

PATENT COOPERATION TREATY

RECIBIDO 27 JUL 2023

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

20.07.2023

Applicant's or agent's file reference
907 178

IMPORTANT NOTIFICATION

International application No.
PCT/EP2022/062374

International filing date (day/month/year)
06.05.2022

Priority date (day/month/year)
06.05.2021

Applicant
Institut d'Investigacions Biomèdiques August

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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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 907 178		FOR FURTHER ACTION		See Form PCT/IPEA/416
International application No. PCT/EP2022/062374		International filing date (day/month/year) 06.05.2022		Priority date (day/month/year) 06.05.2021
International Patent Classification (IPC) or national classification and IPC INV. C07K16/28				
Applicant Institut d'Investigacions Biomèdiques August				
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>8</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 statement 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 06.03.2023		Date of completion of this report 20.07.2023		
Name and mailing address of the international preliminary examining authority:  European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016		Authorized officer Pérez-Mato, Isabel Telephone No. +49 89 2399-2128		



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2022/062374

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

1-42 as originally filed

Sequence listings, SEQ ID NO

1-13 as originally filed

Claims, Numbers

1-11 filed with the letter of

06-03-2023

Drawings, Sheets

1/16-16/16 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.
 - ☐ 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/EP2022/062374

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 66.1 ter and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 06.07.2023 (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>1-11</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>1-11</u>
	No: Claims	
Industrial applicability (IA)	Yes: Claims	<u>1-11</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.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."

Summary

The application relates to antibodies to CD19 and their use in CARs.

Cited documents

Reference is made to the following documents:

- D1 WO 2020/180551 A1 (PROMAB BIOTECHNOLOGIES INC [US]; FOREVERTEK BIOTECHNOLOGY CO LTD [CN]) 10 September 2020 (2020-09-10)
- D2 WO 2019/159193 A1 (INDIAN INST TECHNOLOGY BOMBAY [IN]) 22 August 2019 (2019-08-22)
- D3 US 10 221 245 B2 (NOVARTIS AG [CH]; UNIV PENNSYLVANIA [US]) 5 March 2019 (2019-03-05)
- D4 US 2021/069244 A1 (PANG TE-LING [TW] ET AL) 11 March 2021 (2021-03-11)
- D5 WO 2020/180882 A1 (NKARTA INC [US]) 10 September 2020 (2020-09-10)
- D6 US 2020/384023 A1 (LEE JONG SEO [KR] ET AL) 10 December 2020 (2020-12-10)
- D7 WO 2014/184143 A1 (CELLECTIS [FR]) 20 November 2014 (2014-11-20)
- D8 WO 2019/137518 A1 (LI HUASHUN [CN]) 18 July 2019 (2019-07-18)
- D9 FREY NOELLE V ET AL: "Optimizing Chimeric Antigen Receptor T-Cell Therapy for Adults With Acute Lymphoblastic Leukemia", JOURNAL OF CLINICAL ONCOLOGY, vol. 38, no. 5, 9 December 2019 (2019-12-09), pages 415-422, XP055948471, DOI: 10.1200/JCO.19 Retrieved from the Internet: URL:<https://ascopubs.org/doi/pdf/10.1200/JCO.19.01892>
- D10 STEPHANIE VAIRY ET AL: "CTL019 (tisagenlecleucel): CAR-T therapy for relapsed and refractory B-cell acute lymphoblastic leukemia", DRUG DESIGN, DEVELOPMENT AND THERAPY, vol. Volume 12, 1 November 2018 (2018-11-01), pages 3885-3898, XP055610598, DOI: 10.2147/DDDT.S138765

- D11 FREY NOELLE V ET AL: "Cytokine release syndrome with novel therapeutics for acute lymphoblastic leukemia", HEMATOLOGY / THE EDUCATION PROGRAM OF THE AMERICAN SOCIETY OF HEMATOLOGY, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 2016, no. 1, 2 December 2016 (2016-12-02), pages 567-572, XP008184859, ISSN: 1520-4383, DOI: 10.1182/ASHEDUCATION-2016.1.567
- D12 MOSTAFA KAMEL YASSER: "CAR-T Therapy, the End of a Chapter or the Beginning of a New One?", CANCERS, vol. 13, no. 4, 18 February 2021 (2021-02-18), page 853, XP055948452, DOI: 10.3390/cancers13040853
- D13 HAO ZHANG ET AL: "Engineering better chimeric antigen receptor T cells", EXPERIMENTAL HEMATOLOGY & ONCOLOGY, BIOMED CENTRAL LTD, LONDON, UK, vol. 9, no. 1, 2 December 2020 (2020-12-02), pages 1-13, XP021285035, DOI: 10.1186/S40164-020-00190-2
- D14 Wang Zhicai ET AL: "A long way to the battlefield: CAR T cell therapy against solid cancers", JOURNAL OF CANCER, vol. 10, no. 14, 1 January 2019 (2019-01-01), pages 3112-3123, XP093030614, AU ISSN: 1837-9664, DOI: 10.7150/jca.30406

Article 34(2)(b) PCT

The amendments filed with the letter dated 06.03.2023 do not appear to introduce subject-matter which extends beyond the content of the application as filed, thus fulfilling the requirements of **Article 34(2)(b) PCT**.

Re Item V

Novelty, inventive step and industrial applicability

D9 can be regarded as being the closest prior art to the subject-matter of claims 1-11, and discloses treatment of acute lymphoblastic leukemia patients with anti-CD19 CAR-T cell therapy, wherein the CAR-T cells were administered fractionated over 3 days (day 1, 10%; day 2, 30%; day 3, 60%), see above. The scFv present in the CAR is FMC63 (see D10, page 3886).

The subject-matter of claim 1 therefore differs from this known D9 in that the antibody present in the CAR comprises different CDR sequences, and is therefore new (**Article 33(2) PCT**).

The application shows that the claimed CAR, while having similar cytotoxic potency to the CAR of D9, i.e.: FMC63 (see page 17, lines 10-12, page 18, lines 1-4, and figure 3), results in significantly reduced CRS (cytokine release syndrome). This effect is indicated in table 7, page 37 and further supported by comparative data furnished post-filing with letter dated 18.05.2023.

The problem to be solved by the present invention may therefore be regarded as the provision of improved (safer) anti-CD19 CARs for use in CAR-T cell therapy.

The solution, as in present claim 1, is considered inventive because the skilled person starting from D9 would not have arrived at the claimed CAR having the recited CDRs and would not have been able to anticipate that said CDRs would give rise to the stated improved properties.

Claims 2-11 are dependent on claim 1 and as such also meet the requirements of the **PCT** with respect to novelty and inventive step.



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European Patent Office

80298 Munich

Madrid, March 06, 2023

Our Ref.: 907 178

International Application PCT/EP2022/062374

Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) ET AL.

In response to the Written Opinion of the International Searching Authority

We herein demand for International Preliminary Examination (Art. 31 PCT) of the application of reference before the European Patent Office as the International Preliminary Examining Authority.

It is requested that the new set of claims attached herein is declared admissible under the regulations of the PCT treaty.

Amendments

Amended claim 1 refers to a composition which comprises a plurality of cells, wherein the cells comprise a chimeric antigen receptor (CAR) which in turn comprises an antibody, F(ab')₂, Fab, scFab or scFv with a light chain variable region (VL) and a heavy chain variable region (VH), wherein said VH comprises HCDR1, HCDR2 and HCDR3 polypeptides and VL comprises LCDR1, LCDR2 and LCDR3 polypeptides, and wherein HCDR1 consists of the sequence SEQ ID NO: 1, HCDR2 consists of the sequence SEQ ID NO: 2, HCDR3 consists of the sequence SEQ ID NO: 3, LCDR1 consists of the sequence SEQ ID NO: 4, LCDR2 consists of the sequence SEQ ID NO: 5 and LCDR3 consists of the sequence SEQ ID NO: 6, for use in the treatment of CD19+ malignancies.

Basis for the term "*composition*" can be found, for instance on pages 7 and 8 of the application as originally filed which discloses the "*composition of the invention*". Moreover, **Examples 2.1.3** and **2.2.4** refer to "*the product*".

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composition" of the invention. Basis for the expression "*plurality of cells which comprise a chimeric antigen receptor (CAR)*" can be found for example on page 7. CDRs sequences were already included in the application as originally filed. The expression "for use in the treatment of CD19+ malignancies" can be found for example on pages 7 and 8.

The fractionated administration is a preferred, but not an essential feature of the invention. See for instance page 8 of the application as originally filed wherein it is indicated that "*In a preferred embodiment, a fractionated administration of the cell composition of the invention, particularly a progressive dose fractionation, was carried out*".

Novelty

Such as it is indicated by the Examiner at item 1 of the ISR-WO, none of the prior art documents discloses a CAR comprising an antibody or fragments thereof, which in turn comprises the CDR sequence of claim 1.

So, the claims are novel over the cited prior art.

Inventive step

Regarding the inventive step, **D9** can be considered as the closest prior art because it discloses the treatment of acute lymphoblastic leukemia patients with anti-CD19 CART-T cell therapy. The CAR of **D9** comprises the scFv FMC63.

The present invention differs from **D9** in that the CART-cells of the invention comprises different CDR sequences as compared with the CART-cells disclosed in **D9**. So, in other words, the CAR of the invention is structurally different from the CAR disclosed in **D9**.

Contrary to the Examiner's opinion, the CART-cells of the invention are associated with an improved technical effect derived from said structural difference.

As shown in **Figure 1**, an increase in T-cell proliferation was observed in A3B1-CAR (the CAR of the invention) and FMC63-CAR after 12 days of expansion. The percentage of CAR-expressing cells on membrane was also different between the two, with a milder expression observed for A3B1. A milder CAR-expression level has been shown to lead to prolonged CAR-T cell persistence, which correlates with the increased T-cell proliferation observed. Increased proliferation capacity of A3B1-transduced T-cells also correlates with more differentiated phenotype of these cells (**Figure 2**). A3B1-CAR expressing cells showed a higher proportion of EM phenotype and lower proportion of CM phenotype compared to FMC63-CAR expressing cells, at days 9 and 12 of expansion. EM cells are known to have a higher cytotoxic potential and higher cytokine production, compared to CM cells, which are less differentiated. As shown in **Figure 3**, no significant differences in cytotoxicity against NALM6 cells were observed when using A3B1 or FMC63 CAR-T cells that had been expanded for 7 days. However, significant differences were detected in the levels of IL-8 and IL-2 produced. A3B1 CAR-T cells produce

more IL-8 and less IL-2 upon activation through antigen-binding than FMC63 CAR-T cells. Also, the ratio $\text{TNF}\alpha/\text{IL-8}$ showed significant differences. Differences in levels of cytokine production have an impact on the anti-tumor activity and Cytokine Release Syndrome (CRS) through modulation of the activity of the T-cells themselves and modulation of recruitment and function of other immune cells. IL-8 is known to act as a chemokine for neutrophils, which have an inhibitory effect on the anti-tumor effect of CAR-T cells. IL-2 and $\text{TNF}\alpha$ are activators of T-cell function. Therefore, all these data combined may indicate A3B1-CAR T cells have a safer cytokine production profile while having a similar cytotoxic potential.

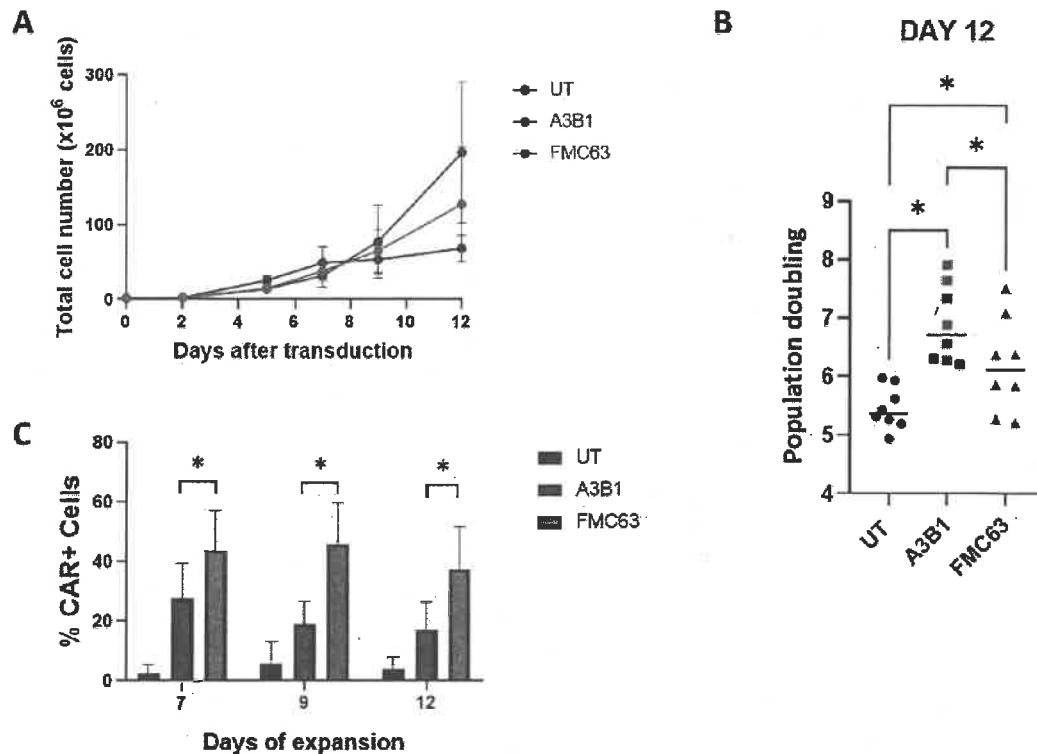


Figure 1. T-cell expansion. T-cells from 8 different donors were left untransduced (UT) or transduced with A3B1-based CAR or FMC63-CAR. Cells were expanded for up to 12 days after transduction. (A) Number of viable cells was determined every 2-3 days to monitor T-cell expansion (B) Number of population doublings at final day of expansion (day 12) was calculated. (C) Percentage of CAR-expressing cells during cell expansion (*) Indicates statistical significance $p \leq 0.05$

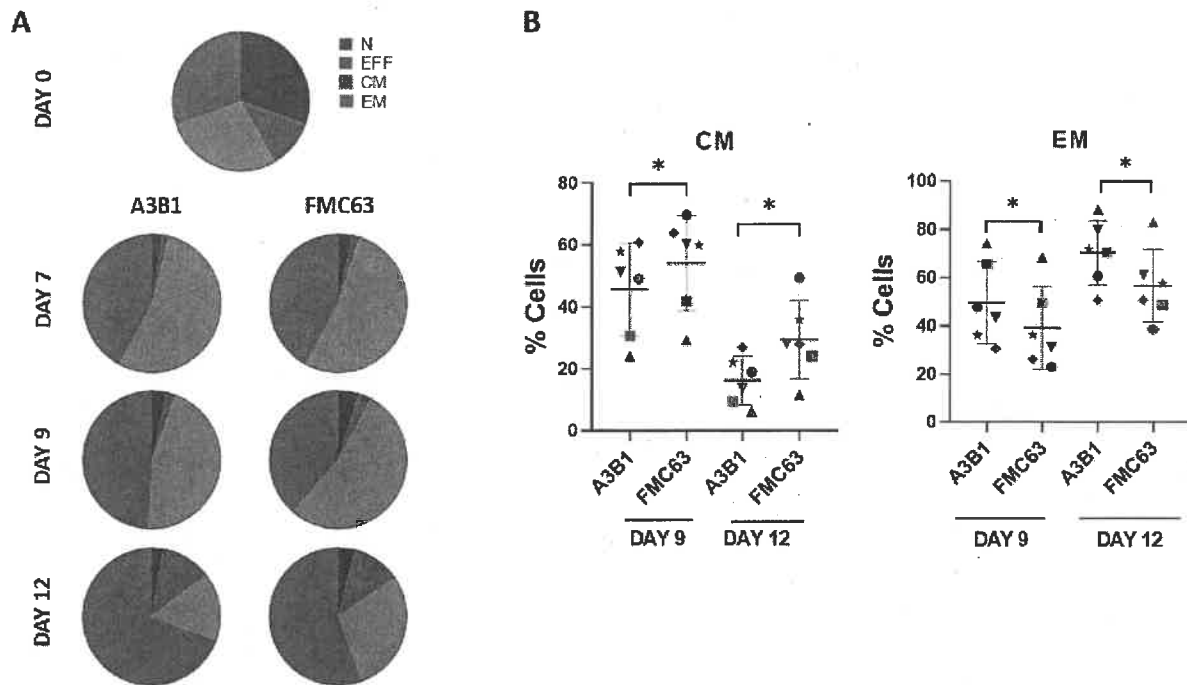


Figure 2. T-cell phenotype. T-cell phenotype of A3B1- or FMC63-transduced cells from 6 different donors was determined at several times during T-cell expansion. Percentage of Naive (N), Effector (EFF), Central memory (CM) or Effector memory (EM) was determined by flow cytometry for CAR-expressing cells, based on CD45RA and CCR7 expression. (A) Graphs show proportion of each T-cell subpopulation at different days during expansion. (B) Percentage of CM and EM cells in A3B1 or FMC63 transduced cells at days 9 and 12 of expansion. (*) Indicates statistical significance $p \leq 0.05$ (Paired t-test)

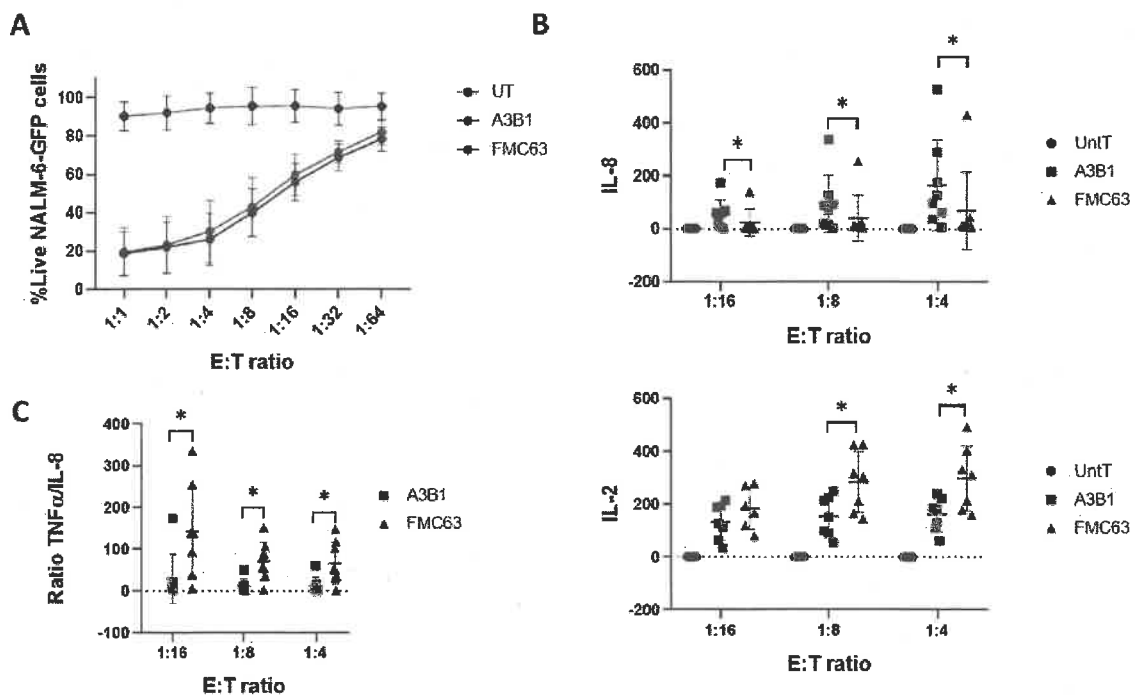


Figure 3. Cytotoxicity and cytokine production. T-cells from 7 different donors were left untransduced (UT) or transduced with A3B1-based CAR or FMC63-CAR. After 7 days of expansion, CAR-T cell cytotoxicity and cytokine production was evaluated. Percentage of CAR-expressing cells was adjusted to 50% for each donor before establishment of co-cultures. (A) CAR-T cell mediated cytotoxicity against target cells (NALM6-GFP) was evaluated at different effector (E): target (T) ratios. Co-cultures were incubated for 20h, and then absolute number of viable GFP-expressing cells (target cells) was measured by flow cytometry. (B) Cytokine levels were measured in the supernatants of co-cultures using Luminex platform. Results for IL-2 and IL-8 are shown. (C) Ratio between TNF α and IL-8 levels (*) Indicates statistical significance $p \leq 0.05$ (Paired t-test)

So, in summary, said structural difference between both CARs, (i.e., the use of A3B1-CAR instead of FMC63-CAR), is associated with:

- i. Improved T-cell proliferation with a milder expression of CAR on membrane (Figure 1) which leads to prolonged CAR-T cell persistence, which correlates with the increased T-cell proliferation observed,
- ii. More differentiated phenotype of these cells (Figure 2) and
- iii. Significant differences in levels of cytokine production (particularly IL-8, IL-2 and ratio TNF α /IL-8) which is an indication of a safer cytokine-production profile (reduced levels of cytokine release syndrome) while maintaining an equivalent cytotoxic activity (Figure 3).

So, the problem to be solved by the present invention is the provision of CART-cells, for use in the treatment of CD19+ malignancies, with i) improved T-cell proliferation capacity and milder percentage of CAR-expressing cells which leads to prolonged CAR-T cell persistence, ii) more differentiated phenotype and iii) safer cytokine production-profile (reduced levels of cytokine release syndrome) compared with the CART-cells of D9.

The present invention solves this problem by using the CART-cells of the invention characterized by the CDRs of claim 1.

In our opinion, departing from the prior art, particularly D9, the skilled person in the art would not be prompted to implement the solution proposed in the present invention (using precisely the CART-cells of the invention characterized by the CDRs of claim 1) in order to solve the proposed objective technical problem, simply because the prior does not disclose the CDR sequences of the invention, let alone its possible use to design CAR-T cells with improved T-cell proliferation capacity and milder percentage of CAR-expressing cells which leads to prolonged CAR-T cell persistence, more differentiated phenotype and safer cytokine production-profile (reduced levels of cytokine release syndrome) compared with the CART-cells of D9.

The person skilled in the art would never learn from D9, or from the common general knowledge, that precisely the use of the CDRs of the invention would give rise to CART-cells with improved T-cell proliferation capacity and milder percentage of CAR-expressing cells which leads to prolonged CAR-T cell persistence, more differentiated phenotype and safer cytokine production-profile (reduced levels of cytokine release syndrome) compared with the CART-cells of D9.

Finally, the Examiner indicates at item 2.1 of the ISR-WO that *"an inventive step could only be acknowledged if the antibodies would show unexpected properties..."*. In our opinion, the above comparative data between the CART-cells of the invention and the CART-cells of **D9** clearly show the required unexpected properties. So, an inventive step should be acknowledged.

Concluding remarks

For the above reasons the new set of amended claims should be declared admissible under the provisions of the PCT treaty.

Further Procedure

If anything remains which can be resolved over the phone the Examiner is kindly invited to call the applicant's representative.

Finally, if needed, we kindly ask you to issue a second written opinion thus giving the applicant a further opportunity to file further amendments and/or arguments to overcome any objection which may be raised in the first written opinion.

Respectfully submitted,



MIGUEL ANGEL MARTINEZ

European Patent Attorney
Hoffmann Eitle
Association No. 151

Encl.:

- New amended set of claims (working and clean copy of the claims)

CLAIMS

1. A composition which comprises a plurality of cells, wherein the cells comprise a chimeric antigen receptor (CAR) which in turn comprises an antibody, F(ab')₂, Fab, scFab or scFv with a light chain variable region (VL) and a heavy chain variable region (VH), wherein said VH comprises HCDR1, HCDR2 and HCDR3 polypeptides and VL comprises LCDR1, LCDR2 and LCDR3 polypeptides, and wherein HCDR1 consists of the sequence SEQ ID NO: 1, HCDR2 consists of the sequence SEQ ID NO: 2, HCDR3 consists of the sequence SEQ ID NO: 3, LCDR1 consists of the sequence SEQ ID NO: 4, LCDR2 consists of the sequence SEQ ID NO: 5 and LCDR3 consists of the sequence SEQ ID NO: 6, for use in the treatment of CD19+ malignancies.
2. A composition which comprises a plurality of cells, wherein the cells comprise a chimeric antigen receptor (CAR) which in turn comprises an antibody, F(ab')₂, Fab, scFab or scFv with a light chain variable region (VL) and a heavy chain variable region (VH), wherein said VH comprises HCDR1, HCDR2 and HCDR3 polypeptides and VL comprises LCDR1, LCDR2 and LCDR3 polypeptides, and wherein HCDR1 consists of the sequence SEQ ID NO: 1, HCDR2 consists of the sequence SEQ ID NO: 2, HCDR3 consists of the sequence SEQ ID NO: 3, LCDR1 consists of the sequence SEQ ID NO: 4, LCDR2 consists of the sequence SEQ ID NO: 5 and LCDR3 consists of the sequence SEQ ID NO: 6, for use, according to claim 1, in the treatment of CD19+ malignancies, characterized in that a progressive fractionated administration of the cells is carried out wherein the percentage of cells administered is progressively increased in each consecutive fraction administered.
3. A composition which comprises a plurality of cells, wherein the cells comprise a chimeric antigen receptor (CAR) which in turn comprises an antibody, F(ab')₂, Fab, scFab or scFv with a light chain variable region (VL) and a heavy chain variable region (VH), wherein said VH comprises HCDR1, HCDR2 and HCDR3 polypeptides and VL comprises LCDR1, LCDR2 and LCDR3 polypeptides, and wherein HCDR1 consists of the sequence SEQ ID NO: 1, HCDR2 consists of the sequence SEQ ID NO: 2, HCDR3 consists of the sequence SEQ ID NO: 3, LCDR1 consists of the sequence SEQ ID NO: 4, LCDR2 consists of the sequence SEQ ID NO: 5 and LCDR3 consists of the sequence SEQ ID NO: 6, for use in the treatment of CD19+ malignancies, according to claims 1 or 2, characterized in that a fractionated

administration of the cells is carried out by administering a first fraction comprising around 10% of the total dose on day 0, followed by a second fraction comprising around 30% of the total dose and by a third fraction comprising around 60% of the total dose.

- 5 4. Composition for use, according to any of the previous claims, wherein the antibody, F(ab')₂, Fab, scFab or scFv comprises a VL domain and a VH domain, wherein the VL domain consists of SEQ ID NO: 7 and the VH domain consists of SEQ ID NO: 8.
- 10 5. Composition for use, according to any of the previous claims, wherein the CAR, further comprises a transmembrane domain, a costimulatory signalling domain and/or an intracellular signalling domain.
- 15 6. Composition for use, according to any of the previous claims, wherein the hinge and transmembrane domain of the CAR consists of CD8a of SEQ ID NO: 9, the costimulatory signalling domain consists of 4-1BB of SEQ ID NO: 10, and the intracellular signalling domain consists of CD3δ of SEQ ID NO: 11.
- 20 7. Composition for use, according to any of the previous claims, wherein the CAR comprises the SEQ ID NO: 12.
- 25 8. Composition for use, according to any of the previous claims, characterized in that the cells are T-cells or NK-cells.
9. Composition for use, according to any of the previous claims, characterized in that it is a pharmaceutical composition comprising pharmaceutically acceptable carriers or diluents.
10. Composition for use, according to any of the previous claims, in the treatment of acute lymphoblastic leukaemia, non-Hodgkin's lymphoma or chronic lymphocytic leukaemia or any CD19⁺ disorder.
11. Composition for use, according to any of the previous claims, characterized in that the total dose is 0.5-5 x 10⁶ cells/Kg, preferably 1 x 10⁶ cells/Kg.