NEW YORK STATE BAR ASSOCIATION

ANNUAL MEETING | 2018
JANUARY 22 – 26

NYSBA
NEW YORK CITY
New York Hilton Midtown
www.nysba.org/AM2018

Intellectual Property Considerations for CAR-T Gene Therapy

VICTORIA M. MALIA, J.D.
SENIOR COUNSEL, NEW YORK GENOME CENTER

JANUARY 25, 2018

The following presentation reflects the personal views and thoughts of Victoria Malia and is not to be construed as representing in any way the corporate views or advice of the New York Genome Center and its Affiliates, Subsidiaries or Divisions, nor the views or advice of the New York State Bar Association.

The content is solely for purposes of discussion and illustration, and is not to be considered legal advice.

Overview of Today's Agenda:

PATENTS:

How statutory requirements promote innovation & competition

ST. JUDE CHILDREN'S RESEARCH HOSPITAL

v.

TRUSTEES OF UNIVERSITY OF PENNSYLVANIA

Why MTAs matter

Outcome

US 8,399,645

Claims

Prosecution history

- **$475k for a 1-time Kymriah™ treatment [1]**
- Novartis established an outcomes-based approach to reimbursement for Kymriah™ with the Centers for Medicare and Medicaid Services (CMS) that "allows for full payment only when these patients respond to Kymriah™ by the end of the first month after treatment."[1]
- Many people are concerned about the cost of healthcare. ***Some people believe patents are to blame for the high costs of therapies. They are especially suspicious of patenting discoveries that were funded with tax dollars.***[2]

What should we tell them
(and the people who listen to them)?

[1] Arlene Weintraub, How to cover Novartis' $475K CAR-T drug Kymriah? A 'new payment model' is the only way, Express Scripts says, Fierce Pharma, https://www.fiercepharma.com/financials/car-t-and-other-gene-therapies-need-new-payment-model-says-express-scripts (2017).

[2] Jim Kozubek, The Broad Institute is testing the limits of what 'nonprofit' means, STAT, https://www.statnews.com/2017/04/25/broad-institute-nonprofit-crispr/ (2017)..

Patents Benefit the Public

Inventions must meet high standards to qualify for patent protection and patent applications undergo rigorous examination

- Patents are only granted for ***claimed*** subject matter ***that didn't exist before***

  35 U.S.C. §101 (Subject matter) **35 U.S.C. § 102 (Novelty)** **35 U.S.C. §103 (Non-obviousness)**

- Patents ***require information to be shared***, rather than kept trade secret

  35 U.S.C. §112 (Specification)

- Patent rights are granted for a limited time and once expired, everyone is free to use the invention

  35 U.S.C. § 154 (Contents & term of patent; provisional rights) **35 U.S.C. § 156 (Extension of patent terms)**

- Various mechanisms currently exist to address abuse

  Antitrust Laws **35 U.S.C. § 203 (gov't-funded inventions "March-in rights")**

- **Patent status isn't the sole factor that determines the price of a drug**

  e.g., Daraprim® pyrimethamine went from $13.50 a tablet to $750 (in the United States) after Turing Pharmaceuticals acquired the drug from Impax Laboratories.

- **Other complex patented technologies have come down in price**

  e.g., cell phones, computers, whole genome sequencing

  Expect that gene therapies will eventually come down in price as gene therapy becomes more routine

- **The NIH funds basic research, but gene therapies (and clinical interventions in general) are not directly commercializable**

  It takes a *tremendous investment* to prove that a therapy is safe and effective.

  Companies, not universities or the government, are the ones who take the risks to develop and commercialize therapies

- St. Jude Children's Research Hospital, Inc. v. Trustees of the University of Pennsylvania, Civil Action No. 12-2579
  - Breach of contract action filed on July 11, 2012
  - Involved 2 material transfer agreements ("MTAs")
- Trustees of the University of Pennsylvania v. St. Jude Children's Research Hospital, Inc., Civil Action No. 12-4122
  - Penn filed a counter-claim for alleged tortious interference with prospective contractual relations on July19, 2012
  - Cases were consolidated. Penn's counter-claim dismissed
  - Penn filed for Declaratory Judgment of non-infringement & invalidity, once St. Jude's patent issued
  - St. Jude counter-claimed for willful patent infringement
- Case settled in April 2015

https://www.paed.uscourts.gov/documents2/search-documents

News Release

University of Pennsylvania and Novartis Form Alliance to Expand Use of Personalized T Cell Therapy for Cancer Patients

Industry-Academic Partnership Will Establish New Research Center to Expedite Study and Development of Gene Transfer Approach

August 06, 2012

PHILADELPHIA — In an alliance aimed at bringing a new, personalized immunotherapy approach to patients with a wide variety of cancers, the University of Pennsylvania and Novartis announced today an exclusive global research and licensing agreement to further study and commercialize novel cellular immunotherapies using chimeric antigen receptor (CAR) technologies. The agreement, which follows a Penn research team's 2011 publication of breakthrough results in several chronic lymphocytic leukemia patients treated with this personalized immunotherapy technique, paves the way for pivotal studies that have the potential to expand the use of CAR therapies for additional cancers.

Contacts

Holly Auer
C: 215-200-2313
O: 215-349-5659

Expectations: Material Transfer Agreements

- Journal policies require authors to share materials used in published research so that others may replicate the published work.
- NIH Guidelines require scientists to share materials generated from federally-funded research under reasonable terms.
- The definition of materials provided for use in federally-funded research must not include all derivatives, as the Bayh-Dole Act prohibits the transfer of title to inventions resulting from federally-funded research.
- The definition of "Material" takes on special significance when biological materials are involved.

Uniform Biological Material Transfer Agreement "UBMTA"

5.ORIGINAL MATERIAL: The description of the material being transferred will be specified in an implementing letter.

6.MATERIAL: ORIGINAL MATERIAL, PROGENY, and UNMODIFIED DERIVATIVES. The MATERIAL shall not include: (a) MODIFICATIONS, or (b) other substances created by the RECIPIENT through the use of the MATERIAL which are not MODIFICATIONS, PROGENY, or UNMODIFIED DERIVATIVES.

7.PROGENY: Unmodified descendant from the MATERIAL, such as virus from virus, cell from cell, or organism from organism.

8.UNMODIFIED DERIVATIVES: Substances created by the RECIPIENT which constitute an unmodified functional subunit or product expressed by the ORIGINAL MATERIAL. Some examples include: subclones of unmodified cell lines, purified or fractionated subsets of the ORIGINAL MATERIAL, proteins expressed by DNA/RNA supplied by the PROVIDER, or monoclonal antibodies secreted by a hybridoma cell line.

9.MODIFICATIONS: Substances created by the RECIPIENT which contain/incorporate the MATERIAL.

1.The PROVIDER retains ownership of the MATERIAL, including any MATERIAL contained or incorporated in MODIFICATIONS.

2.The RECIPIENT retains ownership of: (a) MODIFICATIONS (except that, the PROVIDER retains ownership rights to the MATERIAL included therein), and (b) those substances created through the use of the MATERIAL or MODIFICATIONS, but which are not PROGENY, UNMODIFIED DERIVATIVES or MODIFICATIONS (i.e., do not contain the ORIGINAL MATERIAL, PROGENY, UNMODIFIED DERIVATIVES). If either 2 (a) or 2 (b) results from the collaborative efforts of the PROVIDER and the RECIPIENT, joint ownership may be negotiated.

EXHIBIT A

St. Jude Children's Research Hospital
ALSAC · Danny Thomas, Founder

December 10, 2003

Collaboration and Materials Transfer Agreement

Dr. Carl June
Professor of Pathology and Laboratory Medicine
University of Pennsylvania School of Medicine
Room 554 BRB II/III
421 Curie Boulevard
Philadelphia, PA 19104-6160

Dear Dr. June:

This Agreement, effective upon signing, governs an arrangement whereby Dr. Dario Campana of St. Jude Children's Research Hospital, Inc., ("St. Jude") agrees to provide biological material that is proprietary to St. Jude, for use in a collaborative research study with Dr. Carl June ("Recipient Scientist") of the University of Pennsylvania ("Recipient"), subject to the terms and conditions set forth below.

Trustees of the University of Pennsylvania

1. The biological material to be provided to Recipient Scientist is the anti-CD19-BB-ζ chimeric T-cell receptor construct, including any progeny, portions, unmodified derivatives and any accompanying know-how or data ("Material"). Legal title to the Material shall remain with St. Jude. The Recipient acknowledges that the Material is or may be the subject of a patent application. Except as provided in this Agreement, no express or implied licenses or other rights are provided to the Recipient under any patents, patent applications, trade secrets or other proprietary rights of St. Jude, including any altered forms of the Material made by St. Jude.

2. The Material is for use by Recipient Scientist or persons directly supervised by Recipient Scientist. The Material may not be transferred or taken to any other laboratory or made available to any other person or third party, but is to remain under the immediate and direct control of Recipient Scientist.

3. Recipient Scientist agrees that the Material will only be used to create a lentiviral chimeric T-cell receptor construct to be used in pre-clinical studies.

4. The Material may not be used in humans and will be stored, used, and disposed of in accordance with applicable law and regulations. The Material will not be used for any commercial purpose.

5. St. Jude retains the unrestricted right to distribute the Material to other commercial or noncommercial entities.

6. Recipient agrees that any publications that result from the collaborative research study between St. Jude and Recipient Scientist using the Material will be jointly published in accordance with academic standards.

7. The transfer of the Material grants to Recipient no rights in the Material other than those specifically set forth in the Agreement. This agreement may be terminated upon thirty (30) days written notice by either party to the other. Upon termination of the agreement, Recipient shall destroy all unused Materials.

8. Recipient shall not commercialize any product that contains Material without the prior written approval of St. Jude. The Recipient is free to file patent application(s) claiming inventions made by Recipient through use of the Material but agrees to notify St. Jude within sixty (60) days of filing any patent application which claims subject matter that contains or incorporates the Material or which claims a method of manufacture or use of the Material. Recipient grants to St. Jude a non-exclusive, royalty-free license to use for non-commercial purposes any inventions that arise from the use of the Materials. INVENTORSHIP WILL BE DETERMINED ACCORDING TO US PATENT LAW TJR 12/17/03

9. The Material provided is experimental in nature, and it is provided WITHOUT ANY WARRANTIES, EXPRESS OR IMPLIED, INCLUDING WITHOUT LIMITATION WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR USE. St. Jude MAKES NO REPRESENTATION AND PROVIDES NO WARRANTY THAT THE USE OF THE MATERIAL WILL NOT INFRINGE ANY PATENT OR OTHER PROPRIETARY RIGHT. 12/19/03

10. Except to the extent prohibited by law, the Recipient assumes all liability for damages that may arise from its use, storage or disposal of the Materials. St. Jude and corporate affiliates of St. Jude and their respective Boards of Governors, Directors, officers, staff, representatives and agents will not be liable to the Recipient for any damages, expenses (including without limitation legal expenses), losses, claims, demands, suit or other actions (collectively hereinafter "Claims") made by the Recipient, or made against the Recipient by any other party, due to or arising from the use, storage or disposal of the Materials by the Recipient, except to the extent such Claims are solely caused by the gross negligence or willful misconduct of St. Jude.

If Recipient Scientist and Recipient agree to the above, please sign and have an authorized official of Recipient sign and return a copy of this letter to Esther Allay in the Office of Technology Licensing.

Sincerely,

J. Scott Elmer
Director
Office of Technology Licensing

Agreed and Accepted

Carl June
Dr. Carl June

12/16/2003
Date

Institution Official

Name: Timothy J. Raynor
Director, Intellectual Property
Center for Technology Transfer
University of Pennsylvania

Title

12/17/03
Date

St. Jude refers to the June Construct as containing an "exact copy of all but one of the approximately 1,500 base pairs comprising the cDNA supplied by St. Jude", St. Judge MSJ at 20, and describes it as a "lentiviral vector clone", id. at 8 (emphases added). St. Jude thus does not appear to contend that the June Construct contains a physical portion of the Campana Construct -- instead, St. Jude argues that by using a gene sequence identical to that of the Campana Construct, except for the differences we just mentioned, Dr. June has created a construct that "contains" a "portion" of the anti-CD19-BB-ζ and is thus subject to the commercialization and crediting restrictions of the MTAs.

Thus, whether the copy of the Campana Construct sequence in the June Construct constitutes a "portion" under the MTA is a matter not of factual dispute but of contract interpretation.[1]

[1] November 13, 2013 Court's Memorandum at page 34 *(emphasis added)*

Penn argues that the June Construct does not contain a "portion" of the materials ***because it does not contain "a physical part of the whole provided by St. Jude***", Penn Resp. in Opp. at 20, but instead contains a modified derivative.

Penn also points to paragraph five of the 2007 MTA which provides that with regard to patents "[o]wnership shall follow inventorship according to US patent law." Penn reads this as demonstrating a "clear intent . . . To allow the University to research and create a new substance in which it would presumably have its own rights", while under St. Jude's interpretation, "even a copy of a single nucleotide, molecule, or even atom from the Campana Construct would constitute a 'portion' of the Materials", Penn Resp. in Opp. At 20-21.[1]

[1]April 12, 2013 Court's Memorandum at pages 38 & 39 *(emphasis added)*

Representative CAR-T Receptor

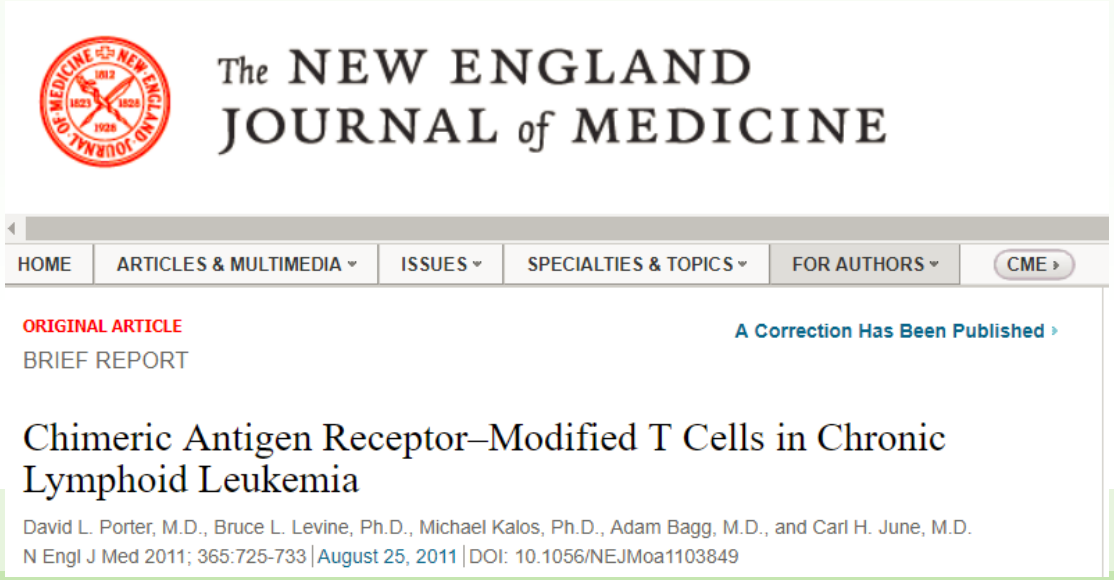
From page 11 of Juno Therapeutics, Inc. Form 10-K (fiscal year ended December 31, 2015)

Outcome

St. Jude's exclusive licensee, Juno Therapeutics, Inc. entered into a sublicense agreement with Novartis and Penn:

1. **Novartis was granted a non-exclusive, royalty-bearing sublicense under certain patents, including the '645 patent, to develop, make, and commercialize licensed products and licensed services for all therapeutic, diagnostic, preventative and palliative uses in the United States.**
   - $12.3 million up-front
   - Mid-single digit royalty on the US net sales of products and services related to the disputed contract and patent claims
   - Low double-digit percentage of the royalties Novartis pays to Penn for global net sales of those products
   - Milestone payments upon the achievement of specified clinical, regulatory and commercialization milestones for licensed products. Juno to reimburse 50% upon reaching same milestones. Novartis' obligation will be reduced by 50% if they reach the same milestone after Juno.

2. **Penn required to issue correction to Penn's publications acknowledging the contribution of St. Jude's researchers.**



The NEW ENGLAND JOURNAL of MEDICINE

HOME | ARTICLES & MULTIMEDIA | ISSUES | SPECIALTIES & TOPICS | FOR AUTHORS | CME

ORIGINAL ARTICLE

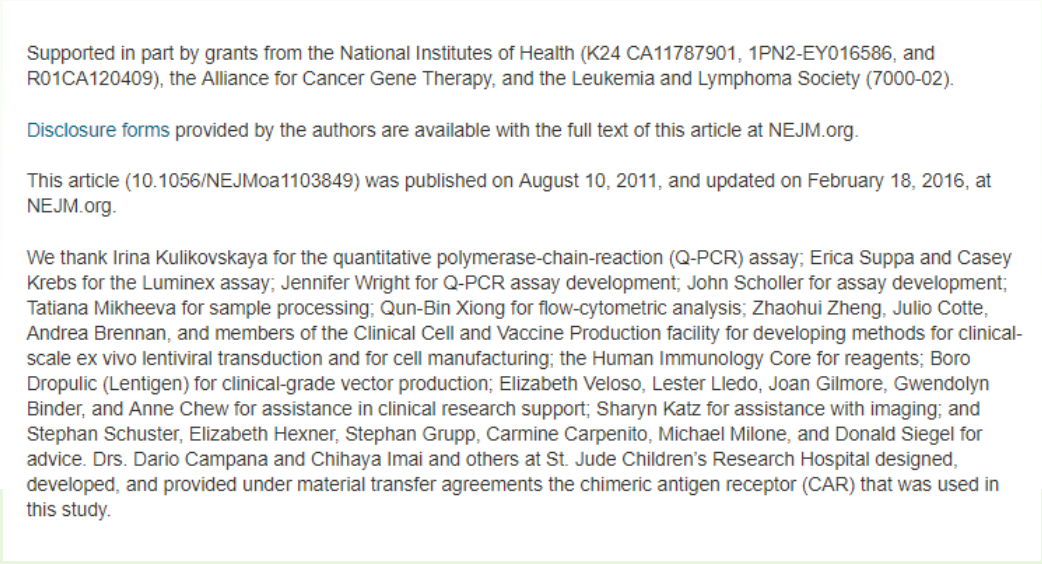
BRIEF REPORT

A Correction Has Been Published

Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

N Engl J Med 2011; 365:725-733 | August 25, 2011 | DOI: 10.1056/NEJMoa1103849



Supported in part by grants from the National Institutes of Health (K24 CA11787901, 1PN2-EY016586, and R01CA120409), the Alliance for Cancer Gene Therapy, and the Leukemia and Lymphoma Society (7000-02).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

This article (10.1056/NEJMoa1103849) was published on August 10, 2011, and updated on February 18, 2016, at NEJM.org.

We thank Irina Kulikovskaya for the quantitative polymerase-chain-reaction (Q-PCR) assay; Erica Suppa and Casey Krebs for the Luminex assay; Jennifer Wright for Q-PCR assay development; John Scholler for assay development; Tatiana Mikheeva for sample processing; Qun-Bin Xiong for flow-cytometric analysis; Zhaohui Zheng, Julio Cotte, Andrea Brennan, and members of the Clinical Cell and Vaccine Production facility for developing methods for clinical-scale ex vivo lentiviral transduction and for cell manufacturing; the Human Immunology Core for reagents; Boro Dropulic (Lentigen) for clinical-grade vector production; Elizabeth Veloso, Lester Lledo, Joan Gilmore, Gwendolyn Binder, and Anne Chew for assistance in clinical research support; Sharyn Katz for assistance with imaging; and Stephan Schuster, Elizabeth Hexner, Stephan Grupp, Carmine Carpenito, Michael Milone, and Donald Siegel for advice. Drs. Dario Campana and Chihaya Imai and others at St. Jude Children's Research Hospital designed, developed, and provided under material transfer agreements the chimeric antigen receptor (CAR) that was used in this study.

US 8,399,645

uspto.GOV
The United States Patent and Trademark Office
an agency of the Department of Commerce

Patent Application Information Retrieval

Home Patents Trademarks Other

Patent eBusiness

- Electronic Filing
- Patent Application Information (PAIR)
- Patent Ownership
- Fees
- Supplemental Resources & Support

Patent Information

- Patent Guidance and General Info
- Codes, Rules & Manuals
- Employee & Office Directories
- Resources & Public Notices

Patent Searches

- Patent Official Gazette
- Search Patents & Applications
- Search Biological Sequences
- Copies, Products & Services

Other

- Copyrights
- Trademarks
- Policy & Law
- Reports

Patent Application Information Retrieval

Global Dossier | Order Certified Application As Filed | Order Certified File Wrapper | View Order List

13/548,148 CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN 35531-0101004

Select New Case | Application Data | Transaction History | Image File Wrapper | Patent Term Adjustments | Continuity Data | Fees | Published Documents | Address & Attorney/Agent | Supplemental Content | Assignments | Display References

Parent Continuity Data

Description	Parent Number	Parent Filing or 371(c) Date	AIA(First Inventor to File)	Parent Status	Patent Number
This application is a Continuation of	13/244,981	09-26-2011	No	Abandoned	-
is a continuation of	12/206,204	09-08-2008	No	Patented	8,026,097
is a continuation of	11/074,525	03-08-2005	No	Patented	7,435,596
is a Continuation-in-part of	10/981,352	11-04-2004	No	Abandoned	-
Claims Priority from Provisional Application	60/517,507	11-05-2003	-	Expired	-

Child Continuity Data

13/761,917 filed on 02-07-2013 which is Abandoned claims the benefit of 13/548,148
13/826,258 filed on 03-14-2013 which is Abandoned claims the benefit of 13/548,148
14/301,122 filed on 06-10-2014 which is Patented claims the benefit of 13/548,148
14/303,331 filed on 06-12-2014 which is Patented claims the benefit of 13/548,148
14/872,947 filed on 10-01-2015 which is Patented claims the benefit of 13/548,148
15/470,678 filed on 03-27-2017 which is Pending claims the benefit of 13/548,148
15/802,968 filed on 11-03-2017 which is Pending claims the benefit of 13/548,148
15/837,715 filed on - which is Pending claims the benefit of 13/548,148

If you need help:

- *Contact the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail EBC@uspto.gov for specific questions about Patent Application Information Retrieval (PAIR).*
- *If you experience technical difficulties or problems with PAIR outside normal Patent Electronic Business Center hours (M-F, 6AM to 12AM ET), please call 1 800-786-9199.*
- *Send general questions about USPTO programs to the USPTO Contact Center (UCC).*

WHAT IS CLAIMED IS:

1. A chimeric receptor comprising an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, a hinge and transmembrane domain, and a cytoplasmic domain comprising a 4-1BB signaling domain.

2. The chimeric receptor of claim 1, wherein the 4-1BB signaling domain comprises amino acids 214-255 of SEQ ID NO:2.

3. The chimeric receptor of claim 2, wherein the cytoplasmic domain further comprises a CD3ζ signaling domain in addition to the 4-1BB signaling domain.

4. The chimeric receptor of claim 3, wherein the hinge and transmembrane domain is the hinge and transmembrane domain of CD8α.

5. The chimeric receptor of claim 4, wherein the extracellular ligand-binding domain further comprises a signal peptide of CD8α.

6. A polynucleotide encoding the chimeric receptor of claim 1.

7. A vector comprising a polynucleotide encoding the chimeric receptor of claim 1 operatively linked to at least one regulatory element for expression of the chimeric receptor.

8. A host cell comprising a polynucleotide encoding the chimeric receptor of claim 1.

9. The host cell of claim 8 which is a T lymphocyte or an NK cell.

10. The host cell of claim 9 which is a T lymphocyte.

11. A host cell comprising the chimeric receptor of claim 1.

12. The host cell of claim 11 which is a T lymphocyte or an NK cell.

13. The host cell of claim 11 which is a T lymphocyte.

14. A method of enhancing a T lymphocyte or an NK cell activity in an individual comprising introducing into the individual a T lymphocyte or NK cell, which T lymphocyte or NK cell comprises a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, (b) a hinge and transmembrane domain, and (c) a cytoplasmic domain comprising a 4-1BB signaling domain.

15. The method of claim 14 wherein the 4-1BB signaling domain of the chimeric receptor comprises amino acids 214-255 of SEQ ID NO:2.

16. The method of claim 15 wherein the cytoplasmic domain of the chimeric receptor further comprises a CD3ζ signaling domain in addition to the 4-1BB signaling domain.

17. The method claim 16, wherein the hinge and transmembrane domain of the chimeric receptor is a CD8α hinge and transmembrane domain.

18. The method of claim 17, wherein the extracellular ligand-binding domain of the chimeric receptor further comprises a signal peptide of CD8α.

19. The method of claim 14, wherein the individual is suffering from a cancer of B-cell origin.

20. The method of claim 19, wherein the cancer is selected from the group consisting of B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma.

21. The method of claim 14, wherein the individual is suffering from lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer,

neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma, acute lymphoblastic leukemia, small cell lung cancer, Hodgkin's lymphoma, or childhood acute lymphoblastic leukemia.

22. A method for treating an individual suffering from cancer comprising introducing into the individual a T lymphocyte or an NK cell, which T lymphocyte or NK cell comprises a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 scFv domain; (b) a hinge region and transmembrane domain of CD8α; and (c) a cytoplasmic domain comprising a signaling domain of 4-1BB.

23. The method of claim 22, wherein the 4-1BB signaling domain of the chimeric receptor comprises amino acids 214-255 of SEQ ID NO:2.

24. The method of claim 23, wherein the cytoplasmic domain of the chimeric receptor further comprises a CD3ζ signaling domain in addition to the 4-1BB signaling domain.

25. The method claim 24, wherein the hinge and transmembrane domain of the chimeric receptor is a CD8α hinge and transmembrane domain.

26. The method of claim 25, wherein the extracellular ligand-binding domain of the chimeric receptor further comprises a signal peptide of CD8α.

27. The method of claim 22, wherein the individual is suffering from a cancer of B-cell origin.

28. The method of claim 27, wherein the cancer is selected from the group consisting of B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia and B-cell non-Hodgkin's lymphoma.

29. The method of claim 22, wherein the cancer is selected from the group consisting of lung cancer, melanoma, breast cancer, prostate cancer, colon cancer, renal cell carcinoma, ovarian cancer, neuroblastoma, rhabdomyosarcoma, leukemia and lymphoma, acute

lymphoblastic leukemia, small cell lung cancer, Hodgkin's lymphoma, and childhood acute lymphoblastic leukemia.

US008399645B2

(12) **United States Patent**
Campana et al.

(10) **Patent No.: US 8,399,645 B2**
(45) **Date of Patent: Mar. 19, 2013**

(54) **CHIMERIC RECEPTORS WITH 4-1BB STIMULATORY SIGNALING DOMAIN**

(75) Inventors: **Dario Campana**, Germantown, TN (US); **Chihaya Imai**, Niigata (JP)

(73) Assignee: **St. Jude Children's Research Hospital, Inc.**, Memphis, TN (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/548,148**

(22) Filed: **Jul. 12, 2012**

(65) **Prior Publication Data**

US 2012/0282256 A1 Nov. 8, 2012

Related U.S. Application Data

(63) Continuation of application No. 13/244,981, filed on Sep. 26, 2011, now abandoned, which is a continuation of application No. 12/206,204, filed on Sep. 8, 2008, now Pat. No. 8,026,097, which is a continuation of application No. 11/074,525, filed on Mar. 8, 2005, now Pat. No. 7,435,596, which is a continuation-in-part of application No. 10/981,352, filed on Nov. 4, 2004, now abandoned.

(60) Provisional application No. 60/517,507, filed on Nov. 5, 2003.

(51) **Int. Cl.**
C07H 21/04 (2006.01)
C12N 15/00 (2006.01)

(52) **U.S. Cl.** **536/23.4**; 435/320.1; 435/455

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,359,046	A	10/1994	Capon et al.	
5,674,704	A	10/1997	Goodwin et al.	
5,686,281	A	11/1997	Roberts	
6,103,521	A	8/2000	Capon et al.	
6,303,121	B1	10/2001	Kwon	
7,070,995	B2	7/2006	Jensen	
7,435,596	B2	10/2008	Campana et al.	
7,446,190	B2	11/2008	Sadelain et al.	
8,026,097	B2	9/2011	Campana et al.	
2003/0147869	A1	8/2003	Riley et al.	
2003/0215427	A1 *	11/2003	Jensen	424/93.21
2004/0038886	A1	2/2004	Finney et al.	
2004/0043401	A1 *	3/2004	Sadelain et al.	435/6
2004/0126363	A1 *	7/2004	Jensen et al.	424/93.21
2005/0113564	A1	5/2005	Campana et al.	
2012/0015434	A1	1/2012	Campana et al.	

OTHER PUBLICATIONS

Imai et al. (Blood, 102 (11): p. 66a-67a; Nov. 16, 2003).*
Imai et al. (Journal of Biological Regulators and Homeostatic Agents, 18 (1): p. 62-71; Jan. 2004; abstract only).*
Koehler et al. (Advances in Hematology, vol. 2012, Article ID 595060, 13 pages; doi:10.1155/2012/595060.*
Alderson MR, et. al., "Molecular and biological characterization of human 4-1BB and its ligand. Eur J Immunol", Sep. 1994; 24 (9) :2219-27.
Brentjens RJ, et. al., "Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15", Nat Med. Mar. 2003; 9 (3) :279-86.
Bukczynski J, et. al., "Costimulation of human CD28- T cells by 4-1BB ligand", Eur J Immunol. Feb. 2003; 33 (2) :446-54.
Burkett PR, et. al., "Coordinate expression and trans presentation of interleukin (IL)-15Ralpha and IL-15 supports natural killer cell and memory CD8+ T cell homeostasis", J Exp Med. Oct. 4, 2004; 200 (7):825-34.
Campana D, et. al., "Immunophenotyping of leukemia. J Immunol Methods", Sep. 21, 2000; 243 (1-2):59-75.
Carson WE, et. al., "A potential role for interleukin-15 in the regulation of human natural killer cell survival", J Clin Invest. Mar. 1, 1997; 99 (5) :937-43.
Cheung NK, et. al., "Anti-idiotypic antibody facilitates scFv chimeric immune receptor gene transduction and clonal expansion of human lymphocytes for tumor therapy. Hybrid Hybridomics", Aug. 2003; 22 (4) :209-18.
Cooper LJ, et. al., "T-cell clones can be rendered specific for CD19: toward the selective augmentation of the graft-versus-B-lineage leukemia effect", Blood. Feb. 15, 2003; 101 (4) :1637-44.
Cooper MA, et. al., "In vivo evidence for a dependence on interleukin 15 for survival of natural killer cells", Blood. Nov. 15, 2002; 100 (10) :3633-8.
DeBenedette MA, et. al., "Costimulation of CD28- T lymphocytes by 4-1BB ligand. J Immunol", Jan. 15, 1997; 158 (2) :551-9.
Eshhar Z, et. al., "Functional expression of chimeric receptor genes in human T cells", J Immunol Methods. Feb. 1, 2001; 248 (1-2) :67-76.
Farag SS, et. al., "Natural killer cell receptors: new biology and insights into the graft-versus-leukemia effect", Blood. Sep. 15, 2002; 100 (6) :1935-47.
Fehniger TA, et. al.; "Ontogeny and expansion of human natural killer cells: clinical implications", Int Rev Immunol. Jun. 2001; 20 (3-4) :503-34.
Finney HM, et. al., "Activation of resting human primary T cells with chimeric receptors: costimulation from CD28, inducible costimulator, CD134, and CD137 in series with signals from the TCR zeta chain", J Immunol. Jan. 1, 2004; 172 (1) :104-13.
Geiger TL, et. al., "Integrated src kinase and costimulatory activity enhances signal transduction through single-chain chimeric receptors in T lymphocytes", Blood. Oct. 15, 2001; 98 (8) :2364-71.
Goodwin RG, et. al., "Molecular cloning of a ligand for the inducible T cell gene 4-1BB: a member of an emerging family of cytokines with homology to tumor necrosis factor", Eur J Immunol. Oct. 1993; 23 (10) :2631-41.
Greenwald RJ, et. al., "The B7 family revisited", Annu Rev Immunol. 2005; 23:515-48.

(Continued)

Primary Examiner — Ilia Ouspenski
(74) *Attorney, Agent, or Firm* — Jones Day

(57) **ABSTRACT**

The present invention relates to a chimeric receptor capable of signaling both a primary and a co-stimulatory pathway, thus allowing activation of the co-stimulatory pathway without binding to the natural ligand. The cytoplasmic domain of the receptor contains a portion of the 4-1BB signaling domain. Embodiments of the invention relate to polynucleotides that encode the receptor, vectors and host cells encoding a chimeric receptor, particularly including T cells and natural killer (NK) cells and methods of use.

22 Claims, 2 Drawing Sheets

US 8,399,645

What is claimed is:

1. A polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

2. A vector comprising a polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain, (b) a transmembrane domain, and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain, wherein the polynucleotide encoding the chimeric receptor is operatively linked to at least one regulatory element for expression of the chimeric receptor.

3. An isolated host cell comprising a polynucleotide encoding a chimeric receptor comprising: (a) an extracellular ligand-binding domain comprising an anti-CD19 single chain variable fragment (scFv) domain; (b) a transmembrane domain; and (c) a cytoplasmic domain comprising a 4-1BB signaling domain and a CD3ζ signaling domain.

4. The isolated host cell of claim **3** which is a T lymphocyte or an NK cell.

5. The isolated host cell of claim **3** which is a T lymphocyte.

6. The polynucleotide of claim **1** wherein the signaling domain is a human 4-1BB signaling domain.

7. The polynucleotide of claim **6**, Wherein the 4-1BB signaling domain comprises amino acids 214-255 of SEQ ID NO:2.

8. The polynucleotide of claim **7**, wherein the nucleotide sequence encoding the human 4-1BB signaling domain comprises nucleotide residues 129-893 of SEQ ID NO:1.

9. The polynucleotide of claim **1**, wherein the transmembrane domain is the transmembrane domain of CD8α.

10. The polynucleotide of claim **9**, wherein the extracellular ligand-binding domain further comprises a signal peptide of CD8α.

11. The vector of claim **2** which is a viral vector.

12. The vector of claim **11** which is a retroviral vector.

13. The isolated host cell of claim **3** which is an NK cell.

14. The isolated host cell of claim **3** which is an autologous cell isolated from a patient having a cancer of B cell origin.

15. The isolated host cell of claim **14**, wherein the autologous cell is an autologous T lymphocyte.

16. The isolated host cell of claim **15**, wherein the autologous T lymphocyte is derived from a blood or tumor sample of a patient having a cancer of B cell origin and activated and expanded in vitro.

17. The isolated host cell of claim **5**, wherein the T lymphocyte is an activated T lymphocyte.

18. The isolated host cell of claim **5**, wherein the T lymphocyte is isolated from a blood or tumor sample of a patient having a cancer of B cell origin.

19. The isolated host cell of claim **18** wherein the host cell is isolated from a patient having lymphoblastic leukemia, B-lineage acute lymphoblastic leukemia, B-cell chronic lymphocytic leukemia or B-cell non-Hodgkin's lymphoma.

20. The polynucleotide of claim **1**, wherein the chimeric receptor further comprises a hinge domain.

21. The vector of claim **2**, wherein the chimeric receptor further comprises a hinge domain.

22. The isolated cell of claim **3**, wherein the chimeric receptor further comprises a hinge domain.

* * * * *

March-in rights under 35 U.S.C. § 203

(a) With respect to any subject invention in which a small business firm or nonprofit organization has acquired title under this chapter, the Federal agency under whose funding agreement the subject invention was made shall have the right, in accordance with such procedures as are provided in regulations promulgated hereunder to require the contractor, an assignee or exclusive licensee of a subject invention to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such request, to grant such a license itself, if the Federal agency determines that such —

(1) action is necessary because the contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use;

(2) action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees;

(3) action is necessary to meet requirements for public use specified by Federal regulations and such requirements are not reasonably satisfied by the contractor, assignee, or licensees; or

(4) action is necessary because the agreement required by section 204 has not been obtained or waived or because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of its agreement obtained pursuant to section 204.

- **35 U.S.C. § 101. Inventions patentable**

  Whoever invents or discovers *any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof,* may obtain a patent therefor, subject to the conditions and requirements of this title.

  Judicially recognized exceptions: *laws of nature, natural phenomena, and abstract ideas*[1]

  - A gene sequence is not patentable subject matter, as it occurs in nature;
    But, a cDNA is patentable subject matter because it doesn't occur in nature
  - Polyclonal antibodies aren't patentable subject matter, as they occur in nature;
    But, monoclonal antibodies are patentable subject matter because they don't occur in nature

[1]Alice Corp. Pty. Ltd. v. CLS Bank Int'l, 573 U.S. _, 134 S. Ct. 2347, 2354, 110 USPQ2d 1976, 1980 (2014) (citing Association for Molecular Pathology v. Myriad Genetics, Inc. 569 U.S. _, 133 S. Ct. 2107, 2116, 106 USPQ2d 1972, 1979 (2013)). See also Bilski v. Kappos, 561 U.S.593, 601, 130 S. Ct. 3218, 3225, 95 USPQ2d 1001, 1005-06 (2010) (stating "The Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: 'laws of nature, physical phenomena, and abstract ideas.'") (quoting Diamond v. Chakrabarty, 447 U.S. 303, 309, 206 USPQ 193, 197 (1980)).

- **35 U.S.C. §102. Conditions for patentability; novelty**

  A claim is not novel if each and every element of the claim is found in a single prior art reference ***"That which infringes if later anticipates if earlier."***[2]

- **35 U.S.C. §103. Conditions for patentability; non-obvious subject matter**

  A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, ***if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious*** before the effective filing date of the claimed invention ***to a person having ordinary skill in the art to which the claimed invention pertains***. Patentability shall not be negated by the manner in which the invention was made.

[2] Polaroid Corp. v. Eastman Kodak Co., 789 F.2d 1556, 1573, 229 USPQ 561, 574 (Fed.Cir.1986) (citing Peters v. Active Mfg. Co., 129 U.S. 530, 537, 9 S.Ct. 389, 32 L.Ed. 738 (1889)). See generally Lewmar Marine, Inc. v. Barient, Inc., 827 F.2d 744, 747, 3 USPQ2d 1766, 1768 (Fed.Cir.1987).

Patents Contribute to Public Knowlege

- **35 U.S.C. § 112. Specification**

  The specification shall contain a ***written description*** of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to ***enable*** any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the ***best mode*** contemplated by the inventor or joint inventor of carrying out the invention.

Patent Rights Exist for a Finite Time

- US Constitution, Article I, Section 8: To promote the Progress of Science and useful Arts, by securing *for limited Times* to Authors and Inventors the *exclusive Right* to their respective Writings and Discoveries
- In general, patents exclude others from practicing claimed invention for 20 years from the original filing date.

  35 U.S.C. §154. Contents and term of patent; provisional rights

  35 U.S.C. § 156. Extension of patent term

US 7,638,325

uspto.gov
The United States Patent and Trademark Office
an agency of the Department of Commerce

Patent Application Information Retrieval

Home Patents Trademarks Other

Patent eBusiness

- Electronic Filing
- Patent Application Information (PAIR)
- Patent Ownership
- Fees
- Supplemental Resources & Support

Patent Information

- Patent Guidance and General Info
- Codes, Rules & Manuals
- Employee & Office Directories
- Resources & Public Notices

Patent Searches

- Patent Official Gazette
- Search Patents & Applications
- Search Biological Sequences
- Copies, Products & Services

Other

- Copyrights
- Trademarks
- Policy & Law
- Reports

Patent Application Information Retrieval

Global Dossier | Order Certified Application As Filed | Order Certified File Wrapper | View Order List

10/336,224 ACTIVATION AND EXPANSION OF T-CELLS USING AN ENGINEERED MULTIVALENT SIGNALING PLATFORM **46483-5064-00-US (207148)**

Select New Case | Application Data | Transaction History | Image File Wrapper | Patent Term Adjustments | Continuity Data | Fees | Published Documents | Address & Attorney/Agent | Assignments | Display References

Parent Continuity Data

Description	Parent Number	Parent Filing or 371(c) Date	AIA(First Inventor to File)	Parent Status	Patent Number
This application Claims Priority from Provisional Application	60/346,092	01-03-2002	-	Expired	-

Child Continuity Data

10/462,207 filed on 06-13-2003 which is Patented claims the benefit of 10/336,224
10/461,283 filed on 06-13-2003 which is Patented claims the benefit of 10/336,224
12/777,053 filed on 05-10-2010 which is Patented claims the benefit of 10/336,224
15/233,397 filed on 08-10-2016 which is Pending claims the benefit of 10/336,224
14/134,873 filed on 12-19-2013 which is Patented claims the benefit of 10/336,224

If you need help:

- *Contact the Patent Electronic Business Center at (866) 217-9197 (toll free) or e-mail EBC@uspto.gov for specific questions about Patent Application Information Retrieval (PAIR).*
- *If you experience technical difficulties or problems with PAIR outside normal Patent Electronic Business Center hours (M-F, 6AM to 12AM ET), please call 1 800-786-9199.*
- *Send general questions about USPTO programs to the USPTO Contact Center (UCC).*