Appeal decision

Appeal No. 2019-1485

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The case of appeal against the examiner's decision of refusal of Japanese Patent Application No. 2016-512043, entitled "Compositions and Methods for Treatment of Type 1 Diabetes" (International publication No. WO2014/179586 published on November 6, 2014, and National Publication of International Patent Application No. 2016-518844 published on June 30, 2016) has resulted in the following appeal decision.

Conclusion

The appeal of the case was groundless.

Reason

No. 1 History of the procedures

The present application was filed on May 1, 2014 as an international filing date (the claim of priority under the Paris Convention was received by the foreign receiving office on May 2, 2013 in the US) to which a written amendment was submitted on January 5, 2016, reasons for refusal were noticed dated March 13, 2018, and a written opinion and the written amendment were submitted on June 20, 2018. However, an examiner's decision of refusal was issued on September 25, 2018. Against this, a request for appeal and the written amendment of claims were submitted on February 4, 2019. Then, a written amendment of the request for appeal was submitted on April 8, 2019.

No. 2 Decision to dismiss amendment on the amendment dated February 4, 2019

[Conclusion of decision to dismiss amendment]

The amendment dated February 4, 2019 shall be dismissed.

[Reason]

1 Details of Amendment

The amendment dated February 4, 2019 (hereinafter, referred to as "the Amendment") is described in Claim 1 according to the Scope of Claims for patent amended by the written amendment submitted on June 20, 2018:

to delete the wording "in treatment or prevention of insulin-dependent diabetes mellitus (IDDM)"

from the wording "A use of a self-vector having a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 (BHT-3021) in preparation of a composition for reducing the frequency of proinsulin-reactive CD8 T cells <u>in treatment or prevention of insulin-dependent diabetes mellitus (IDDM)</u> in a subject" in Claim 1 of the Scope of Claims, which has been amended by the written amendment submitted on June 20, 2018 to read "A use of a self-vector having a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 (BHT-3021) in preparation of a composition for reducing the frequency of proinsulin-reactive CD8 T cells in a subject."

(Note that the underline was added by the body. The same shall apply hereinafter.).

2 Propriety of amendment

(1) New matters

A After the Amendment, the composition of Claim 1 can encompass a composition for "reducing the frequency of proinsulin-reactive CD8 T cells" in cases other than "treatment or prevention of insulin-dependent diabetes mellitus (IDDM)."

First, consideration is given to whether the Amendment has been made within the scope of matters described in the translation of the specification or the drawings (limited to the descriptions in the drawings), the translation of the scope of claims, or the drawings (other than the descriptions in the drawings) (hereinafter, collectively referred to as "the translation, etc.") of the international patent application as of the international application date of the present application.

B Paragraphs [0002], [0009], and [0021] of the translation, etc. include the following descriptions:

(a) "[0002] FIELD OF THE INVENTION

This invention relates to compositions and methods for treating insulin-dependent diabetes mellitus in a subject." ([0002])

(b) "[0009]

BRIEF SUMMARY OF THE INVENTION

The present invention provides compositions and methods for treating insulin-dependent diabetes mellitus in a subject comprising administration of a self-vector encoding and capable of expressing human proinsulin." ([0009])

(c) "[0021] Accordingly, the present invention provides compositions and methods for treating, preventing, reducing, inhibiting, and/or delaying, e.g., the symptoms of or the severity of IDDM in a subject comprising administration of a modified self-vector encoding and capable of expressing human proinsulin, in particular, the self-vector BHT-3021 (SEQ ID NO: 1). ... " ([0021]).

As such, the translation, etc. consistently states that the present invention relates to "providing compositions and methods for treating insulin-dependent diabetes mellitus in a subject."

C On the other hand, the description "a composition for reducing the frequency of proinsulin-reactive CD8 T cells in treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject" was added to Claim 1 by the written amendment dated June 20, 2018 in the examination process of the original examination. In paragraphs [0058] and [0093] of the specification of the present application, which the Appellant points out as the bases for the amendment, the "proinsulin-reactive CD8 T cells" are

described as follows:
(d) "[0058] ... Proinsulin-reactive CD8 T cells, but not T cells against unrelated islet or foreign molecules, declined in the BHT-3021 arm ($p<0.006$). ... Thus, we demonstrate that a plasmid encoding proinsulin reduces the frequency of CD8 T cells reactive to proinsulin, while preserving C-peptide over the course of dosing." (paragraph [0058]); and
(e) "[0093] ... We also demonstrate that as the C-peptide increases there is a deletion of CD8 T cells reactive to proinsulin, but there is no effect on other antigen specific T cell responses. " ([0093]).

All of these descriptions are related to changes in proinsulin-reactive CD8 T cells when T1D patients with insulin-dependent diabetes mellitus (IDDM) were treated with a DNA plasmid (BHT-3021) encoding proinsulin, and do not disclose anything about reducing the frequency of proinsulin-reactive CD8 T cells in cases other than treatment or prevention of insulin-dependent diabetes mellitus.

Further, regarding the "proinsulin-reactive CD8 T cells," in addition to the above descriptions in the specification of the present application, the following descriptions are made in paragraphs [0082] and [0097]. These descriptions also do not disclose anything about reducing the frequency of proinsulin-reactive CD8 T cells in cases other than treatment or prevention of insulin-dependent diabetes mellitus.
(f) "[0082] ... BHT-3021 induced antigen-specific reductions in CD8 cells reactive to proinsulin, but not to other antigens, and the magnitude of the reduction was inversely correlated with the improvement in C-peptide ([0082]).
(g) "[0097] ... We demonstrate antigen specific reduction in CD8 cells reactive to proinsulin, but not to other antigens, and that the magnitude of the reduction was inversely correlated with the improvement in C-peptide (Figure 4)." ([0097]).

D Then, even considering the common general knowledge at the time of filing of the present application, a new technical matter (new matter) is introduced by the amendment for deleting the wording "in treatment or prevention of insulin-dependent diabetes mellitus (IDDM)" from "for reducing the frequency of proinsulin-reactive CD8 T cells in treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject."

Therefore, it cannot be recognized that the Amendment is made within the scope of the matter described in the translation, etc. and does not meet the requirement under Article 17-2(3) of the Patent Act (see Article 184-12(2) of the Patent Act).

(2) Amendment for other than the prescribed purposes

The Amendment is to delete the wording "in treatment or prevention of insulin-dependent diabetes mellitus (IDDM)" from "a composition for reducing the frequency of proinsulin-reactive CD8 T cells in treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject" before the Amendment. Thus, it means that "a composition for reducing the frequency of proinsulin-reactive CD8 T cells," which was limited to one for "treatment or prevention of insulin-dependent diabetes mellitus (IDDM)" before the Amendment, is no longer limited to "treatment or prevention of insulin-dependent diabetes mellitus (IDDM)." Therefore, the Amendment does not fall under "the restriction of the scope of claims."

In addition, the Amendment does not limit any of matters specifying the invention of Claim 1 before the amendment and thus does not fall under "the category of restricting matters necessary for specifying the invention recited in Claim 1 under the provisions of Article 36(5) of the Patent Act."

Furthermore, it is clear that the Amendment does not correspond to any of " deletion of a claim," " correction of errors," and "clarification of an ambiguous statement."

Therefore, the Amendment does not intend to fall under any of the items (i) to (iv) of Article 17-2(5).

(3) Appellant's allegation

Regarding the Amendment, a person who appeals (hereinafter, referred to as "the Appellant") alleges as follows in the written amendment of the request for appeal:
"The invention recited in new Claim 1 of the present application specifies 'a use of a self-vector having a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 (BHT-3021) in preparation of a composition for reducing the frequency of proinsulin-reactive CD8 T cells in a subject.'

Specifically, the use of a composition in old Claim 1 was specified by the wording '(a composition) for treatment or prevention of insulin-dependent diabetes mellitus (IDDM) reducing the frequency of proinsulin-reactive CD8 T cells in a subject.' In other words, the substantial use of the self-vector BHT-3021 was specified by the wording 'treatment or prevention of insulin-dependent diabetes mellitus (IDDM).' For this, the Appellant made an amendment to further limit the above use by the wording 'for reducing the frequency of proinsulin-reactive CD8 T cells in a subject' to specify the invention."

However, it is obvious that the invention recited in Claim 1 before the amendment is not further limited by the deletion of the matter stated as "for treatment or prevention of insulin-dependent diabetes mellitus (IDDM)," which indicates the practical use of the self-vector BHT-3021. Therefore, the Appellant's allegation cannot be adopted.

(4) Summary

Therefore, the Amendment does not comply with Article 17-2(3) and does not coincide with any of the purposes listed in Article 17-2(5)(i) to (iv) of the Patent Act.

3 Conclusion of decision to dismiss amendment

As stated above, the Amendment violates the provisions of Article 17-2(iii) of the Patent Act and also does not comply with the requirement under Article 17-2(v) of the Patent Act. Thus, the Amendment should be dismissed under the provisions of Article 53(1) of the Patent Act which is applied mutatis mutandis pursuant to Article 159(1) of the Patent Act.

Therefore, the decision is made in accordance with the above "conclusion of decision to dismiss amendment."

No. 3 Regarding the Invention

1 The Invention

As the amendment dated on February 4, 2019 was dismissed as above, the inventions recited in Claims 1 to 8 of the present application are specified by the matters stated in Claims 1 to 8 amended by the amendment dated June 20, 2018. Among them, the invention recited in Claim 1 (hereinafter, referred to as "Invention 1") is one specified by the matters stated in Claim 1 as follows:

"A use of a self-vector having a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 (BHT-3021) in preparation of a composition for reducing the frequency of proinsulin-reactive CD8 T cells in treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject."

2 Matters described in the Detailed Description of the Invention of the specification of the present application

The Detailed Description of the Invention of the specification of the present application includes the following descriptions:

(1) "[0002]
FIELD OF THE INVENTION

This invention relates to compositions and methods for treating insulin-dependent diabetes mellitus in a subject." ([0002])

(2) "[0009]
BRIEF SUMMARY OF THE INVENTION

The present invention provides compositions and methods for treating insulin-dependent diabetes mellitus in a subject comprising administration of a self-vector encoding and capable of expressing human proinsulin." ([0009])

(3) "[0016]
DETAILED DESCRIPTION

In Type 1 diabetes mellitus there is an intense inflammatory response that destroys the β cells in the islets of Langerhans in the pancreas, the site where insulin is produced and released. Proinsulin is a major target of the adaptive immune response in Type 1 Diabetes (T1D). The present invention provides an engineered DNA plasmid encoding proinsulin (BHT-3021) that preserves β cell function in T1D patients through reduction of insulin-specific CD8 T cells. BHT-3021 is designed to decrease the antigen-specific autoimmune response against proinsulin in T1D. The plasmid was engineered with reduced numbers of pro-inflammatory hexa-nucleotide motifs, termed CpG motifs. CpG hexanucleotide sequences activate innate immune responses by binding to Toll Like Receptor 9 (TLR9) and other DNA sensors (13). ... This antigen-specific plasmid vaccine approach has the theoretical advantage of decreasing the autoimmune response while leaving intact other important, desirable, physiologic roles of the immune system, such as immune regulatory responses against proinsulin, immune surveillance against tumors, and immune responses against infectious agents." ([0016])

(4) "[0017]

The present invention provides compositions and methods of treating, reducing, preventing, and inhibiting insulin-dependent diabetes mellitus (IDDM) by administration of a self-vector encoding and capable of expressing human proinsulin.

As described above, in IDDM, prior to the onset of overt diabetes, there is a long presymptomatic period during which there is a gradual loss of pancreatic β cell function. Markers that can be evaluated include, without limitation, in-blood or in-serum levels of C-peptide as indicative of pancreatic β cell function, the presence of insulitis in the pancreas, the level and frequency of islet cell antibodies, islet cell surface antibodies, the presence and concentration of autoantibodies against autoantigens targeted in IDDM, aberrant expression of Class II MHC molecules on pancreatic β cells, glucose concentration in the blood, and the plasma concentration of insulin. An increase in the number of T lymphocytes in the pancreas, islet cell antibodies, and blood glucose is indicative of the disease, as is a decrease in insulin concentration." ([0017])

(5) "[Examples]
[0058]

In Type 1 diabetes there is an intense inflammatory response that destroys the β cells in the islets of Langerhans in the pancreas, the site where insulin is produced and released. Proinsulin is a major target of the adaptive immune response in Type 1 Diabetes (T1D). The present invention provides an engineered DNA plasmid encoding proinsulin (BHT-3021) that preserves β cell function in T1D patients through reduction of insulin-specific CD8 T cells. ... .proinsulin-reactive CD8 T cells, but not T cells against unrelated islet or foreign molecules, declined in the BHT-3021 arm ($p<0.006$). ... No significant changes were noted in Interferon-γ, IL-4, or IL-10 production in CD4 T cells. Thus, we demonstrate that a plasmid encoding proinsulin reduces the frequency of CD8 T cells reactive to proinsulin, while preserving C-peptide over the course of dosing." (paragraph [0058])

(6) "[0093] ... In this study we have attempted to modulate, in an antigen-specific manner, the adaptive immune response to proinsulin with an engineered DNA vaccine encoding proinsulin. The vaccine is engineered to reduce the immunogenicity of the encoded proinsulin by substituting CpG hexameric motifs, which stimulate the innate immune response, with GpG hexameric nucleotide sequences, known to modulate innate immunity (13). Here we show that this approach modulated C-peptide, with an actual rise in this marker of β cell function during the dosing period at two doses. We also demonstrate that as the C-peptide increases there is a deletion of CD8 T cells reactive to proinsulin, but there is no effect on other antigen specific T cell responses. This is a firm indication that antigen specific modulation has occurred." ([0093])

3. Reasons for refusal stated in the examiner's decision

Among the reasons for refusal stated in the examiner's decision, the outline of the reason citing Article 29(1)(iii) of the Patent Act against Invention 1 is as follows:

The invention recited in Claim 1 of the present application is the invention disclosed in Cited Document 1 that was made publicly available through an electric telecommunication line in Japan or a foreign country before the priority date of the present application and thus falls under the provisions of Article 29(1)(iii) of the Patent Act. Therefore, the Appellant should not be granted a patent for it.

<List of Cited Documents, etc.>

1. International Publication No. WO 2010-151420

4 Described matters in Cited Document 1 and the invention disclosed in Cited Document 1

(1) Matters described in Cited Document 1 (International Publication No. WO 2010-151420) cited in the examiner's decision

Since Cited Document 1 is an English document, the corresponding descriptions were translated into Japanese by the body. The underlines were added by the body.

A "1. A method of reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM), the method comprising administering intramuscularly to the subject a DNA plasmid vector encoding a self-protein comprising an epitope associated with IDDM, wherein the administration of the DNA plasmid vector is according to a regimen comprising a combination of:

(a) a therapeutically effective amount of the DNA plasmid vector of 0.3 to 6 mg;

(b) a dose frequency of weekly or bi-weekly dosing; and,

(c) a period of dosing selected from the group consisting of continuous dosing, four (4) weeks, six (6) weeks, twelve (12) weeks, twenty-four (24) weeks, one (1) year, eighteen (18) months, and two (2) years.

3. The method of Claim 1, wherein the DNA plasmid is BHT-3021.

19. The method of Claim 1, wherein a reduction in the severity of IDDM in the subject is indicated by one or more measures selected from the group consisting of increased or stabilized levels of C-peptide, increased or stabilized levels of glycosylated hemoglobin,

decreased hyperglycemia, increased plasma insulin, decreased glucosuria, decreased insulitis, decreased destruction of β cells, and decreased presence of autoantibodies.

21. A method of reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM), the method comprising administering intramuscularly to the subject a DNA plasmid vector of SEQ ID NO: 1 (BHT-3021), wherein the administration of the DNA plasmid vector is according to a regimen comprising administering a dose of 0.3 to 6 mg of the DNA plasmid vector weekly for 12 weeks followed by administering a dose of 0.3 to 6 mg of the DNA plasmid vector bi-weekly for 6 weeks; wherein the regimen is repeated once per year."
(The Scope of Claims, Claims 1, 3, 19, and 21)

B "[0125] Figure 3: Reduction in antibodies to insulin in patients treated with a proinsulin encoding DNA plasmid vector. In a phase 1/2 trial, type 1 diabetic patients who were positive for anti-insulin antibodies at baseline (week 0) were treated with 12 weekly intramuscular 1 mg injections of a proinsulin encoding DNA plasmid vector (BHT-3021) constructed from the pBHT1 plasmid backbone. Antibody titers to three pancreatic autoantigens were measured at weeks 0, 2, 4, 6, 8, and 15 where available. The three antibodies, measured by radioimmunoassay and expressed as radioactivity index units, are antibodies to GAD, ICA512, and insulin (mIAA). In panel A is a patient treated with placebo (saline) injections who had positive antibody titers to GAD and insulin at baseline, but whose antibody titers did not change with treatment. In panel B is a patient treated with BHT-3021 who had positive antibody titers to GAD and insulin at baseline, and whose antibody titers to insulin decreased with treatment. In panel C is a patient treated with BHT-3021 who had positive antibody titers to ICA512 and insulin at baseline, and whose antibody titers to insulin decreased with treatment. These data demonstrate that BHT-3021 causes antigen-specific immune tolerance as demonstrated by rapid and sustained reductions in anti-insulin titers.
[0126] Figure 4: Preservation of C-peptide in human patients treated with a proinsulin encoding DNA plasmid vector. As a measure of residual pancreatic β cell function, blood C-peptide levels were measured in these same patients at baseline (BL), week 5, week 15, and month 6, where available. In panel A is the patient treated with placebo whose C-peptide level steadily declines with no treatment. In panel B are the two patients treated with BHT-3021 whose C-peptide levels show either a less rapid decline or a slight increase in value, thus indicating preservation of β cell function.
[0127] Figure 5 illustrates the preservation of C-peptide in human patients receiving

anti-CD3 antibody (according to the protocol published in Herold, et al, Diabetes (2005) 54:1763-1769) or different doses of BHT-3021. Weekly administration of 1 mg, 3 mg, and 6 mg doses of BHT 3021 over a period of 12 weeks demonstrated comparable C-peptide preservation at 6 months in comparison to the non-specific therapy of administration of anti-CD3 antibody.

[0128] Figure 6 illustrates mean C-peptide levels in human patients receiving different weekly doses of BHT-3021 over a period of 6 months. Whereas C-peptide levels decreased in patients receiving the BHT-placebo, patients receiving weekly administration of 1 mg, 3 mg, and 6 mg doses of BHT 3021 over a period of 12 weeks had stabilized or increased mean C-peptide levels measured at 6 months after the first administration.

...

[0132] Figure 10 demonstrates changes in glycosylated hemoglobin HbAIc levels over a period of 6 and 12 months in patients receiving weekly administration of 0.3 mg, 1 mg, 3 mg, or 6 mg doses of BHT 3021 over a period of 12 weeks. HbAIc is lower in blood from patients treated with BHT-3021 in comparison to blood from patients receiving the placebo." ([0125] to [0132])

C "[0135] The Non-Obese Diabetic (NOD) mouse is an animal model with many clinical, immunological, and histopathological features in common with human IDDM. NOD mice spontaneously develop inflammation of the islets and destruction of the β cells, which leads to hyperglycemia and overt diabetes. Both CD4+ and CD8+T cells are required for diabetes to develop, although the roles of each remain unclear. It has been shown that administration of insulin or GAD, as proteins, under tolerizing conditions to NOD mice prevents disease and down-regulates responses to the other autoantigens."

D "[0177] In some embodiments, the present invention provides a self-vector or DNA plasmid vector of SEQ ID NO:1 (BHT-3021). The self-vector BHT-3021 comprises a BHT-I expression vector backbone and a polynucleotide encoding human proinsulin.

[0178] ... The pVAX1 vector is known in the art and is commercially available from Invitrogen (Carlsbad, CA). ... " ([0177] to [0178])

E "[0219] ...

Example 2:

Reduction in antibodies to insulin in patients treated with a DNA vector encoding

proinsulin (BHT-3021).

[0220] This study investigated whether treatment of patients having IDDM with BHT-3021 reduced the level of anti-insulin antibody titers in the patients.

[0221] In a phase 1/2 trial, type 1 diabetic patients who were positive for anti-insulin antibodies at baseline (week 0) were treated with 12 weekly intramuscular 1 mg injections of a proinsulin encoding DNA plasmid vector (BHT-3021) constructed from the pBHT1 plasmid backbone. Each patient was also taking insulin. The plasmid vector was delivered in a pharmaceutically acceptable carrier containing a physiological concentration of calcium (about 0.9 mM). Antibody titers to three pancreatic autoantigens were measured at weeks 0, 2, 4, 6, 8, and 15 where available. The three antibodies, measured by radioimmunoassay and expressed as radioactivity index units, are antibodies to GAD, ICA512, and insulin (mIAA).

[0222] For a patient treated with placebo (saline) injections, positive antibody titers to GAD and insulin were detected at baseline, but those antibody titers did not change with treatment (Figure 3A). A patient treated with BHT-3021 also had positive antibody titers to GAD and insulin at baseline (Figure 3B); with treatment, the patient's antibody titers to insulin decreased. Another patient treated with BHT-3021 had positive antibody titers to ICA512 and insulin at baseline (Figure 3C); with treatment, that patient's antibody titers to insulin decreased. These data demonstrate that BHT-3021 causes antigen-specific immune tolerance as demonstrated by rapid and sustained reductions in anti-insulin titers.

Example 3:

Preservation of C-peptide as an indicator of β cell function in patients treated with a DNA plasmid vector encoding proinsulin (BHT-3021).

[0223] This study investigated whether treatment of patients having IDDM with BHT-3021 preserved the function of β cells.

[0224] In the same type I diabetic patients represented in Example 2, blood C-peptide levels were determined as a measure of residual pancreatic β cell function. Blood C-peptide levels were measured at baseline (BL), week 5, week 15, and month 6, where available. The patient who received placebo (saline) injections exhibited a blood C-peptide level that steadily declined with no treatment (Figure 4A). The two patients who were treated with BHT-3021, however, exhibited either blood C-peptide levels that declined less rapidly or that increased in value slightly (Figure 4B), indicating preservation of β cell function.

Example 4:

Treatment Regimen 1:

Dose (1 mg), Dose Frequency (Weekly) and Dose Period (Twelve Weeks)

[0225] BHT-3021 or BHT-placebo was co-administered intramuscularly to human subjects weekly for 12 weeks (Weeks 0 to 11), along with insulin. Approximately 72 subjects were enrolled overall. Evaluation of four dose levels of BHT-3021 was carried out: 0.3 mg, 1 mg, 3 mg, and 6 mg.

[0226] BHT-3021 and BHT-placebo were given as intramuscular (IM) injections into the deltoid muscles administered once weekly for 12 weeks. If the subject could not tolerate an IM injection in the deltoid muscle, then IM injection in the quadriceps femoris muscle was performed. The volumes injected were adjusted based upon the dose level: 0.15 mL for the 0.3 mg dose (i.e., 2 mg/ml), 0.5 mL for the 1 mg dose, 1.5 mL for the 3 mg dose, and 3 mL (two injections) for the 6 mg dose. The 0.15 mL, 0.5 mL, and 1.5 mL volume injections were given into a single muscle site. Injection sites were rotated as necessary. For example, if the drug was injected in the right deltoid in Week 0, the drug was injected in the left deltoid the following week. The 3 mL volume injections for delivering 6 mg of the drug were divided into two 1.5 mL volume injections and were given into two separate muscle sites.

[0227] The results of patient evaluations at the 6-month and 12-month time points, as indicated by preservation of C-peptide levels and glycosylated hemoglobin HbAIc levels, are shown in Figures 5-9.

(Note by the body: Considering the description of Figure 10 of [0132] and the fact that the number of subjects is the same for each prescription amount (Figures 6 and 10), it is recognized that the evaluation results of [0227] include Figure 10 in addition to Figures 5 to 9.)

F "Figure 3

Figure 3A

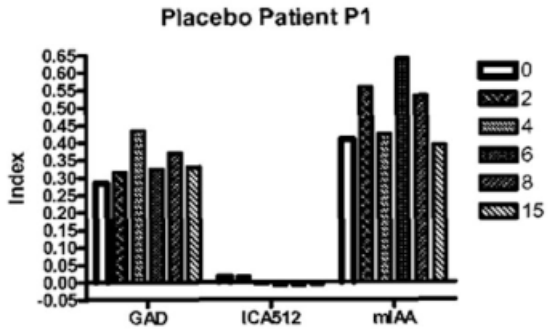


Figure 3B

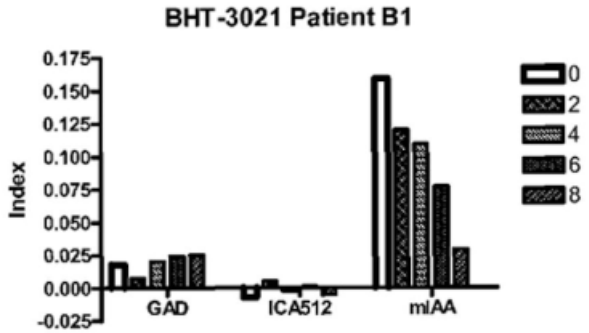


Figure 3C

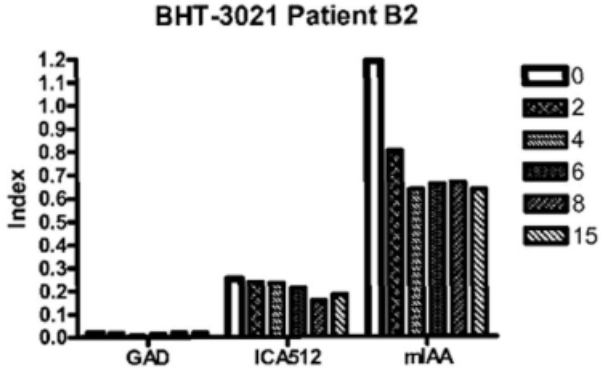


Figure 4A

Figure 4A

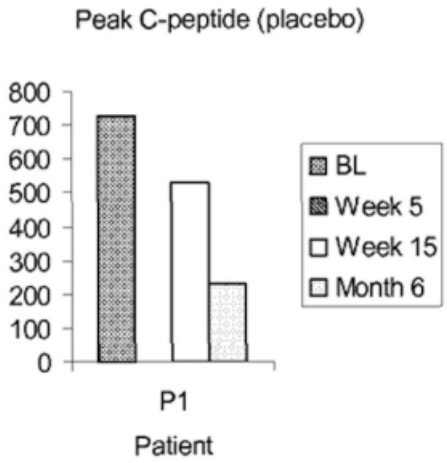


Figure 4B

Figure 4B

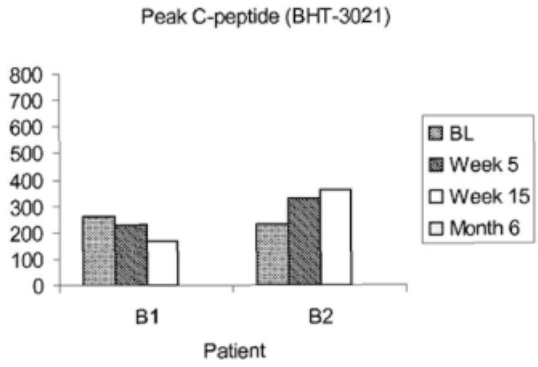


Figure 5

Figure 5

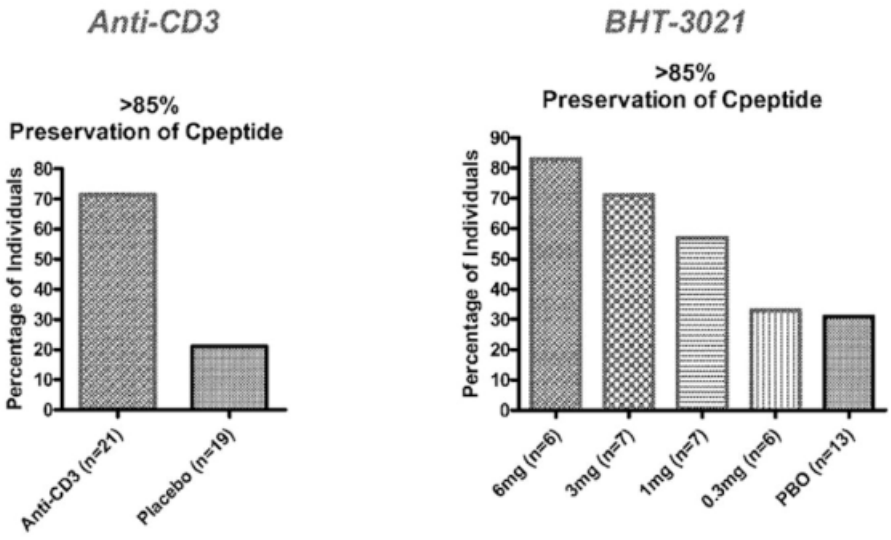


Figure 6

Figure 6

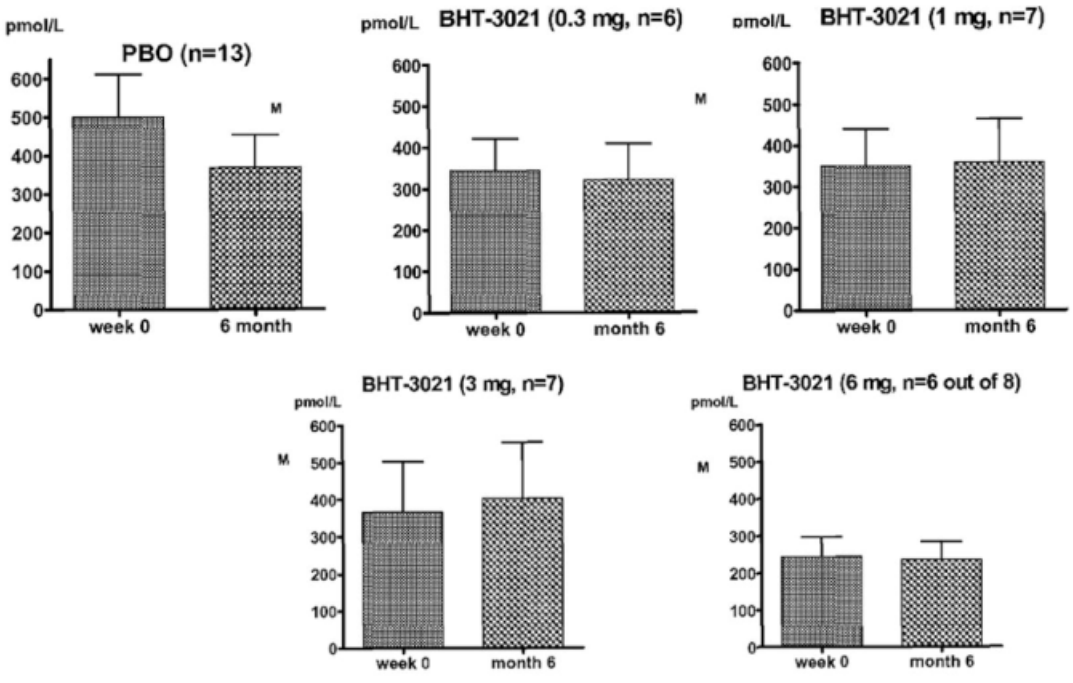
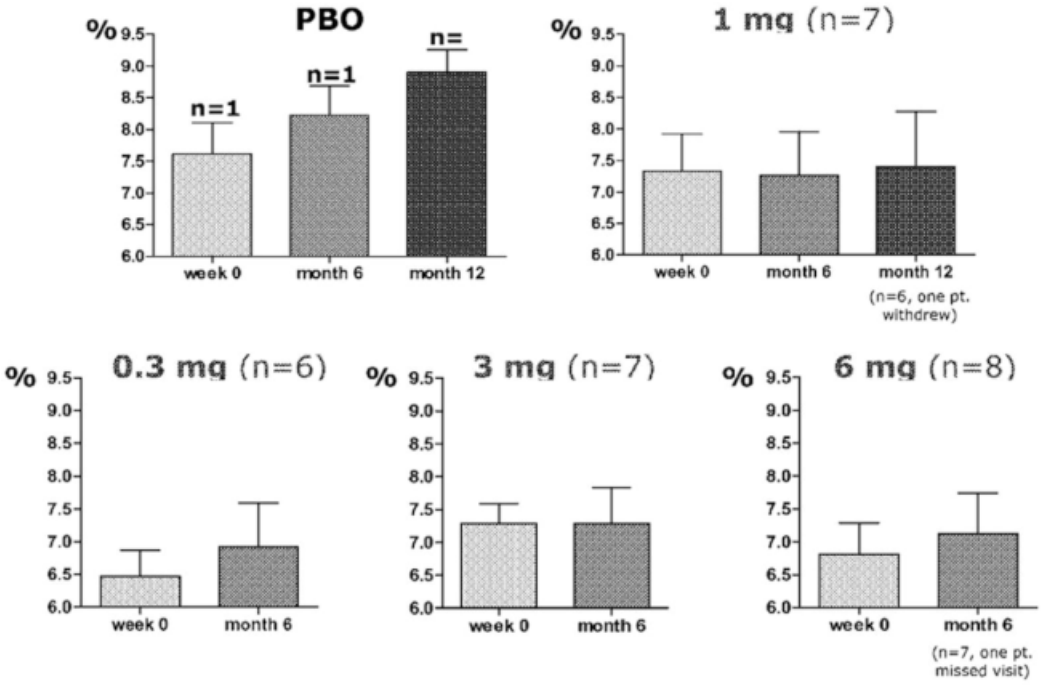


Figure 10

Figure 10



" (Figures 3, 4A, 4B, 5, 6, and 10)

G "

SEQ ID NO:1 (BHT-3021)

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GCATGCTGGGGATGCGGTGGGCTCTATGGCTTCTACTGGGCGGTTTTATGGACAGCAAGCGAACCGGAATTGCCA
GCTGGGGCGCCCTCTGGTAAGGTTGGGAAGCCCTGCAAAGTAAACTGGATGGCTTTCTTGCGGCCAAGGATCTGA
TGGCGCAGGGGATCAAGCTCTGATCAAGAGACAGGATGAGGATGGTTTCGCATGATTGAACAAGATGGATTGCAC
GCAGGTTCTCCGGCAGCTTGGGTGGAGAGGCTATTCGGCTATGACTGGGCACAACAGACAATCGGCTGCTCTGAT
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CCTGCCGAGAAAGTATCCATCATGGCTGATGCAATGCGGCGGCTGCATACGCTTGATCCGGCTACCTGCCCATTC
GACCACCAAGCGAAACATCGCATCGAGCGAGCACGTACTCGGATGGAAGCCGGTCTTGTCGATCAGGATGATCTG
GACGAAGAGCATCAGGGGCTCGCGCCAGCCGAACTGTTCGCCAGGCTCAAGGCGAGCATGCCCGACGGCGAGGAT
CTCGTCGTGACCCATGGCGATGCCTGCTTGCCGAATATCATGGTGGAAAATGGCAGGTTTTCTGGATTCATCGAC
TGTGGCCGGCTGGGTGTGGCGGACAGGTATCAGGACATAGCGTTGGCTACCCGTGATATTGCTGAAGAGCTTGGC
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CTTCTTGACGAGTTCTTCTGAATTATTAACGCTTACAATTTCCTGATGCGGTATTTTCTCCTTACGCATCTGTGC
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CAAGAACTCTGTAGCACCGCCTACATACCTCGCTCTGCTAATCCTGTTACCAGTGGCTGCTGCCAGTGGCGATAA
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GTGCACACAGCCCAGCTTGGAGCGAACGACCTACACCGAACTGAGATACCTACAGCGTGAGCTATGAGAAAGCGC
CACGCTTCCCGAAGGGAGAAAGGCGGACAGGTATCCGGTAAGCGGCAGGGTCGGAACAGGAGAGCGCACGAGGGA
GCTTCCAGGGGGAAACGCCTGGTATCTTTATAGTCCTGTCGGGTTTCGCCACCTCTGACTTGAGCGTCGATTTTT
GTGATGCTCGTCAGGGGGGCGGAGCCTATGGAAAAACGCCAGCAACGCGGCCTTTTTACGGTTCCTGGCCTTTTG
CTGGCCTTTTGCTCACATGTTCTT

" (SEQ ID NO:1, BHT-3021)

(2) Cited Invention

In the above (1)A, Claim 3, which depends from Claim 1, is as follows:

"A method of reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM), the method comprising administering intramuscularly to the subject a DNA plasmid vector encoding a self-protein comprising an epitope associated with IDDM, wherein the DNA plasmid is BHT-3021 and the administration of the DNA plasmid vector is according to a regimen comprising a combination of:

(a) a therapeutically effective amount of the DNA plasmid vector of 0.3 to 6 mg;

(b) a dose frequency of weekly or bi-weekly dosing; and,

(c) a period of dosing selected from the group consisting of continuous dosing, four (4) weeks, six (6) weeks, twelve (12) weeks, twenty-four (24) weeks, one (1) year, eighteen (18) months, and two (2) years."

In addition, it can be said that a plasmid vector is used in the preparation of "a composition for reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM)" from the descriptions relating a formulation; i.e., the description "The plasmid vector was delivered in a pharmaceutically acceptable carrier containing a physiological concentration of calcium (about 0.9 mM)." in Example 2 of Description E as well as the description "the volumes injected were adjusted based upon the dose level: 0.15 mL for the 0.3 mg dose (i.e., 2 mg/ml), 0.5 mL for the 1 mg dose, 1.5 mL for the 3 mg dose, and 3 mL (two injections) for the 6 mg dose." in Example 4.

Furthermore, in Examples 3 and 4 of Description E, there is described preservation of C-peptide as an indicator of β cell function in type 1 diabetic patients who were patients having IDDM (see Description B for the descriptions in the figures mentioned in the examples).

Then, Cited Document 1 can be recognized to disclose the following invention:

"A use of a DNA plasmid encoding a self-protein comprising an epitope associated with IDDM, which is BHT-3021, in preparation of a composition that preserves C-peptide as an indicator of β cell function, wherein the composition is a composition for reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM)." '(hereinafter, referred to as "Cited Invention 1")

(3) Comparison / Judgment

A Comparison

Invention 1 and Cited Invention 1 are compared.

"A subject afflicted with insulin dependent diabetes mellitus (IDDM)" in Cited Invention 1 corresponds to "a subject" in Invention 1, and "reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM)" in Cited Invention 1 corresponds to "treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject." in Invention 1.

Furthermore, considering that a nucleic acid sequence represented by SEQ ID NO: 1 of Description A is the same as the nucleic acid of SEQ ID NO: 1 of the present application in addition to considering the descriptions " a DNA plasmid vector of SEQ ID NO: 1" in Claim 21 of Description A and "SEQ ID NO: 1 (BHT-3021) and " self-vector BHT-3021" in Description D, "a DNA plasmid encoding a self-protein

comprising an epitope associated with IDDM, which is BHT-3021" in Cited Invention 1 corresponds to "a self-vector having a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 (BHT-3021)" in Invention 1.

Then, Invention 1 and Cited Invention 1 are in correspondence in the following point:
"a use of a self-vector having a nucleic acid sequence at least 95% identical to SEQ ID NO: 1 (BHT-3021) in preparation of a composition" for
"treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject,"
and are prima-facie different from each other in the following different feature.

<Different Feature>

In Invention 1, "a composition" is one "for reducing the frequency of proinsulin-reactive CD8 T cells" in "treatment or prevention of IDDM in a subject." In Cited Invention 1, on the other hand, "a composition" is one "that preserves C-peptide as an indicator of β cell function" but is not specified as one "for reducing the frequency of proinsulin-reactive CD8 T cells."

B Judgment

Considering the descriptions in Example 3 of the above 4(1)E, the wording "preserves C-peptide as an indicator of β cell function" in Cited Invention 1 indicates "preservation of β cell function" in a subject afflicted with IDDM.

On the other hand, as stated in the above 2(1) and (2), Invention 1 relates to a composition for treating insulin-dependent diabetes mellitus. As stated in the above 2(2) to (6), the Detailed Description of the Invention of the specification of the present application describes that the self-vector BHT-3021 reduces the frequency of CD8 T cells reactive to proinsulin, while preserving C-peptide serving as a marker of pancreatic β cell function to preserve β cell function in T1D patients with IDDM.

Then, the two inventions are identical in that each of them discloses a use of a self-vector BHT-3021 in preparation of a composition that preserves β cell function for treating or preventing IDDM in a subject. Thus, it cannot be said that the description about the functional mechanism "for reducing the frequency of proinsulin-reactive CD8 T cells" allows the composition recited in Invention 1 to be provided with a new application in which therapeutic objects and the like are different from those for the composition disclosed in Cited Invention 1 "for reducing disease severity in a subject afflicted with insulin dependent diabetes mellitus (IDDM)"; i.e., for "treatment of

insulin-dependent diabetes mellitus (IDDM) in a subject."

Therefore, the above Different Feature is not a substantial difference. Invention 1 is an invention disclosed in Cited Document 1.

C Appellant's allegation

Against the reasons for refusal stated in the examiner's decision in the above 3, the Appellant alleges in the written opinion and the written amendment of the request for appeal as follows:

a. The Invention is provided based on the fact that the self-vector BHT-3021 is capable of reducing the frequency of proinsulin-reactive CD8 T cells. The correlation between the reduction in the frequency of proinsulin-reactive CD8 T cells and an improvement in C-peptide levels; i.e., the correlation between the reduction and the therapeutic or prophylactic effect on IDDM, is not described in Cited Document 1 (the written opinion, 2. (1)(iii) and (2)(i) and (ii); and the written amendment of the request for appeal, V.1.(2) and (3)).

b. The Invention is one that adopts "proinsulin-reactive CD8 T cells" as a new constituent element, which has not been known to those skilled in the art, from among many autoimmune responses. In other words, there is provided an invention having a completely new effect that the reduction of proinsulin-reactive CD8 T cells has a correlation with the therapeutic effect of IDDM. (the written opinion, 2. (1)(vii)).

However, as stated in the above A, Invention 1 and Cited Invention 1 are inventions each using the self-vector BHT-3021 in preparation of a composition used for treatment or prevention of IDDM patients. Incidentally, as stated in the above 4(1), the self-vector BHT-3021 is a DNA plasmid vector encoding proinsulin. Even though Invention 1 reveals that treatment of IDDM patients with this vector reduces proinsulin-reactive CD8 T cells, as stated in the above B, this is not the reason why the use of a self-vector in preparation of a composition is different from Cited Invention 1.

Therefore, it cannot be said that the reasons for refusal stated in the examiner's decision have been resolved by the Appellant's allegation.

The Appellant also alleges in the same written opinion as follows:

" Cited Document 1 has no description or suggestion that the adoption of self-vector BHT-3021 should have been chosen to attempt reducing the frequency of proinsulin-reactive CD8 T cells for the purpose of providing a composition effective for treatment or prevention of insulin-dependent diabetes mellitus (IDDM) in a subject. Conceiving

such a constituent element is nothing but an act that deviates greatly from the technical common sense before the priority date of the present application. ... " (the written opinion, 2. (3)).

The Appellant's allegation does not constitute a direct counterargument to the reasons for refusal stated in the examiner's decision in the above 3 (corresponding to Article 29(1)(iii) of the Patent Act). As stated in the above 4(1)C, Cited Document 1 describes that inflammation of the islets and destruction of the β cells leads to progression of obvious diabetes in the Non-Obese Diabetic (NOD) mouse, which is an animal model with many clinical, immunological, and histopathological features in common with IDDM and also includes the description about CD8+T cells: "Both CD4+ and CD8+T cells are required for diabetes to develop."

As stated above, although the Appellant's allegations in the written opinion and the written amendment of the request for appeal were examined, Invention 1 is still the invention disclosed in Cited Document 1.

D Summary

Therefore, Invention 1 is the invention disclosed in Cited Document 1 and falls under the provisions of Article 29(1)(iii) of the Patent Act. The Appellant should not be granted a patent for the Invention.

No. 4 Closing

As stated above, the Appellant should not be granted a patent for the invention recited in Claim 1. Thus, the present application should be rejected without considering other claims.

Therefore, the appeal decision shall be made as described in the conclusion.

March 13, 2020

Chief administrative judge: MITSUMOTO, Minako
Administrative judge: YOSHIDA, Tomomi
Administrative judge: OKAZAKI, Miho