutant (poly)peptides were polyepitopic. Where more than one mutation (neoantigen) was to be administered in document D2, it was more than one (poly)peptide that was administered, not a single (poly)peptide having more than one mutation.

Sufficiency of disclosure (Article 100(b) EPC)

The patent provided evidence - in the form of extensive *in vitro* and *in vivo* data - that an individualised cancer vaccine as defined in claim 1 of the patent was suitable for the treatment of cancer. Furthermore, confirmatory data were presented by the inventors in their post-published scientific article D34, which described the first-in-human application of the claimed RNA-based poly-neo-epitope approach in melanoma and showed (i) the development of T-cell responses against multiple neo-epitopes encoded by the RNA vaccine, (ii) vaccine-induced T-cell infiltration and neo-epitope-specific killing of autologous tumour cells and (iii) a

reduction of the cumulative rate of metastatic events, resulting in a sustained progression-free survival.

Paragraphs [0285] to [0291] of the patent identified each algorithm and filter and their order in the mutation prioritisation pipeline. Further algorithms, including algorithms for epitope prediction of MHC I and MHC II epitopes, were available to the skilled person.

There was no explicit or implicit requirement in the definitions of claim 1 to exclude peptide epitopes not tested in an immunogenicity assay. Even if immunogenicity testing were necessary, this could equally be carried out *in vitro* using isolated human immune cells as routinely carried out in immunology.

The appellants failed to provide verifiable facts to show that the lack of a linker or having the wrong linker in the polypeptide resulted in the neo-epitopes not being presented to T cells.

Inventive step (Article 100(a) EPC and Article 56 EPC)

The disclosure of document D5 was non-enabling. Moreover, document D5 did not disclose a library of neo-epitopes or a polyepitopic polypeptide comprising two or more neo-epitopes.

Documents D5, D24, D25 and D26 all might be considered common general knowledge, but there still needed to be a pointer to combine the teachings in the prior art to show that the claimed subject-matter was obvious. It was not sufficient to merely show that the general concept was known or speculated about in the prior art. The administration of an RNA molecule encoding the

mutation-based neo-epitopes provided for an unexpectedly more effective immune response against the cancer. As demonstrated in the patent in Figure 13, neo-epitopes that did not induce an immune response when given as a peptide (as seen in Table 7) were able to induce an immune response when an RNA encoding the neo-epitopes was given. The skilled person could not have reasonably expected improved immunogenicity when substituting the library of peptides with a single RNA encoding the peptides.

The claimed invention was also not obvious when choosing document D27 as the starting point. The skilled person would not have considered replacing the RNA library (entire transcriptome of a tumour) of D27 with a single RNA encoding a single polyepitopic polypeptide.

There was also no suggestion in document D27 that only cancer-specific somatic mutations should be used for immunotherapy of a cancer patient. Many of the 30 most abundant transcripts of the patient's melanoma RNA library of D27 were simply overexpressed proteins also expressed in healthy tissue. D27 did not mention that any of these proteins comprised a single mutation-based neo-epitope, let alone two or more neo-epitopes as required by claim 1.

XII. The appellants (opponents 2 and 3) requested that the decision under appeal be set aside and the patent be revoked. Appellant II (opponent 3) requested the correction of an obvious error concerning its name and address under Rule 101(2) EPC and Rule 139 EPC.

The respondents (patent proprietors) requested that the appeals be dismissed and the decision to reject the

oppositions be upheld. Alternatively, they requested maintenance of the patent in amended form based on one of the sets of claims of auxiliary requests 1 to 9.

Reasons for the Decision

Correction of an obvious error concerning the name and address of the appellant (Rule 101(2) EPC and Rule 139 EPC)

1. Appellant II filed its notice of appeal on 13 December 2021 "[i]*n the name and on behalf of CureVac AG*". With its statement of grounds of appeal dated 18 March 2022, it requested correction of the name of the appellant to "*Withers & Rogers LLP*", arguing that this was the name of opponent 3 in first-instance proceedings represented by the same representative as current appellant II. Furthermore, the reference part of the notice of appeal ("*Our reference*") contained the name of the opponent, "*Withers & Rogers LLP*".

2. The board allowed the correction of appellant II's name as an obvious error under Rule 139 EPC. This rule permits corrections at all stages of the proceedings and applies to all documents filed with the EPO. "*CureVac AG*" was previously not a party to the proceedings so that it is immediately apparent that it cannot be the appellant. The correct name of the appellant is equally immediately apparent from the opposition proceedings where only one further opponent was present (opponent 1's opposition having been withdrawn), "*Withers & Rogers LLP*", whose name also appears as the only named opponent in the reference section on page 1 of the notice of appeal of appellant II. A further indication as to what the correction had

to be is the identity of the representative for opponent 3 and appellant II.

3. The correction thus relates to an obvious error under Rule 101(2) EPC and Rule 139 EPC (see decision G 1/12).

Admissibility of the appeal by appellant II (opponent 3) (Article 109 EPC)

4. Since all other requirements are fulfilled, the appeal by appellant II is admissible (Article 109 EPC).

Technical background

5. Cancers may arise from the accumulation of genomic mutations and epigenetic changes, of which only a fraction may have a causative role. **Tumour-specific antigens (TSAs)** are present only on tumour cells and not on any other cell, while **tumour-associated antigens (TAAs)** are present on some tumour cells and also on some normal cells. TSAs are particularly interesting targets for immunotherapy because they allow targeting the tumour without damaging normal cells. Human cancers carry on average 100 to 120 non-synonymous mutations, i.e. DNA-level mutations which lead to a change in the encoded protein. More than 95% of tumour mutations are unique and patient specific (see patent, paragraph [0005]). Non-synonymous point mutations resulting in amino acid changes that will be presented by the patient's **major histocompatibility complex** (**MHC**) molecules provide **novel epitopes** (**neo-epitopes**) which are specific to the patient's cancer and not found in normal cells of the patient (see patent, paragraph [0010]).

6. Vaccination can be carried out in a variety of formats, such as inactivated or attenuated pathogens, recombinant proteins, peptides, viral vectors, DNA and RNA.

7. The advantages of using RNA as "a *kind of reversible gene therapy*" for vaccination include transient expression and a non-transforming character. "*RNA does not need to enter the nucleus in order to be expressed and moreover cannot integrate into the host genome, thereby eliminating the risk of oncogenesis. Transfection rates attainable with RNA are relatively high. Furthermore, the amounts of protein achieved correspond to those in physiological expression*" (patent, paragraph [0012]). mRNA "*has an intrinsic adjuvant effect by triggering mechanisms of innate immunity through pattern recognition receptors (PRRs) expressed by antigen-presenting cells (APCs) such as dendritic cells (DCs)*" (D35, page 399, left-hand column).

Main request (patent as granted)
Claim interpretation

8. Claim 1 reads as follows:
"1. An individualized cancer vaccine for use in a method of treating a cancer patient, said method comprising the steps:
(a) providing said individualized cancer vaccine by a method comprising the steps:
(aa) identifying cancer specific somatic mutations in a tumor specimen of the cancer patient to provide a cancer mutation signature of the patient; and
(ab) providing an RNA vaccine featuring the cancer mutation signature obtained in step (aa), wherein the RNA vaccine featuring the mutation signature of the

patient comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes; and
(b) administering said individualized cancer vaccine to the patient."

9. The appellants argued that because the individualised cancer vaccine in the claim results from a process, the subject-matter of the claim was limited only by the structural features conferred to the product for use as such, i.e. the "individualized cancer vaccine" obtainable by the process, and the steps of the process for its production were not limiting features of the claim. The board takes a different view.

10. The claim is in the format of a purpose-limited product claim in line with Article 54(5) EPC. Both method steps (a) and (b), including the sub-steps (aa) and (ab), constitute characterising and limiting features of the claimed subject-matter because they form an integral part of the method of treating a patient, which is a method referred to in Article 53(c) EPC. Without these steps, the claimed "*individualized cancer vaccine*" cannot be implemented.

11. The claim wording also makes clear that there is a direct, specific and treatment-related link between the "individualized cancer vaccine", its process of production and the administration to the patient within the method for treating cancer. Indeed, **said** individualised cancer vaccine of steps (a) and (b), which is the same as that of the preamble of the claim, is provided in step (a) "as an RNA vaccine featuring **the** cancer mutation signature obtained in step (aa)" and is "administer[ed] to **the** patient" in step (b). Step (aa) further prescribes that "**the** cancer mutation

signature of **the** patient" is provided by "identifying cancer specific mutations in a tumor specimen of **the** cancer patient". The patient to which an individualised cancer vaccine is administered is therefore the same patient from which a tumour specimen for the identification of cancer-specific mutations originated giving rise to a cancer mutation signature of this very patient. Since these steps are mandatory to obtain the individualised cancer vaccine under consideration, the legal fiction of a purpose-limited product claim in accordance with Article 54(5) EPC applies to all steps of the method, which are thus limiting on the claim. This situation is to be distinguished from a purpose-limited product claim according to Article 54(5) EPC in which a compound for use would be defined by a production process unrelated to the patient to be treated (e.g. "wherein the RNA is expressed in bacteria").

12. The wording in claim 1 "RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes" requires the RNA in the vaccine to encode a single polypeptide which contains several ("poly") epitopes, among which are more than one mutation-based neo-epitopes.

Amendments (Article 100(c) EPC)

13. The board agrees with the decision under appeal that the claims do not contain added subject-matter. The board considers that the subject-matter of claim 1 (see wording in point 8. above) is disclosed in claims 1, 9, 16 and 21 as filed in combination with the disclosure on pages 9 and 10 of the application as filed.

Claim 21 as filed reads:
"*21. A method of treating a cancer patient comprising the steps:*
(a) providing an individualized cancer vaccine by the method according to any one of claims 1 to 17; and (b) administering said vaccine to the patient."

Claim 1 as filed reads:
"*1. A method for providing an individualized cancer vaccine comprising the steps:*
(a) identifying cancer specific somatic mutations in a tumor specimen of a cancer patient to provide a cancer mutation signature of the patient; and (b) providing a vaccine featuring the cancer mutation signature obtained in step (a)."

Claim 9 as filed reads:
"*9. The method according to any one of claims 1 to 8, wherein the vaccine featuring the mutation signature of the patient comprises a polypeptide comprising mutation based neoepitopes, or a nucleic acid encoding said polypeptide.*"

Claim 16 as filed reads:
"*16. The method according to any one of claims 1 to 15, wherein the vaccine is an RNA vaccine.*"

14. Polyepitopic RNA is a particularly preferred embodiment (see description page 9, third paragraph and page 10 last paragraph as filed) so that the combination of this feature with the subject-matter of claims 1, 9, 16 and 21 as filed is also disclosed.

15. No objections were raised against the subject-matter of dependent claims 2 to 10 for added subject-matter.

Priority (Article 87 EPC)

16. The parties did not contest the finding of the opposition division on priority. The board agrees with the decision under appeal that claims 1 to 7, 9 and 10 are entitled to priority from the first and second priority documents (P1 and P2) while claim 8 is only entitled to priority from P2 for the reasons given in the decision under appeal (see point 16 therein).

Novelty (Articles 100(a) and Article 54 EPC)

17. The appellants consider documents D2/D3 and D5 to disclose the subject-matter of claim 1. In light of the claim interpretation in points 8. to 12. above, the board agrees with the decision under appeal that the subject-matter of the claims is novel. None of the cited prior-art documents discloses all features of the claim, in particular "wherein the RNA vaccine featuring the mutation signature of the patient comprises RNA encoding a recombinant polyepitopic polypeptide comprising mutation based neo-epitopes". The cited state of the art furthermore does not disclose achieving a therapeutic effect, this being a functional feature of the claim.

18. The same applies to dependent claims 2 to 10, which share all features of claim 1. The claimed subject-matter is novel (Article 54 EPC).

Disclosure of the invention (Article 100(b) EPC)
Therapeutic effect

19. The experiments with polyepitopic RNA in mice reported in the application as filed (see Example 8) render achieving a therapeutic effect in tumours credible

because the underlying principle, i.e. vaccination with tumour-specific antigens not present in normal tissue, applies to all cancer types. Those antigens are used to design polyepitopic mRNA vaccines which achieve an anti-tumoural effect in a mouse melanoma model (see Figure 21). The board has also not been presented with any evidence why the principle of using mRNA as a vaccine should not be applicable to all cancer types. Achieving the therapeutic effect is therefore credible from the disclosure of the application as filed.

20. The post-published evidence in document D34 confirms that anti-cancer mRNA vaccination is applicable to human melanoma patients and shows (i) the development of T-cell responses against multiple neo-epitopes encoded by the RNA vaccine, (ii) vaccine-induced T-cell infiltration and neo-epitope-specific killing of autologous tumour cells and (iii) a reduction of the cumulative rate of metastatic events, resulting in a sustained progression-free survival.

21. The board therefore concludes that attaining the therapeutic effect is sufficiently disclosed.

Mutation prioritisation

22. The appellants questioned whether the prioritisation of individual cancer mutations which involved further steps based on specific computer tools was sufficiently disclosed. The statement in the second paragraph on page 77 of the application as filed that the used "*method, called 'individual cancer mutation detection pipeline' (iCAM) identifies and prioritizes somatic mutations through a series of steps incorporating multiple cutting edge algorithms and bioinformatics methods*" shed doubts on whether these algorithms and

methods could be identified and used by the skilled person without an undue burden.

23. The appellants also referred to an editorial in the renowned journal Nature Biotechnology (D36) which considered still in 2017: "*The truth is then that current neoepitope prediction algorithms return a vast number of candidates, of which only a tiny handful are ever found to trigger bona fide antitumor responses in patients. Despite the profundity of cancer cell mutations, immunogenic neoantigens are the exception rather than the rule. This means there is a great deal more research to do before neoepitope prediction and validation becomes routine and personalized immunotherapy a clinical reality.*" Also, a doctoral thesis (D37) on identifying mutated peptides on the surface of human tumour cells and published in 2012, i.e. shortly after the filing date, failed to detect any tumour-specific neoantigens (see page 89). Of the, on average, 582 somatic mutations per tumour detected (see page 92, first paragraph and Table 3.1), no TSAs could be confirmed at the level of ligands (see page 98, last paragraph).

24. The board finds that the application as filed provides a complete workflow for the identification of neo-epitopes (see pages 71 to 79 and Example 9), including several known computer algorithms for mutation prioritisation. The statement in the post-published editorial D36 provides a retrospective view on the developments after the filing date, but does not establish the skilled person's knowledge at the time of filing. Moreover, becoming a "clinical reality" cannot be equated with the requirement of sufficient disclosure for the person skilled in the art of cancer vaccines. With regard to the failed attempts to

identify tumour-specific neoantigens in document D37, the board accepts the argument by the respondents that the techniques used (e.g. "*experimental massspectrometry-based HLA-ligandome analysis*") differ from those employed in the patent and that an individual failed attempt would not have raised serious doubts for the skilled person. Moreover, document D37 also states that "*we are [...] on the right path to identify TSAs in the near future*" (see page 98, last paragraph, translation by the board). This hope was confirmed by the experiments disclosed in the patent.

25. The appellants have not provided evidence that applying the methods disclosed in the application to identify and prioritise somatic cancer mutations would have put an undue burden on the skilled person. Applying this workflow led to a list of 50 validated mutations in the mouse model (see Table 1), several of which were confirmed to be effective in an mRNA vaccine (see Table 8; Figures 13 and 21).

In vivo tests for immunogenicity

26. The appellants further considered that the results obtained in mice could not be transferred to humans without undue burden. The post-published review article D18 stated: "*Clinical translation from syngeneic mice to humans who have 'one-of-a-kind' cancers is more complex because it requires personalization of the process, including identification of mutations, prediction of potential neoepitopes and design and manufacture of the vaccine (Fig. 1). This was recently accomplished by three first-in-human studies in malignant melanoma patients (20–22)*" (page 1, right-hand column, last paragraph). The in-human studies

cited in document D18 were published in 2015 and 2017, i.e. after the relevant date of the patent.

27. The board finds that although immunogenicity was tested *in vivo* (see Example 2), the application as filed also discloses alternative *in vitro* methods to test immunogenicity (see page 8, first paragraph), e.g. with an enzyme-linked immunospot assay (ELISpot; see page 93 to 94) using dendritic cells or tumour cell lines.

28. The board therefore considers that in the present case *in vivo* testing of immunogenicity is not necessary to establish the claimed therapeutic method in human beings. Moreover, the patent shows that some of the peptide epitopes included in the polyepitopic polypeptide encoded by the mRNA of Example 8 (see Table 8) showed no immune response when tested individually in a peptide immunogenicity assay *in vivo* (see Table 7). Still, the same peptide epitopes in the format of a polyepitopic RNA induced an immune response against various epitopes (MUT08, MUT27 and MUT33) and strongly improved survival of tumour mice (see Figures 13 and 21; page 102, paragraph following Table 8; page 103, last two paragraphs). This indicates that the polyepitopic RNA format allows for the induction of an immune response.

Linkers in polyepitopic RNA

29. The appellants objected that linkers of a particular type (Gly-Ser) and length for separating multiple epitopes in a polyepitopic mRNA were not defined in the claims even though they are considered "*critically important for the creation of bad* [sic] *MHC binding epitopes*" (see page 86, first sentence of the

application). Such non-immunogenic glycine/serine linkers were also used in the post-published study D34.

30. However, the appellants failed to provide verifiable facts to show that the lack of a linker or the use of the wrong linker in the polypeptide resulted in the neo-epitopes not being presented to T cells or the RNA vaccine not being effective. The board therefore has no reason to doubt that the skilled person with the teaching of the application in hand and applying common general knowledge could design the polyepitopic mRNA referred to in the claims.

31. The claimed invention is sufficiently disclosed (Article 100(b) EPC).

Inventive step (Article 100(a) EPC and Article 56 EPC)

Admission of arguments using alternative starting points D24, D27 and D38 (Article 12(4) RPBA)

32. Document D27 (then E11) was cited as the closest prior art and document D24 (then E8) was cited as a secondary document by opponent 3 in its notice of opposition. Document D38 (WO 2005/028505) was introduced and cited as the only alternative closest prior art to document D5 by opponent 3 in response to the preliminary opinion of the opposition division in preparation for the oral proceedings.

33. However, the minutes of the oral proceedings state that both appellants "*named D5 as [the] closest prior art*" (see sheet 4, first and second paragraph). None of the appellants requested a correction of the minutes. The board therefore considers that the attacks starting from D24, D27 and D38 were not actively maintained. The

conclusion that the attacks based on these documents were implicitly abandoned or not raised in opposition proceedings is in line with the absence of any mention of them in the impugned decision.

34. In the decision under appeal, documents D5 and D6 are considered "*the only promising springboards*" (point 18.2.10), and the parties "*agreed to use D5 as [the] closest prior art*" (see point 18.2.12).

35. Therefore, in accordance with Article 12(2) RPBA, the attacks starting from documents D24, D27 or D38 as the closest prior art do not *a priori* form part of the appeal proceedings. Their admittance into the appeal proceedings is at the discretion of the board in accordance with Article 12(4) RPBA.

36. The implicit abandonment of the attacks based on D24, D27 and D38 by opponent 3 prevented the opposition division from taking a decision based on any of these documents. A re-introduction of these attacks would be against the purpose of the appeal proceedings to constitute a judicial review of the appealed decision and against procedural economy. Accordingly, these attacks were not admitted into the appeal proceedings (Article 12(4) RPBA).

Document D5 as the starting point

37. Document D5 is a review article summarising steps on the way to "*THE IDEAL THERAPEUTIC CANCER VACCINE*" (see title on page 576, left-hand column). Figure 50.1 discloses a potential approach for "[d]*esigning antigen composition of the ideal tumor vaccine*" (see figure legend). The figure shows three inputs for the "*[d]esign and synthesis of molecularly defined,*

personalized vaccine consisting of peptides and mRNA/ DNA containing all tumor associated/specific structures":
- "*Differential analysis-list of overexpressed genes*"
- "*Differential analysis-list of tumor-specific mutations*"
- "*Differential analysis-list of tumor-associated peptides*"

Differences, effects and objective technical problem

38. According to the claim interpretation in points 8. to 12. above, claim 1 relates to an individualised cancer vaccine generated in two steps:
"(aa) identifying cancer specific somatic mutations in a tumor specimen of the cancer patient to provide a cancer mutation signature of the patient; and
(ab) providing an RNA vaccine featuring the cancer mutation signature obtained in step (aa)".

39. Step (aa) is disclosed in a conceptual manner in document D5 as part of Figure 50.1 ("*Differential list of tumor-specific mutations*"). The first part of step (ab) as reproduced above is equally disclosed in Figure 50.1 ("*synthesis of molecularly defined, personalized vaccine consisting of peptides and mRNA/DNA containing all tumor associated/specific structures*"). The respondents questioned whether the wording "peptides and mRNA/DNA" disclosed an mRNA vaccine. The board, however, finds that claim 1 of the patent does not exclude the presence of additional molecules of different types. Moreover, document D5 contains a dedicated section on messenger RNA-based anti-tumour vaccines (see page 581, right-hand column) so that the skilled person would consider an mRNA vaccine to be a preferred option.

40. The second part of step (ab): "wherein the RNA vaccine featuring the mutation signature of the patient comprises RNA encoding a recombinant polyepitopic polypeptide" is not disclosed in document D5. The relevant statements on page 584, right-hand column that "*RNA or DNA-based vaccines, not dependent on HLA typing, similarly have the potential to be used for multi-epitope vaccines in the near future, again, if immunogenicity can be improved*" and that "[s]*ince tumors are genetically unstable, and tend to lose their antigens and MHC molecules, especially if under immune attack, successful vaccines will contain multiple antigens*" merely predict possible future developments. These passages cannot be seen as enabling disclosure of a medical use of such vaccines. Moreover, they do not specify the form in which the multi-epitopes are encoded in the RNA vaccine, i.e. on separate molecules or a single molecule.

41. The third part of step (ab), "comprising mutation based neo-epitopes", is also not disclosed in document D5. Figure 50.1 of document D5 refers to "*mRNA/DNA containing all tumor associated/specific structures*". This includes overexpressed proteins, proteins comprising tumour-specific mutations and posttranslational modifications (see page 576, right-hand column, second to fourth full paragraphs). But it does not specify neo-epitopes, i.e. a subset of tumour-specific mutations/structures that will be presented by the patient's MHC molecules (see patent, paragraph [0010]). Neo-epitopes are indirectly disclosed in document D5 by referring to the importance of MHC specificity in peptide vaccines (see page 576, paragraph bridging both columns). However, this passage does not apply these considerations to RNA vaccines.

Rather, document D5 suggests that RNA or DNA-based multi-epitope vaccines, in contrast to the previously discussed peptide vaccines, are not dependent on HLA typing (see page 584, right-hand column, penultimate paragraph). This assumption seems to be based on the concept of tumour-derived (differential) RNA libraries encoding entire proteins (see page 577, left-hand column, first paragraph).

42. The board agrees with the appellants that mRNA libraries are likely to also encode neo-epitopes. However, based on the rarity of non-synonymous mutations in human cancers (100 to 120 mutations per cancer, see point 5. above), it would be mere speculation whether any polypeptide encoded by an RNA in such a library would necessarily carry more than one neo-epitope.

43. The board therefore finds that the claimed subject-matter differs from the disclosure of document D5 in the RNA encoding a polyepitopic polypeptide comprising more than one neo-epitope.

44. Document D5 does not contain any experimental data but refers to a number of studies on several aspects of the envisaged "*ideal therapeutic cancer vaccine*". A reference to data for a personalised vaccine relates to "*a RNA (Carralot et al., 2005)* [document D27 in this appeal] *or DNA library from fresh autologous tumor tissue*" (see page 577, left-hand column, first paragraph). In document D27, amplified tumour-derived cRNA libraries are used as vaccines against metastatic melanomas. These libraries contain TAAs (see page 5) and might also allow targeting tumour-specific mutations (see page 6, left-hand column). They, however, also contain antigens present on healthy

cells. The further step envisaged in document D5 in this regard, i.e. "*depleted by the genes expressed in normal tissue*", is not supported by the provided reference D27.

45. The board therefore concludes that a therapeutic effect of a hypothetical "*personalized vaccine*" based on mRNA encoding epitopes from a "[d]*ifferential analysis-list of tumor-specific mutations*" has not been credibly achieved in document D5 and represents a further difference compared to the claimed invention.

46. The respondents argue that these differences result in an improved personalised cancer vaccine. While the board agrees that achieving a therapeutic effect is an "improvement" over a merely speculative vaccine, no comparative evidence has been provided to show an improvement over known cancer vaccines, e.g. in other formats (DNA, peptide or viral) or with multiple epitopes present on separate RNA molecules (RNA libraries). The board therefore concludes that no improved therapeutic effect has been shown to result from the differences.

47. The objective technical problem can be formulated as providing a personalised RNA cancer vaccine with therapeutic efficacy.

Obviousness

48. Opponent 2 considered that document D5 already provided an incentive to the skilled person to use RNA or DNA vaccines for multi-epitope vaccines (see page 584, right-hand column). The disclosure in document D5 of a personalised vaccine (see Figure 50.1) together with the knowledge about polyepitopic vaccines disclosed in

documents D8 to D12 would have provided the skilled person with a reasonable expectation of success for polyepitopic RNA vaccines to be therapeutically effective in cancer patients.

49. The board does not agree with this reasoning. To arrive at the claimed invention, the skilled person starting from the disclosure in document D5 had to make several selections, each of which brought uncertainties with it, and possibly modify the teaching of document D5. The first choice required having to select, from the "multi-epitope vaccines" suggested in document D5, which include libraries of epitopes on separate molecules, a nucleic acid encoding a polyepitopic polypeptide. However, document D5, with regard to nucleic acid vaccines, focuses on total RNA libraries from tumours which contain multiple epitopes on separate molecules (see page 577, left-hand column, first paragraph: "*[...] to get closer to our ideal for a cancer vaccine by using a RNA (Carralot et 2005) or DNA library from fresh autologous tumor tissue of the patient depleted by the genes expressed in normal tissue, in an individualized setting*"). This is also apparent from the section on "*Messenger RNA-Based Anti-Tumor Vaccines*", which refers to total RNA isolated from tumours or to RNA encoding individual TAAs, e.g. PSA. A further choice required selecting RNA over other formats disclosed in document D5, e.g. DNA, viral or peptide. A final modification, not suggested in document D5 (see point 41. above), had to be made to provide several neo-epitopes in polyepitopic format.

50. The appellants referred to page 576, right-hand column, first full paragraph, which highlighted the importance of tumour-specific mutations which elicit T cells and are expected to have higher affinity than those against

overexpressed antigens due to constraints of self-tolerance. However, this passage does not contain any suggestion to identify neo-epitopes among the tumour-specific mutations and to provide them as a vaccine in the form of polyepitopic polypeptides encoded by RNA.

51. The additional documents cited by the appellants (D8 to D12, cited by opponent 2, and D20, D24 to D27, D35 and D38, cited by opponent 3) do not allow the skilled person to arrive, from the disclosure in document D5, in an obvious manner at the claimed invention.

51.1 Document D8 relates to an HPV vaccine in the form of DNA encoding a polyepitopic polypeptide. RNA is mentioned but not tested as a vaccine. Document D8 does not relate to cancer or to cancer mutations or epitopes and thus cannot provide guidance on personalised RNA cancer vaccines with therapeutic efficacy.

51.2 Document D9 relates to an HIV vaccine in the form of mRNA encoding a polyepitope of HIV (13 HLA-A2 epitopes of HIV-1). D9 does not mention somatic cancer mutations or neoantigens and shows only a weak immune response (ELIspot) for the RNA vaccines tested in comparison with DNA vaccines (see Figure 6). Document D9 thus does not suggest to the skilled person to use neoantigens in a polyepitopic RNA vaccine.

51.3 Although document D10 lists a number of known cancer antigens (see paragraph bridging pages 15 and 16) for use in a polyepitopic mRNA vaccine, it does not refer to a personalised vaccine or the identification of neoantigens. Furthermore, document D10 does not contain data on the effect of RNA vaccination but is restricted to computer-based sequence adaptation (G/C content and codon bias). Document D9 thus does not suggest to the

skilled person to use neoantigens in a polyepitopic RNA vaccine.

51.4 Document D11 relates to replicon vectors derived from the Kunjin (KUN) flavivirus, allowing delivery of naked RNA as RNA vaccines (see Figure 1 and paragraph [0004]). It further discloses the murine polytope immunogen which contains four conjoined CTL epitopes restricted by the H-2d HLA type from four different pathogens and the ovalbumin-derived CTL epitope SIINFEKL, permitting examination of tumour protection. Document D11 uses a tumour protection assay based on RNALeuMpt, which is a polyepitopic RNA vaccine, in the B16-OVA mouse model. Vaccination resulted in induction of CD8+CTL responses specific to the encoded epitopes and in the case of naked RNA and VLPs, protected mice from viral and tumour challenges. Document D11, however, does not disclose somatic cancer mutations or neoantigens. While the skilled person would have learned the proof of principle of RNA vaccines encoding polyepitopic polypeptides targeting an artificial tumour marker (OVA) in an established mouse cancer model, they would not have known whether including neo-epitopes in a polyepitopic RNA vaccine was also effective.

51.5 Document D12 contains only data on PBMCs transfected with mRNA encoding the influenza matrix protein, i.e. a single protein. It shows that the cellular vaccine activates T cells. Document D12 does not disclose the use of neo-epitopes in a polyepitopic mRNA format.

51.6 Document D20, which is a review article "*on the use of peptides and mRNA for therapeutic vaccination*", proposes using somatic cancer mutations from a patient's tumour. However, it does not teach to select

neo-epitopes and present them in a polyepitopic mRNA format.

51.7 Document D24 discloses DNA cancer vaccines against melanoma ("*Summary*" on page 402, last line or, e.g. page 404). They encode a multi-epitope polypeptide which might contain, *inter alia,* "*altered self-antigens*" (page 404, right-hand column, line 32). However, D24 cautions that "*the relative therapeutic benefit of generating responses directed at each of these group of epitopes remains to be established*". From D24, it is also not apparent whether the polyepitopic concept could be transferred to RNA.

51.8 Document D25 is a review which discloses "*conjoining T-lymphocyte epitopes, derived from several antigens into a single artificial construct*" (see Abstract) in the form of DNA, viral vectors, recombinant protein or KUN replicons (i.e. RNA, see document D11 in point 51.4 above) or peptide vaccines (see Tables 1 and 2). It fails to disclose neo-epitopes for cancer vaccination.

51.9 Document D26 refers to the multi-epitope approach for "*enhanc*[ing] *the barrier against escape of antigen loss variants of the tumor*" (page 1869, left-hand column, first paragraph), mentions personalised immunotherapy, but also foresees "*tremendous technical and logistic difficulties*" with this approach (page 1862, left-hand column) and would thus provide no reasonable expectation of success for the skilled person.

51.10 Document D27 relates to a vaccine comprising amplified coding regions of a tumour comprised in an mRNA library and suggests: "*this method might also allow the targeting of tumor-specific mutations. These features makes [sic] of the amplification of tumor mRNA the*

method of choice to easily obtain unlimited amounts of RNA coding for patient's specific TAAs that can be applied as anti-tumor immunotherapy" (see page 6, left-hand column). Document D27 fails to disclose an RNA encoding a polyepitopic polypeptide comprising neo-epitopes (see discussion on neo-epitopes in RNA libraries in point 42. above). Document D27 would thus provide the skilled person with no reason to change the mRNA library, which is also referred to in the closest prior art D5, to a polyepitopic format.

51.11 Document D35 has the title "*Tumor vaccination using messenger RNA: prospects of a future therapy*" and indicates that "[a]*ntigen-encoding mRNA is in principle capable of eliciting polyepitopic humoral and cellular immune responses*" (see page 401, left-hand column, third full paragraph) but only discloses immunotherapy by autologous total tumour mRNA or previously known tumour antigens (see Table 1 on pages 402 to 403). It therefore also does not suggest the use of neo-epitopes in a polyepitopic RNA.

51.12 Document D38 relates to multi-epitope polypeptides for use in cancer therapy. It discloses in claims 1 and 3: "*A recombinant nucleic acid sequence encoding a multiepitope polypeptide (MEP), which* [...] *encodes a T cell epitope derived from a tumor associated antigen (TAA)* [...] *wherein said nucleic acid is any one of DNA, RNA and any combination thereof*". Although RNA is mentioned as an expression vector encoding such polypeptides (see e.g. claim 48 or page 32, lines 1 to 2), an RNA vaccine is not disclosed in D38. D38 also does not disclose neo-epitopes as part of the encoded polypeptide and does not disclose an individualised approach.

52. The documents invoked by the appellants thus do not mention the missing features in a context that would have led the skilled person towards the claimed technical features. Furthermore, none of the cited documents contains experimental evidence for the effectiveness of a vaccine based on polyepitopic mRNA encoding neo-epitopes from a patient's tumour. Even if the skilled person had combined the disclosure of a polyepitopic RNA vaccine (see e.g. D11) with the use of neo-epitopes (see e.g. D20), they would have had no reasonable expectation of achieving a therapeutic effect with this approach. The board concludes that none of the cited documents suggests modifying the hypothetical vaccines proposed in document D5 by the use of RNA encoding a polyepitopic polypeptide comprising neo-epitopes.

53. The claimed invention is not obvious over the state of the art (Article 56 EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated