ALMA MATER STUDIORUM - UNIVERSITA' DI BOLOGNA
Corso di Laurea in FARMACIA

CAR-T : PATENT LANDSCAPE

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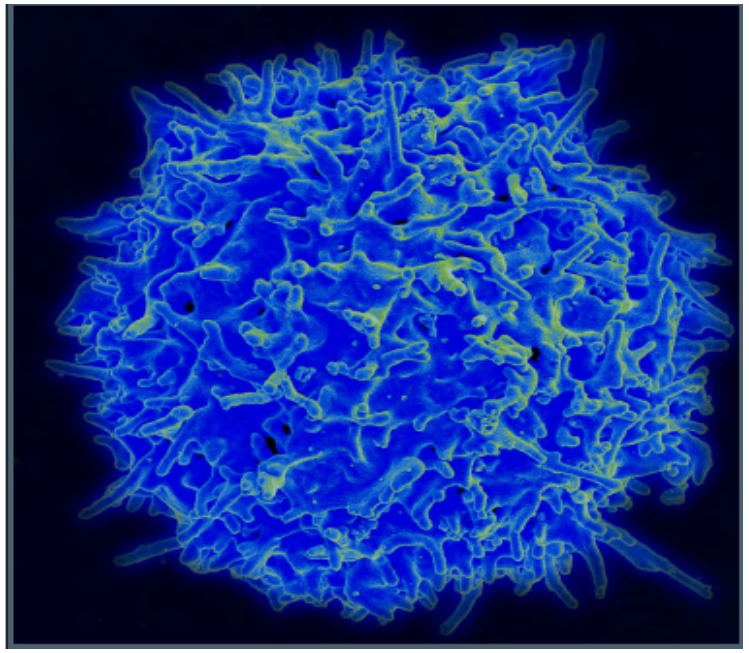
Anno Accademico 2019-2020

Che cosa è il CAR-T

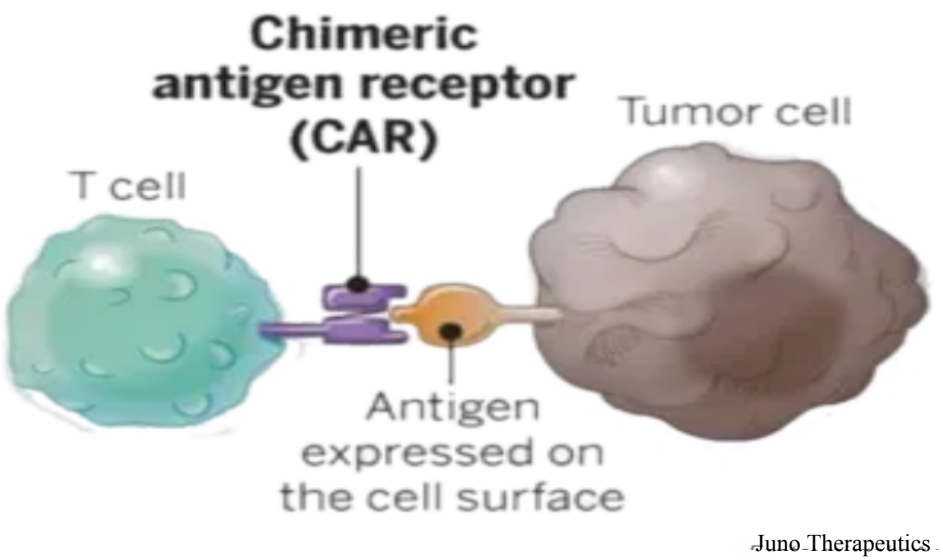


Webinar EPO: The patent landscape T-cell immunotherapy

CAR: CHIMERIC ANTIGEN RECEPTOR

Cellula T, o linfocita T, è un linfocita determinante nell'immunità cellulo-mediata

Riprogrammazione dei linfociti T affinché possano esprimere, sulla loro superfice, un particolare recettore denominato CAR che consente di legarsi in maniera specifica alle cellule tumorali



METODI , STRUMENTI e STRATEGIA DI RICERCA di brevetti e domande brevetto sul Car-T

Indagine approfondita su
PubMed
per comprendere il contenuto scientifico dell'ingegnerizzazione delle T-cells e loro applicazione terapeutica

Quali parole chiave usare in banche dati per estrapolare in maniera completa i brevetti che riguardano il CAR-T ?

Inserendo come keyword : CAR-T OR Chimeric Antigen Receptor si sono ottenuti

in **Espacenet**: 82.712

in **Patentscope**: 487.172 risultati

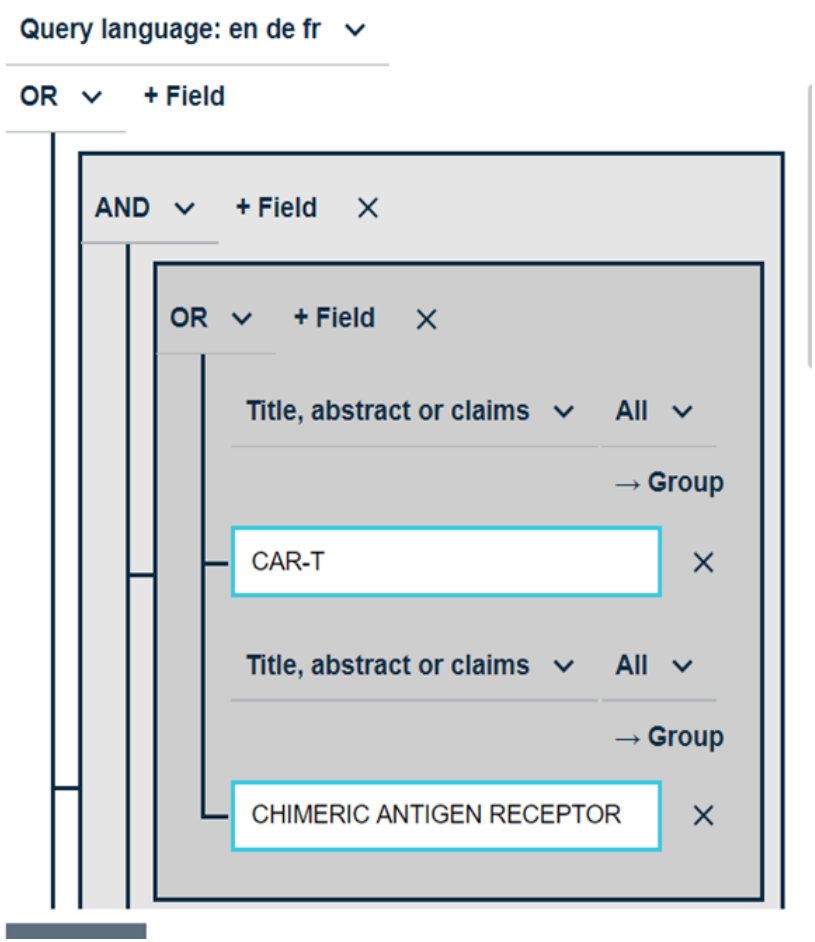
La precisione della ricerca è **fondamentale**, se non si ricerca in modo accurato, si ottiene solo un numero di risultati esorbitante senza utilità pratica.

La strategia di ricerca si basa in genere esclusivamente su parole chiave, ma nel caso di documenti brevettuali, abbiamo un vantaggio: i brevetti sono classificati in base al campo tecnologico, **IPC** e **CPC**

L'insieme di documenti più pertinenti, andranno a costituire il set di dati da analizzare

RICERCA IN BANCHE DATI:

Espacenet (Advanced Search):
https://worldwide.espacenet.com/
Patentscope :
https://www.wipo.int/patentscope/en



CPC e IPC rilevanti:

Classificazione **CPC**: **C07K2319/03, C07K2317/622, C07K2317/55**

Classificazione **IPC**: **C07K**14/705 o **A61K**35/17

PAROLE CHIAVE rilevanti :

Title, Abstract or Claims "**CAR-T or CHIMERIC ANTIGEN RECEPTOR**"

((ctxt all "CAR-T" OR ctxt all "CHIMERIC ANTIGEN RECEPTOR") AND (cl all "A61K35/17" OR cl all "C07K14/705")) OR (cl any "C07K2319/03" AND (ap any "C07K2317/622" OR ap any "C07K2317/55"))

RICERCA IN BANCHE DATI

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2012 (14.06.2012)

W I P O | P C

(51) International Patent Classification:
C07H 21/04 (2006.01) *A61K 39/00* (2006.01)

(21) International Application Number:
PCT/US2011/064191

(22) International Filing Date:
9 December 2011 (09.12.2011)

CPC

C07K2319/03	Chemistry, organic, peptides , fusion polypeptide , containing a transmembrane segment a localisation/targetting motif containing a transmembrane segment
C07K2317/622	Chemistry , organic peptides, fusion polypeptide , Immunoglobulins specific features, characterized by non-natural combinations of immunoglobulin fragments, comprising only variable region components, Single chain antibody (scFv)
C07K2317/55	Chemistry , organic peptides, fusion polypeptides, Immunoglobulins specific features, characterized by immunoglobulin fragments, , F ab or Fab'

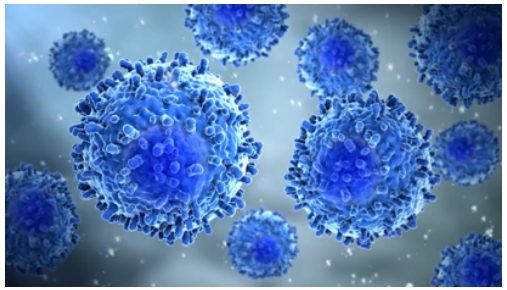
IPC

C07K14/705	Chemistry, organic peptides, peptides having more than 20 amino acids, gastrins, somatostatins, melanotropins, deivatives thereof. Receptors, cell surface antigens, cell surface determinants.
A61K35/17	Human necessities, medical or veterinary science, Lymphocites, Bcells, Tcells, Nkillers cells, interfer-actived or cytokine-actived lymphocytes
C07H21/04	Chemistry, organic, sugar, derivatides threof, nucleosides, nucleotides, nucleic acid, containing two or more mononucleotide units having separate phosphate or polyphosphate groups linked by saccharide radicals of nucleoside groups, e.g. nucleic acids
A61K39/00	Human necessities, medical or veterinary science, devices or methods specially adapted for bringing pharmaceutical products into physical or administering forms

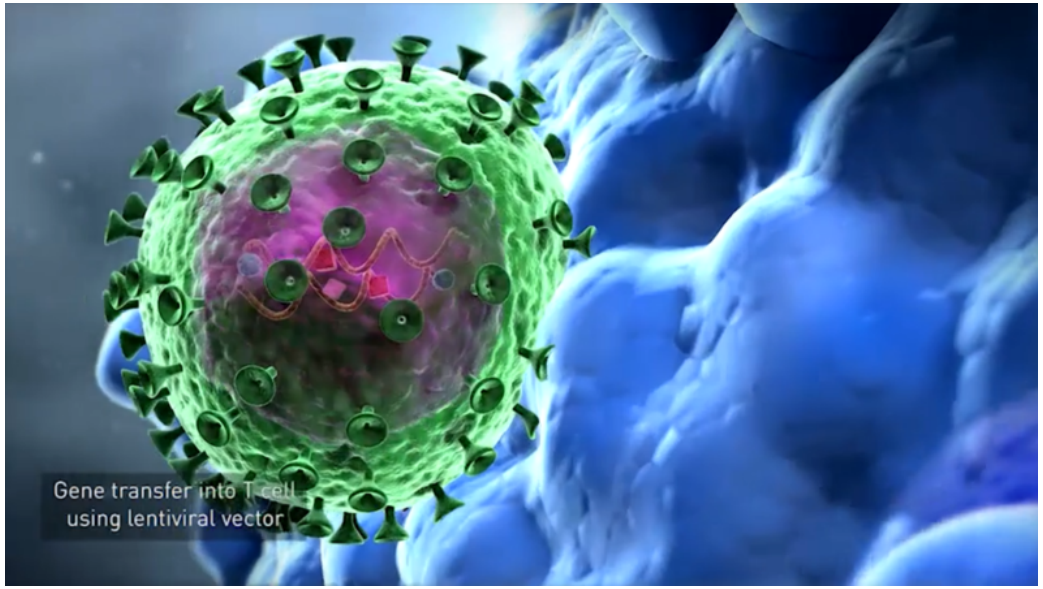
PAROLE CHIAVE

"CAR-T" OR "chimeric antigen receptor"

CREAZIONE CAR-T CELLS

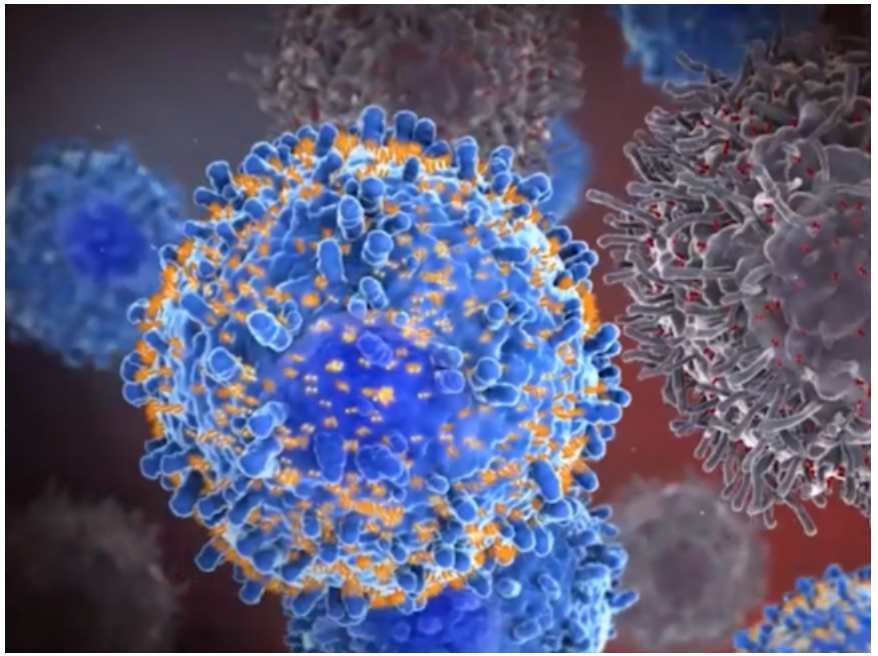


Linfociti T



Kymriah-Novartis Mechanism of action

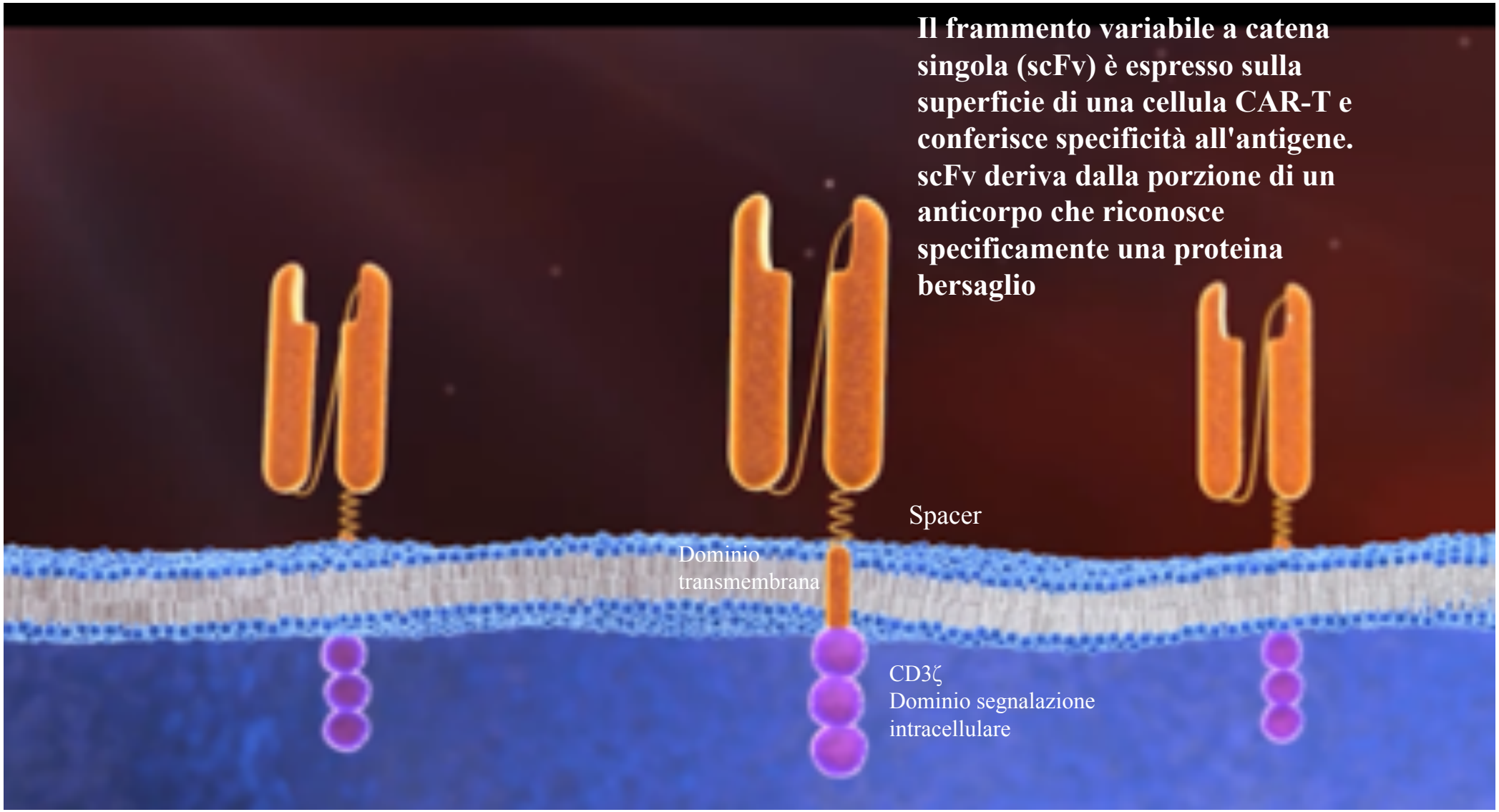
Materiale genetico che codifica per il recettore antigene chimerico (CAR) viene trasferito **nelle cellule T del paziente** utilizzando un vettore virale inattivato



Kymriah-Novartis Mechanism of action

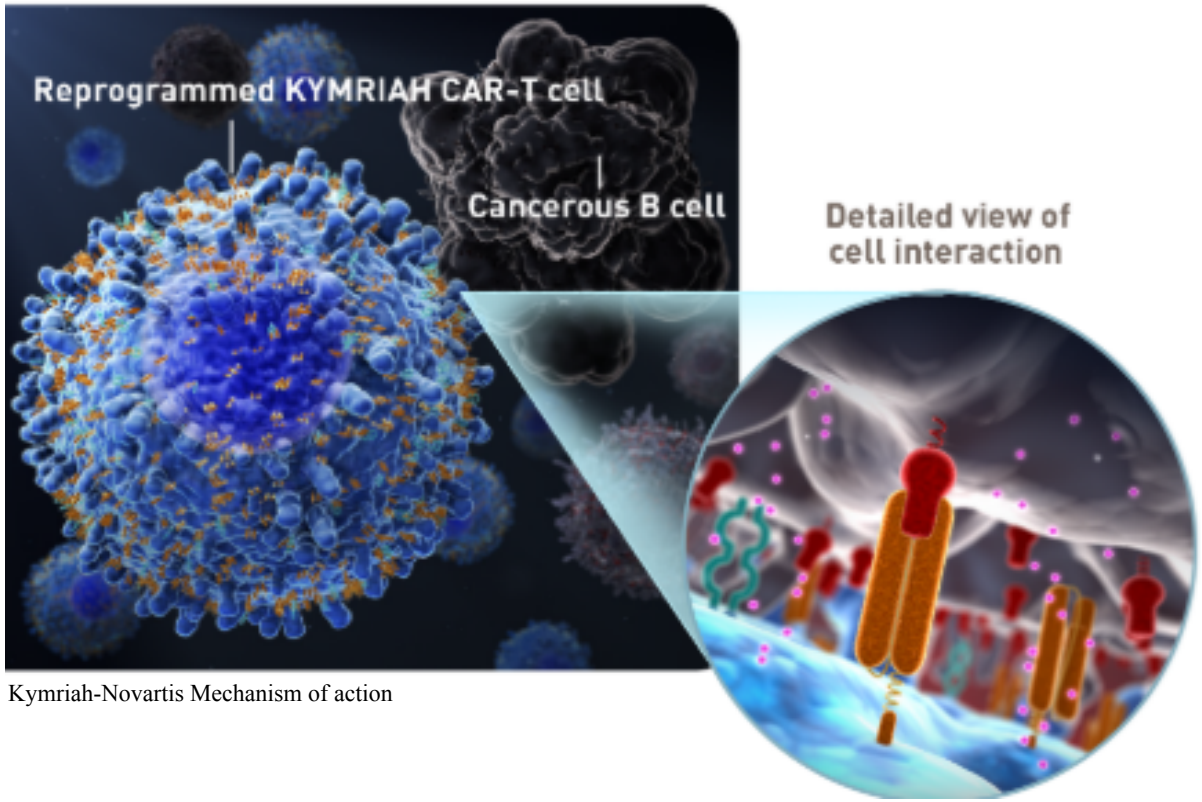
I CAR introdotti sulla superficie dei linfociti T agiscono da "radar" permettendo così l'attacco della cellula tumorale e la sua successiva eliminazione

RECETTORE CAR



Kymriah-Novartis Mechanism of action

CAR-T IN AZIONE

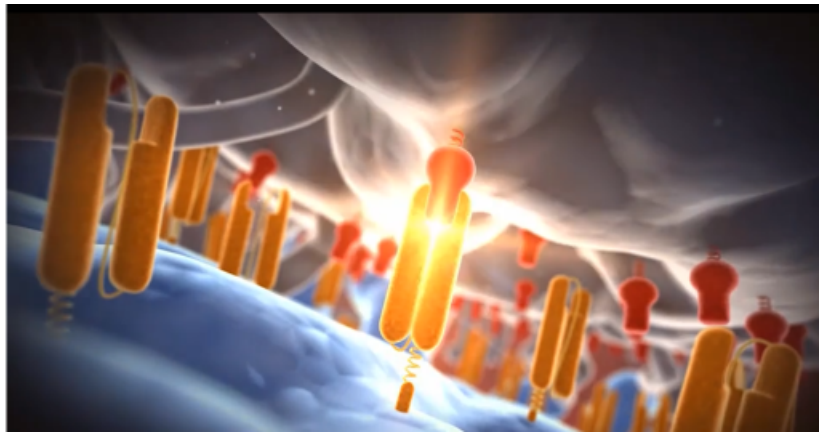


Kymriah-Novartis Mechanism of action

Il linfocita T ingegnerizzato sta riconoscendo e attaccando una **cellula leucemica.**

CAR lega la proteina CD19 sulla superficie della cellula leucemica.

In seguito al legame con le cellule cancerose che esprimono CD19, il CAR trasmette un segnale per promuovere espansione e attivazione delle cellule T e l'eliminazione delle cellule bersaglio


Kymriah-Novartis Mechanism of action

GENERAZIONI CAR-T

QUATTRO GENERAZIONI CAR-T	DOMINI SEGNALAZIONE	DOMANDE DI BREVETTO
Prima generazione	Dominio legame extracellulare, spacer, dominio transmembrana, e uno o più domini intracellulari.	Es. WO2012079000 A1 *USE OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS TO TREAT CANCER*
Seconda generazione	Aggiunto dominio co-stimolatorio CD28 o 4-1BB	Es. WO2014031687 A1 *METHOD AND COMPOSITIONS FOR CELLULAR IMMUNOTHERAPY*
Terza generazione	Aggiunti ulteriori domini co-stimolatori CD3ζ-CD28-OX40 o CD3ζ-CD28-41BB	Es. WO2015123642 A1 *CHIMERIC ANTIGEN RECEPTORS AND METHODS OF MAKING*
Quarta generazione	Aggiunti ulteriori fattori che aumentano l'espansione e attività antitumorale: es. IL-2, IL-5, IL-12 e ligandi co-stimolatori	Es. WO2019/210293 A1 *CAR T CELLS WITH ONE OR MORE INTERLEUKIN*

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 June 2012 (14.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/079000 A1

(51) International Patent Classification:
C07H 21/04 (2006.01) *A61K 39/00* (2006.01)

(21) International Application Number:
PCT/US2011/064191

(22) International Filing Date:
9 December 2011 (09.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/421,470 9 December 2010 (09.12.2010) US
61/502,649 29 June 2011 (29.06.2011) US

(71) Applicant *(for all designated States except US)*: **THE TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA** [US/US]; Center For Technology Transfer, 3160 Chestnut Street, Suite 200, Philadelphia, PA 19104-6283 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **JUNE, Carl, H.** [US/US]; 409 Baird Road, Merion Station, PA 19066 (US). **LEVINE, Bruce, L.** [US/US]; 1258 Liberty Bell Drive, Cherry Hill, NJ 08003 (US). **PORTER, David, L.** [US/US]; 821 Crum Creek Road, Springfield, PA 19064 (US). **KALOS, Michael, D.** [US/US]; 716 Carpenter Lane, Philadelphia, PA 19119 (US).

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2012/079000 A1

(54) **Title**: USE OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS TO TREAT CANCER

(57) **Abstract**: The present invention provides compositions and methods for treating cancer in a human. The invention includes relates to administering a genetically modified T cell to express a CAR wherein the CAR comprises an antigen binding domain, a transmembrane domain, a costimulatory signaling region, and a CD3 zeta signaling domain.

PRIMA GENERAZIONE CAR-T

Domanda brevetto:

WO2012079000 A1

USE OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS TO TREAT CANCER

Priority Date 9.12.10 US – International Filing Date 9.12.11

CLAIMS

What is claimed is:

1. An isolated nucleic acid sequence encoding a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen binding domain, a transmembrane domain, a costinniiatory signaling region, and a CD3 zeta signaling domain, wherein the CD3 zeta signaling domain comprises the amino acid sequence

Corrispondente Brevetto Europeo EP2649086 B1

grant 19.7.17

55 **Claims**

1. A T cell genetically modified to express a CAR wherein the CAR comprises (a) an antigen binding domain that is an anti-CD19 scFv comprising the amino acid sequence of SEQ ID NO:20, (b) a costimulatory 4-1BB signaling region, and (c) a CD3 zeta signaling domain comprising the amino acid sequence of SEQ ID NO: 24, for use in a method for treating cancer in a human, wherein a remission of the cancer is obtained, and wherein the human is resistant to at least one chemotherapeutic agent.

B1 : BREVETTO CONCESSO
È un brevetto di ***uso medico*** che non limita l'attività clinica in accordo con Art. 53 EPC

Article 53 EPC
Exceptions to patentability

European patents shall not be granted in respect of:

(a) …omissis …
(b) …omissis …

(c) methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body;
this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

(19) Europäisches Patentamt / European Patent Office / Office européen des brevets

(11) EP 2 649 086 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
19.07.2017 Bulletin 2017/29

(21) Application number: **11846757.0**

(22) Date of filing: **09.12.2011**

(51) Int Cl.:
A61K 39/00 *(2006.01)* ***A61K 35/17*** *(2015.01)*

(86) International application number:
PCT/US2011/064191

(87) International publication number:
WO 2012/079000 (14.06.2012 Gazette 2012/24)

(54) **USE OF CHIMERIC ANTIGEN RECEPTOR-MODIFIED T CELLS TO TREAT CANCER**

VERWENDUNG VON DURCH EINEN CHIMÄREN ANTIGENREZEPTOR MODIFIZIERTEN T-ZELLEN ZUR BEHANDLUNG VON KREBS

UTILISATION DE LYMPHOCYTES T MODIFIÉS PAR UN RÉCEPTEUR D'ANTIGÈNES CHIMÉRIQUE POUR TRAITER LE CANCER

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME

(30) Priority: **29.06.2011 US 201161502649 P**
09.12.2010 US 421470 P

(43) Date of publication of application:
16.10.2013 Bulletin 2013/42

(60) Divisional application:
16199372.0
17153799.6

(73) Proprietor: **The Trustees of The University of Pennsylvania**
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- **PORTER, David, L.**
  Springfield, PA 19064 (US)
- **KALOS, Michael, D.**
  Philadelphia, PA 19119 (US)
- **MILONE, Michael C.**
  Cherry Hill, NJ 08002 (US)

(74) Representative: **Bassil, Nicholas Charles**
Kilburn & Strode LLP
20 Red Lion Street
London WC1R 4PJ (GB)

(56) References cited:

WO-A1-2010/025177	**WO-A2-2009/091826**
WO-A2-2010/085660	**US-A1- 2004 043 401**
US-A1- 2004 043 401	**US-A1- 2009 297 994**
US-B1- 6 410 319	**US-B2- 7 265 209**
US-B2- 7 319 143	**US-B2- 7 446 190**
US-B2- 7 448 191	**US-B2- 7 514 537**

- **TAMMANA SYAM ET AL: "4-1BB and CD28 Signaling Plays a Synergistic Role in Redirecting Umbilical Cord Blood T Cells Against B-Cell Malignancies", HUMAN GENE THERAPY, vol. 21, January 2010 (2010-01), pages 75-86, XP002732432,**
- **MILONE MICHAEL C ET AL: "Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo.", MOLECULAR THERAPY : THE JOURNAL OF THE AMERICAN SOCIETY OF GENE THERAPY AUG 2009, vol. 17, no. 8, August 2009 (2009-08), pages 1453-1464, XP002732433, ISSN: 1525-0024**

Printed by Jouve, 75001 PARIS (FR)

(Cont. next page)

EP 2 649 086 B1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
27 February 2014 (27.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/031687 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C12N 5/10* (2006.01)
C07K 14/705 (2006.01) *C12N 15/62* (2006.01)

(21) International Application Number:
PCT/US2013/055862

(22) International Filing Date:
20 August 2013 (20.08.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/691,117 20 August 2012 (20.08.2012) US

(71) Applicant: **JENSEN, Michael** [US/US]; 3494 Pleasant Beach Drive, Bainbridge Island, WA 98110 (US).

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(74) Agent: **KOWALCHYR, Katherine, M.**; Merchant & Gould P.C., P.o. Box 2903, Minneapolis, MN 55402-0903 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

WO 2014/031687 A1

(54) **Title**: METHOD AND COMPOSITIONS FOR CELLULAR IMMUNOTHERAPY

(57) **Abstract**: The present invention provides nucleic acids, vectors, host cells, methods and compositions to confer and/or augment immune responses mediated by cellular immunotherapy, such as by adoptively transferring CD8+ central memory T cells or combinations of central memory T cells with CD4+ T cells that are genetically modified to express a chimeric receptor. In embodiments the genetically modified host cell comprises a nucleic acid comprising a polynucleotide coding for a ligand binding domain, a polynucleotide comprising a customized spacer region, a polynucleotide comprising a transmembrane domain, and a polynucleotide comprising an intracellular signaling domain. It has been surprisingly found that the length of the spacer region can affects the ability of chimeric receptor modified T cells to recognize target cells in vitro and affects in vivo efficacy of the chimeric receptor modified T cells. Pharmaceutical formulations produced by the method, and methods of using the same, are also described.

SECONDA GENERAZIONE CAR-T

Domanda brevetto

WO2014031687 A1

METHOD AND COMPOSITIONS FOR CELLULAR IMMUNOTHERAPY

Priority Date 20.8.12 US – International Filing Date 20.8.13

Claims:

10. The chimeric receptor nucleic acid of any one of claims 1 to 9, wherein the lymphocyte activating domain comprises all of a portion of CD3 zeta in combination with a costimulatory domain selected from the group consisting of CD27, CD28, 4-1BB, OX-40, CD30, CD40, PD-1, ICOS, LFA-1, CD2, CD7, NKG2C, B7-H3 and combinations thereof.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 August 2015 (20.08.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/123642 A1

(51) International Patent Classification:
C12N 15/85 (2006.01) *C07K 19/00* (2006.01)
C07K 14/705 (2006.01)

(21) International Application Number:
PCT/US2015/016057

(22) International Filing Date:
16 February 2015 (16.02.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/940,339 14 February 2014 (14.02.2014) US

(71) Applicant: **BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM** [US/US]; 201 West 7th St., Austin, TX 78701 (US).

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(74) Agent: **FINDLAY, Geoffrey, S.**; Parker Highlander PLLC, 1120 S. Capital Of Texas Highway, Building One, Suite 200, Austin, TX 78746 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Published:
— *with international search report (Art. 21(3))*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: CHIMERIC ANTIGEN RECEPTORS AND METHODS OF MAKING

(57) **Abstract**: Provided are methods of generating chimeric antigen receptors (CAR). In some embodiments, library screening of CAR is performed by generating a vector encoding the CAR from random attachment of vectors from libraries of vectors encoding antigen-binding domains (*e.g.*, scFv regions), hinge regions, and endodomains. In some embodiments, the vectors contain a transposon.

WO 2015/123642 A1

TERZA GENERAZIONE CAR-T

Aggiunti ulteriori domini co-stimolatori

CD3ζ-CD28-OX40, CD3ζ-CD28-41BB

Domanda di brevetto

WO2015123642 A1

CHIMERIC ANTIGEN RECEPTORS AND METHODS OF MAKING

Priority Date 14.2.14 US – International Filing Date 16.2.15

Claims:

25. The method of claims 1-24, wherein at least one of the endodomains comprise (CD28 +CD3ζ), (CD28 +CD27 + CD3ζ), (CD28 + OX40 + CD3ζ), (CD28 + 4-1BB + CD3ζ), (CD28 + CD27 + OX40 + CD3ζ), (CD28 + 4-1BB + CD27 + CD3ζ), (CD28 + 4-1BB + OX40 + CD3ζ), (4-1BB + CD3ζ), (4-1BB + OX40 + CD3ζ), (4-1BB + CD27 +CD3ζ), (CD27 + CD3ζ), (CD27 + OX 40 + CD3ζ), (CD28Δ +CD3ζ), (CD28Δ +CD27 + CD3ζ), (CD28Δ + OX40 + CD3ζ), (CD28Δ + 4-1BB + CD3ζ), (CD28Δ + 4-1BB + OX40 + CD3ζ), (CD28Δ + CD27 + OX40 + CD3ζ), (CD28Δ + 4-1BB + CD27 + CD3ζ), (4-1BB + ICOS + CD3ζ), (CD28 + ICOS + CD3ζ), (ICOS + CD3ζ), CD3ζ, CD28 only.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 October 2019 (31.10.2019)

WIPO | PCT

(10) International Publication Number
WO 2019/210293 A1

(51) International Patent Classification:
A61K 35/17 (2015.01) *C12N 5/10* (2006.01)
C07K 14/725 (2006.01) *C12N 15/85* (2006.01)
C12N 5/0783 (2010.01)

(21) International Application Number:
PCT/US2019/029596

(22) International Filing Date:
29 April 2019 (29.04.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/663,410 27 April 2018 (27.04.2018) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) Title: CAR T CELLS WITH ONE OR MORE INTERLEUKINS

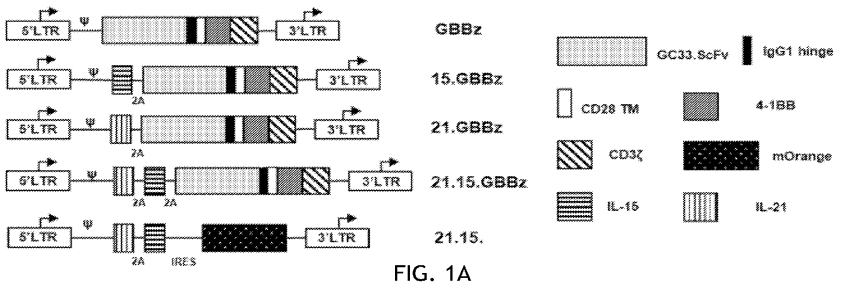

FIG. 1A

(57) Abstract: Embodiments of the disclosure encompass methods and compositions related to targeting of tumor antigen-positive cells with therapy using cells that express a chimeric antigen receptor that targets the tumor antigen-positive cells in the presence of one or more interleukins that enhance efficacy of the tumor antigen-specific chimeric antigen receptors. In specific embodiments, the tumor antigen is glypican-3 and the one or more interleukins are IL-15 and IL-21.

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QUARTA GENERAZIONE CAR-T

Aggiunti fattori che aumentano attività antitumorale: es. **interleuchine** che causano citotossicità antitumorale superiore

Domanda brevetto

WO2019/210293 A1

CAR T CELLS WITH ONE OR MORE INTERLEUKINS

Priority Date 27.4.18 US – International Filing Date 29.4.19

CLAIMS

What is claimed is:

1. An isolated T cell, wherein said T cell comprises a chimeric antigen receptor that targets a tumor antigen, comprises a recombinant T cell receptor that targets a tumor antigen, is viral-specific, and/or is tumor antigen-specific, wherein said cell comprises

one or both of:

(i) at least one recombinant interleukin (IL), and

(ii) induced expression of at least one endogenous IL,

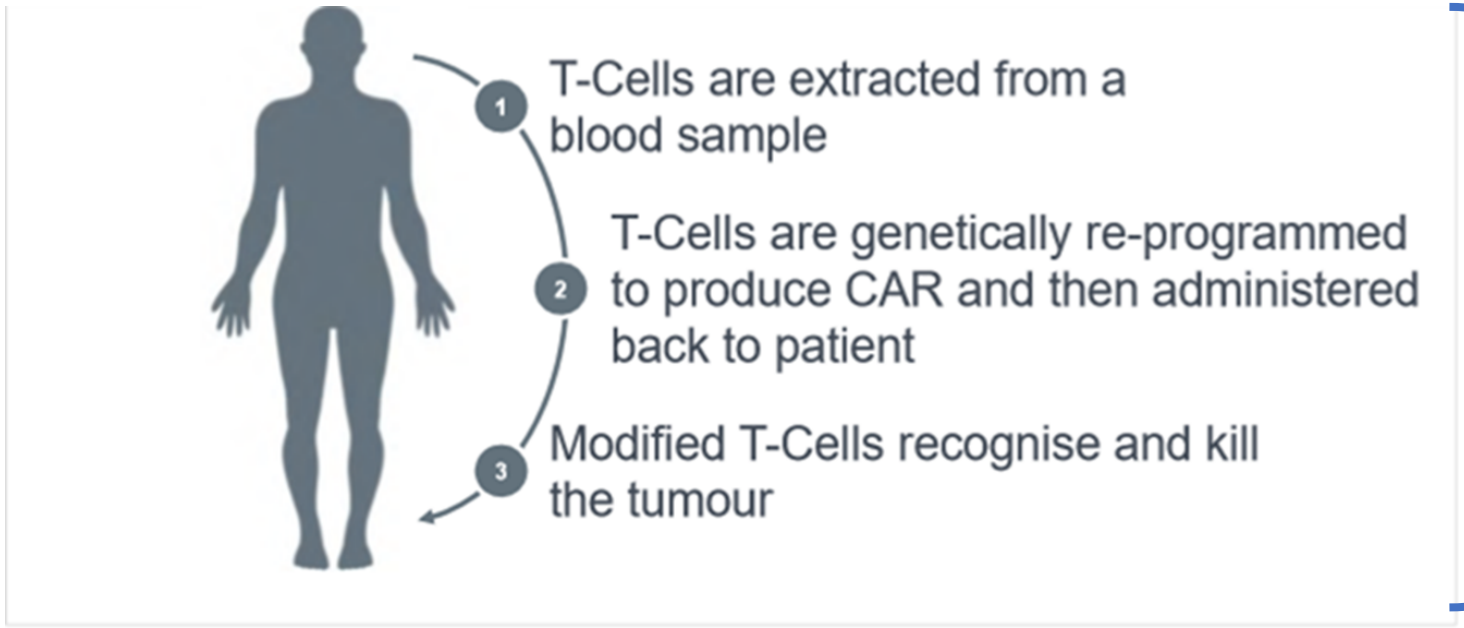
wherein the interleukin is two or more of IL-7, IL-2, IL-12, IL-15, IL-21, and IL-18.

Kymriah-Novartis

Agosto 2017, **FDA** approva **TISAGENLECLEUCEL** commercializzato da Novartis come **KYMRIAH**
Kymriah contains the active substance tisagenlecleucel (consisting of genetically modified white blood cells).

Ottobre 2017, **FDA** approva AXICABTAGENE CILOLEUCEL commercializzato da KitePharma come **YESCARTA**

2018 entrambi i medicinali sono approvati da EMA (European Medicines Agency)

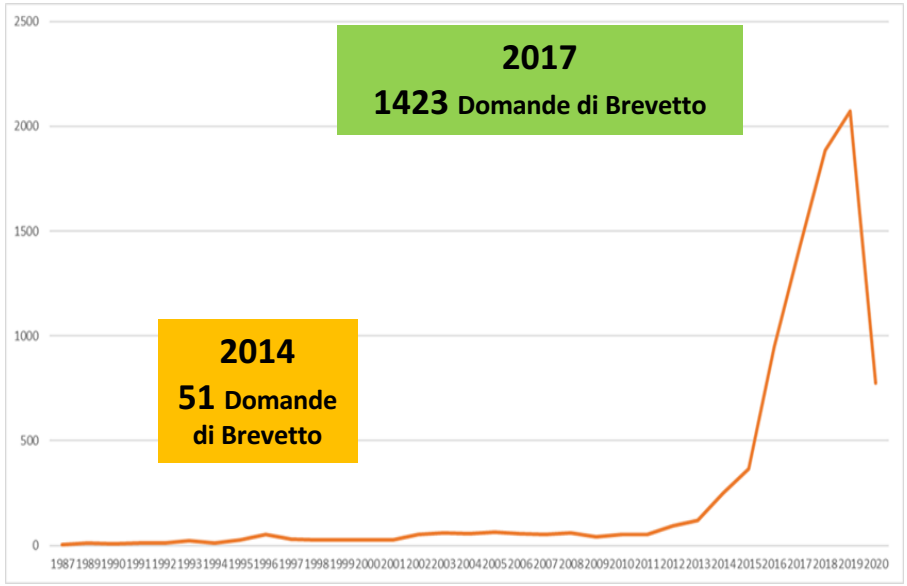


CAR-T CELLS SYSTEM

FASI TRATTAMENTO:

LEUCAFERESI : prelievo linfociti T dal paziente
RIPROGRAMMAZIONE : linfociti T ingegnerizzati usando un virus inattivo (vettore virale) per produrre recettori antigenici chimerici (CAR) che riconoscono cellule tumorali
ESPANSIONE
CONTROLLO QUALITA'
LINFODEPLEZIONE CHEMIOTERAPICA
REINFUSIONE
MONITORAGGIO

CONCLUSIONI



Data pubblicazione domande brevetto M.Miucci©

La tecnologia CAR-T ha visto un incremento esponenziale negli ultimi anni

Lo sviluppo di generazioni e l'aumento delle domande di brevetto mostra il potenziale terapeutico di CAR-T

Ad oggi ha dimostrato efficacia per il trattamento di tumori ematologici e sono in studio nuove applicazioni di CAR-T per ampliare la copertura terapeutica ai tumori solidi

GRAZIE PER L’ATTENZIONE