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Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

— with international search report (Art. 21(3))
— with sequence listing part of description (Rule 5.2(a))

(54) Title: PEPTIDES AND METHODS FOR THE TREATMENT OF DIABETES

(57) Abstract: The invention relates to peptides such as HCPYCSLQPLALEGSLQKRG and their use in the treatment of type 1 diabetes and the generation of cytolytic CD4⁺ T cell.

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ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

DE CLERCQ & PARTNERS
Edgard Gevaertdreef 10a
9830 Sint-Martens-Latem
BELGIQUE

Date of mailing (day/month/year) 20 November 2018 (20.11.2018)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference IMCY-006-PCT	
International application No. PCT/EP2018/055501	International filing date (day/month/year) 06 March 2018 (06.03.2018)

1. The following indications appeared on record concerning:		
☐ the applicant	☒ the inventor	☐ the agent
☐ the common representative		
Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:		
☒ the person	☐ the name	☐ the address
☐ the nationality		
☐ the residence		
Name and Address SAINT-REMY, Jean-Marie Rue du Lambais, 79 1390 Grez-Doiceau Belgium	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	
3. Further observations, if necessary: The person identified in Box 2 has been added as inventor for all designated States.		
4. A copy of this notification has been sent to:		
☒ the receiving Office	☐ the International Preliminary Examining Authority	
☒ the International Searching Authority	☒ the designated Offices concerned	
☐ the Authority(ies) specified for supplementary search	☐ the elected Offices concerned	
	☐ other:	

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Ulhaq Faizan e-mail pct.team5@wipo.int Telephone No. +41 22 338 74 05
Facsimile No. +41 22 338 70 80	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

To:

De Clercq & Partners
Edgard Gevaertdreef 10a
9830 Sint-Martens-Latem
BELGIQUE

Date of mailing
(day/month/year)

12.06.2019

Applicant's or agent's file reference
IMCY-006-PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2018/055501

International filing date (day/month/year)
06.03.2018

Priority date (day/month/year)
09.03.2017

Applicant
ImCyse SA

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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D-80298 Munich
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Authorized Officer

Papiol Rovira, M

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IMCY-006-PCT	FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2018/055501	International filing date (day/month/year) 06.03.2018	Priority date (day/month/year) 09.03.2017	
International Patent Classification (IPC) or national classification and IPC INV. C07K14/62			
Applicant ImCyse SA			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>7</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>5</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned conclusion under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☒ Box No. VIII Certain observations on the international application			
Date of submission of the demand 02.01.2019		Date of completion of this report 12.06.2019	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Voigt-Ritzer, Heike Telephone No. +49 89 2399-7187	



INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2018/055501

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-33 as originally filed

Sequence listings, SEQ ID NO

1-26 as originally filed

Claims, Numbers

1-13 filed in electronic form on 16-04-2019

Drawings, Sheets

1/2, 2/2 as originally filed

- ☒ a sequence listing - see Supplemental Box Relating to Sequence Listing.
3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 1-15
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2018/055501

5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).
6. ☒ With regard to top-up searches (Rules 66.1ter and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 05.02.2019 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-9, 13</u>
	No: Claims	<u>10-12</u>
Inventive step (IS)	Yes: Claims	<u>1-9, 13</u>
	No: Claims	<u>10-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-13</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed:
 - ☒ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13~~ter~~.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search and/or examination:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13~~ter~~.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13~~ter~~.1(b) and Administrative Instructions, Section 713).
 - d. ☐ furnished to this Authority as an amendment* under PCT Article 34 on :
 - ☐ in the form of an Annex C/ST.25 text file, and preferably identified as "Amended" at the first line of text.
 - ☐ on paper or in the form of an image file.
2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

* *If item 4 in Box No. I applies, the sequence listing, which forms part of the basis of the report, may be marked "superseded."*

Reference is made to the following documents:

- D1 WO 2016/059236 A1 (IMCYSE SA [BE]) 21 April 2016 (2016-04-21)
- D3 WO 2008/017517 A1 (DESIRE COLLEN RES FOUNDATION V [BE]; SAINT-REMY JEAN-MARIE [BE]) 14 February 2008 (2008-02-14)

The present application relates to means and methods for the generation of insulin specific cytolytic CD4⁺ T cells for the treatment of diabetes. The T cells are generated by the interaction with APCs presenting a known insulin antigen fused to a modified redox motif.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Novelty

- 1.1 Novelty can be acknowledged for claims 1-9, 13.
- 1.2 Claims 10-12 refer to a cell population which is not defined by technical features but by the way they were produced. The CD4⁺Tc population has been generated for the specific peptide encoded by Seq ID No:26 which comprises the insulin epitope LALEGLSLQK linked to a redox motif by a 4 aa long linker (SLQP). The thus obtained T cell population was compared to the T cell population generated by the peptide encoded by Seq ID No:108 of D1 which differs from Seq ID No:26 only by a 2 aa extension of the linker N-terminally to said epitope (VRSLQP).
- 1.3 There is no teaching in the prior art or in the present application which allows the conclusion that the extension of the linker alters TCR selection.
- 1.4 Comparative experimental data presented in Figure 1 and Table 1 show a marked increase in IFN- γ cytokine secretion and cytotoxic potential (FasL expression) in the CD4⁺ T cell population generated with the peptide encoded

by Seq ID No:26. However, it is considered that the amount of IFN- γ secretion and FasL expression is variable for any given cell population depending on the culture parameters.

It therefore has to be assumed that the claimed CD4+ T cell population carries the same TCRs as the population of D1 and therefore cannot be told apart from it. The subject-matter of claims 10-12 lacks novelty according to Article 33(2) PCT.

2 Inventive step

From the prior art it was known that inclusion of a redox motif within the flanking residues of MHC II epitopes polarizes CD4+ T cells to cytolytic cells capable of inducing apoptosis in APCs displaying peptides through MHCII molecules (D1, D3).

D1 which is considered as closest prior art suggests the use of a fusion peptide (Seq ID No:108, page 49) comprising the insulin epitope LALEGS LQK in combination with a redox motif and a 6 aa linker for the generation of CD4+ cytolytic T-cells (page 4, lines 12-24) and the treatment of diabetes (page 3, lines 10-11).

The problem to be solved in light of D1 is the provision of an alternative mean and method for the treatment of diabetes.

The solution provided by claim 1 is the peptide encoded by Seq ID No:26.

Seq ID No:26 differs from Seq ID No:108 of D1 by the deletion of two amino acids from the linker sequence VRSLQP (giving rise to the linker SLQP). The redox motif and the epitope are identical in both peptides.

Surprisingly, this linker modification gives rise to a peptide (Seq ID No:26) which is superior in producing cytolytic CD4+ T cells. As pointed out by the applicant and in the application as filed does the cytolytic T cell population obtained after stimulation with B cells presenting Seq ID No:26 (called "P17-003") in a MHCII context secretes more IFN- γ and expresses more FasL than the cytolytic T cell population stimulated with Seq ID No:108 (called "P17-001") of D1.

For claim 5 inventive step can be acknowledged. Claims 1-4 are related to the peptides which have the same linker and insulin epitope as Seq ID No:26. It is presently assumed that the contribution of the invention resides in the linker between the thioredox motif and the insulin epitope.

Therefore, inventive step, according to the requirements of Article 33(3) PCT, can be acknowledged for claims 1-9 and 13.

Re Item VIII

Certain observations on the international application

3 Clarity

Claims 10-12 refer to a cell population which is not defined by technical features but by the way they were produced. The skilled person working with a certain population of cytolytic CD4+ cells can test whether or not said cells are responsive to a given insulin epitope and whether this response comprises the secretion of IFN- γ and expression of FasL. The amount of IFN- γ secretion and FasL expression however is variable for any given cell population depending on the culture parameters.

Moreover, amended claim 10 is no longer limited to a CD4+ T population generated by Seq ID No:26 but embraces CD4+ T cell populations generated by partially undefined 50 aa long peptide.

The skilled person therefore cannot clearly determine whether or not he infringes the scope of claims 10-12, contrary to the requirements of Article 6 PCT.

European Patent Office
PB 5818 – Patentlaan 2
NL-2280 HV Rijswijk
Nederland

Online filing

Sint-Martens-Latem, April 16, 2019

Our ref. : IMCY-006-PCT
Subject : International Patent Application No. PCT/EP2018/055501 filed on March 6, 2018
In name of ImCyse SA

Dear Madam,
Dear Sir,

This is in response to the Written opinion of the International Preliminary Examining Authority (PCT/IPEA/408) issued on February 21, 2019. Applicant respectfully requests that examination be continued based on the set of claims as submitted herewith.

It is respectfully submitted that the amendments do not go beyond the disclosure in the International application as filed, thereby complying with Art. 19(2) PCT.

All amendments have been made without prejudice to the possibility of future reinstatement of any excluded subject matter and/or subsequent filing of divisional applications based on any matter contained in the application as filed. Any amendments made by the way of the present letter, and the observations contained herein, are made solely for the purposes of the prosecution of this International patent application and without prejudice to the applicant to other jurisdictions.

Claim amendments

Original claims 10 and 11 have been merged and now form independent claim 1. As you will appreciate, claim 1 is an embodiment of combined claims 10 and 11, limited to the specific insulin epitope, fused to a thioredox motif by the specific linker.

Original claim 15 has been removed from the application. Original claims 12-14 have been moved to now constitute amended claims 2-4. Further, previously independent claim 1 is now incorporated as dependent claim 5. Dependencies of the set of claims have been adjusted accordingly.

These amendments do not extend the subject matter beyond the content of the application as filed.

MAIN OFFICE

Edgard Gevaertdreef 10a
B-9830 Sint-Martens-Latem
Belgium

LEUVEN BRANCH

Groenveldstraat 13
B-3001 Leuven (Heverlee)
Belgium

Clarity

A clarity objection is raised for claims 6-8 (now amended claims 10-12) as these claims allegedly describe the resulting CD4+ T cell population in the way they are produced and not by technical features. The examiner states that a person skilled in the art can test whether or not the cells are responsive to the insulin epitope and whether this response comprises the secretion of IFN- γ and expression of FasL. However, it is stated that the amounts are dependent on cell population and culture parameters.

We respectfully disagree with this objection. Regarding IFN- γ release, example 3 is a comparative example between cytolytic CD4+ T cells co-cultured with LCL B cells loaded with either peptide p17-001 (HCPYCVRSLQPLALEGSLQKRG) or p17-003 (HCPYCSLQPLALEGSLQKRG). The IFN- γ production in the condition using the p17-003 peptide is about 3 times the level of the condition wherein p17-001 is used. Any conducted experiment would result in a similar striking difference of IFN- γ production. Therefore, any experiment investigating IFN- γ production would need to be a comparative experiment that includes a baseline condition. A skilled person can therefore readily confirm whether he infringes the scope of claims 6-8 by including at least one of the peptides p17-001 or p17-003 in his experiment. A skilled person would not use different culture conditions within one experiment. As the examiner rightfully points out, IFN- γ production is in addition variable for any given cell population. Thus, attributing a value to the IFN- γ production holds limited to no value.

The same reasoning applies mutatis mutandis to FasL expression (example 4).

We therefore submit that amended claims 10-12 of the current application are in compliance with Art. 6 PCT, as these have a sufficiently precise meaning taking into account the common general knowledge and having regard to its context in the light of the description.

Novelty

According to the examiner, original claims 6 and 8 allegedly lack novelty due to the disclosure of D1. In D1 a similar epitope, SLQPLALEGSLQKRG, has been used to generate cytotoxic CD4+ T cell populations. It is stated that since the only difference of the epitope used in the current application and D1 is the removal of an N-terminal dipeptide (VR) from the epitope, the resulting CD4+ T cell population carries the same TCRs in both teaching. The resulting cell populations can hence allegedly not be differentiated from each other.

However, we respectfully submit that the CD4+ T cells can be clearly distinguished from CD4+ T cells obtained by different immunogenic epitopes. This is evidenced by examples 3-5 regarding FasL expression and IFN- γ secretion in the application as filed. As elaborated on in the clarity section above, both parameters are clearly defined in the description. The cytolytic CD4+ T cells obtained by the method indicated are different from any cytolytic CD4+ T cells obtained by insulin epitopes described in the art.

Therefore new claims 10-12 fulfill the novelty requirements of Art. 33(2) PCT.

Inventive step

It is stated that original claims 10-15 lack an inventive step. We disagree with this opinion. The peptides covered by these claims share the same linker and insulin epitope to the peptide described in original claim 1. As an inventive step is acknowledged for original claim 1, this should be extended to amended claims 1-5 since the invention resides in the linker between the thioredox motif and the insulin epitope.

D1 is considered as closest prior art and suggests the use of a fusion peptide comprising the insulin epitope LALEGLSLQK, a 6 residue linker and a redox motif. As stated by the examiner, the problem to be solved is the provision of an alternative mean and method for the treatment of diabetes. Surprisingly, using a shorter linker compared to the one used in D1 leads to improved generation of cytolytic CD4+ T cells, with the T cells being characterized by elevated IFN- γ secretion and FasL expression.

An inventive step is acknowledged for original claims 1 to 5. Claim 1 describes a specific immunogenic peptide comprising an N-terminal histidine residue, a thioredox motif, a specific 4 amino acid linker and an insulin epitope. In original claims 11 to 15, the same peptide is claimed but with different thioredox motifs. In the Written Opinion, it is stated that it is unclear which technical problem is solved by original claims 11 to 15.

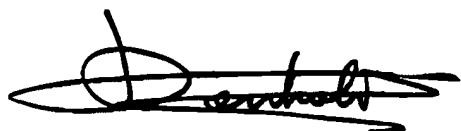
By the amendments indicated above, the claims have been restructured. All peptides described in amended claims 1-5 provide possible results to the problem of providing an alternative means and method for the treatment of diabetes which was deemed to be solved by original claim 1 (now amended claim 5). The claims share a common concept, i.e. the specific linker between the thioredox motif and the specific insulin epitope.

Since an inventive step is acknowledged for original claims 1-5, the presence of an inventive step is evident for the new set of claims regarding the collection of immunogenic peptides.

Amended claims 10-12 focusing on the cytolytic CD4+ T cells are novel and unambiguously derived from the use of the new and inventive immunogenic peptides of claims 1-5. Hence, an inventive step should also be acknowledged for these claims.

We therefore submit that an inventive step should be acknowledged for the set of claims as a whole in compliance with Art. 33(3) PCT.

Respectfully submitted,



Mr. VANHALST, Koen
Professional Representative before the EPO

CLAIMS

1. An isolated immunogenic peptide with a length of between 12 and 50 amino acids, comprising the sequence Cxx[CST]SLQPLALEGSLQK [SEQ ID NO: 4] or [CST]xxCSLQPLALEGSLQK [SEQ ID NO:5].
2. The peptide according to claim 1, comprising the sequence CxxCSLQPLALEGSLQK [SEQ ID NO: 6].
3. The peptide according to claim 1, comprising the sequence HCxx[CST]SLQPLALEGSLQK [SEQ ID NO:7] or H[CST]xxCSLQPLALEGSLQK [SEQ ID NO:8].
4. The peptide according to any one of claims 1 to 3, comprising the sequence HCxxCSLQPLALEGSLQK [SEQ ID NO: 9].
5. The peptide according to any one of claims 1 to 4, consisting of amino acid sequence HCPYCSLQPLALEGSLQKRG [SEQ ID NO: 26].
6. The peptide according to any one of claims 1 to 5 for use as a medicament.
7. The peptide according to any one of claims 1 to 5 for use in the treatment or prevention of type 1 diabetes.
8. A pharmaceutical composition comprising the peptide of any one of claims 1 to 5 and a pharmaceutically acceptable carrier.
9. An in vitro method for the generation of a population of cytolytic CD4+ T cells, against APC presenting insulin epitopes, comprising the steps of:
 - providing peripheral blood cells;
 - contacting said cells in vitro with the peptide of any one of claims 1 to 5; and
 - expanding said cells in the presence of IL-2.
10. A population of cytolytic CD4+ T cells, against APC presenting insulin epitopes, obtainable by the method of claim 9.
11. A population of cytolytic CD4+ T cells, against APC presenting insulin epitopes, obtainable by the method of claim 9, for use as a medicament.

12. A population of cytolytic CD4+ T cells, against APC presenting insulin epitopes, obtainable by the method of claim 9, for use in the treatment or prevention of type 1 diabetes.
13. The isolated immunogenic peptide according to claim 5, for use in treatment or prevention of type 1 diabetes, or for reducing the symptoms of type 1 diabetes.