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June et al.

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(54) **COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER**

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(56) **References Cited**
U.S. PATENT DOCUMENTS

5,359,046 A 10/1994 Capon et al.
5,686,281 A 11/1997 Roberts
5,712,149 A 1/1998 Roberts
5,874,240 A 2/1999 Ni et al.
5,906,936 A 5/1999 Eshhar et al.
6,103,521 A 8/2000 Capon et al.
6,319,494 B1 11/2001 Capon et al.
6,355,779 B1 3/2002 Goodwin et al.
6,410,319 B1 6/2002 Raubitschek et al.
(Continued)

FOREIGN PATENT DOCUMENTS

EP 0574512 B1 2/2003
EP 1226244 7/2004
(Continued)

OTHER PUBLICATIONS

A NCBI Direct Submission NP 000725 dated Nov. 21, 2010.
(Continued)

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(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.

30 Claims, 26 Drawing Sheets

(56)

References Cited

OTHER PUBLICATIONS

U.S. PATENT DOCUMENTS

6,569,997 B1 5/2003 Kwon
 7,049,136 B2 5/2006 Seed et al.
 7,052,906 B1 5/2006 Lawson et al.
 7,070,995 B2 7/2006 Jensen
 7,265,209 B2 9/2007 Jensen
 7,319,143 B2 1/2008 Gross et al.
 7,320,787 B2 1/2008 Seed et al.
 7,402,431 B2 7/2008 Har-Noy
 7,446,190 B2 11/2008 Sadelain et al.
 7,446,191 B2 11/2008 Jensen
 7,514,537 B2 4/2009 Jensen
 7,741,465 B1 6/2010 Esshar et al.
 7,994,298 B2 8/2011 Zhang et al.
 8,211,422 B2 7/2012 Esshar et al.
 8,252,914 B2 8/2012 Zhang et al.
 8,389,282 B2 3/2013 Sadelain et al.
 8,399,645 B2 3/2013 Campana et al.
 8,465,743 B2 6/2013 Rosenberg et al.
 2003/0060444 A1 3/2003 Finney et al.
 2003/0077249 A1 4/2003 Bebbington et al.
 2003/0148982 A1 8/2003 Brenner et al.
 2004/0038886 A1 2/2004 Finney et al.
 2004/0043401 A1 3/2004 Sadelain et al.
 2005/0113564 A1 5/2005 Campana et al.
 2005/0129671 A1 6/2005 Cooper et al.
 2008/0131415 A1 6/2008 Riddell et al.
 2009/0257994 A1 10/2009 Jensen
 2010/0233200 A1 9/2010 Medin
 2011/0052554 A1 3/2011 Zakrzewski et al.
 2012/0148552 A1 6/2012 Jensen
 2013/0071414 A1 3/2013 Dotti et al.
 2013/0149337 A1 6/2013 Cooper et al.
 2016/0208012 A1* 7/2016 June A61K 35/17

FOREIGN PATENT DOCUMENTS

EP 871495 6/2005
 JP 2003-517301 5/2003
 JP 2004-529636 9/2004
 WO WO/92/15322 9/1992
 WO WO/95/30014 11/1995
 WO WO/96/23814 8/1996
 WO WO/96/24671 8/1996
 WO WO/97/015669 5/1997
 WO WO/97/23613 7/1997
 WO WO/98/18809 5/1998
 WO WO/99/00494 1/1999
 WO WO/99/57268 11/1999
 WO WO/00/14257 3/2000
 WO WO/01/34843 5/2001
 WO WO/02/33101 4/2002
 WO WO/02/077029 10/2002
 WO WO/02/077029 10/2002
 WO WO/02/088334 11/2002
 WO WO/2005/019429 3/2005
 WO WO/2005/044996 5/2005
 WO WO/2006/060878 6/2006
 WO WO/2008/045437 4/2008
 WO WO/2009/091826 7/2009
 WO WO/2010/025177 3/2010
 WO WO/2010/085660 7/2010
 WO WO/2011/059836 5/2011
 WO WO/2012/033885 3/2012
 WO WO/2012/058460 5/2012
 WO WO/2012/082841 6/2012
 WO WO/2012/127464 9/2012
 WO WO/2012/135854 10/2012
 WO WO/2012/138858 10/2012
 WO WO/2013/033626 3/2013
 WO WO/2013/040371 3/2013
 WO WO/2013/059593 4/2013

A NCBI Direct Submission NP 932170.1 dated Nov. 21, 2010.
 Baeksgaard et al., "Acute tumor lysis syndrome in solid tumors—a case report and review of the literature." 2003, *Cancer Chemother Pharmacol.*, 51:187-92.
 Bondanza et al., "Suicide gene therapy of graft-versus-host disease induced by central memory human T lymphocytes." 2006, *Blood* 107:1828-1836.
 Brentjens et al., "Eradication of systemic B-cell tumors by genetically targeted human T lymphocytes co-stimulated by CD80 and interleukin-15." 2003, *Nature Medicine*, 9(3): 279-286.
 Brentjens et al., "Genetically targeted T cells eradicate systemic acute lymphoblastic leukemia xenografts." 2007, *Clin Cancer Res* 13:5426-5435.
 Brentjens et al., "Safety and persistence of adoptively transferred autologous CD19-targeted T cells in patients with relapsed or chemotherapy refractory B-cell leukemias." 2011 *Blood* 118(18):4817-4828.
 Brentjens et al., "Treatment of chronic lymphocytic leukemia with genetically targeted autologous T cells: case report of an unforeseen adverse event in a phase I clinical trial." 2010, *Mol Ther*, 18: 666-8.
 Brentjens, et al. "A Phase I Trial for the Treatment of Chemorefractory Chronic Lymphocytic Leukemia with CD19-Targeted Autologous T Cells." *Mol. Therapy*, 2008, p. S15, vol. 16, Suppl 1.
 Brocker and Karjalainen, "Signals through T cell receptor- ζ chain alone are insufficient to prime resting T lymphocytes." 1995, *J. Exp. Med.*, 181:1653-1659.
 Call, et al., "The T cell receptor: critical role of the membrane environment in receptor assembly and function." 2005, *Annu Rev Immunol*, 2005, 23:101-125.
 Campana et al., "T-Cell Immunotherapy for B-Lineage Acute Lymphoblastic Leukemia Using Chimeric Antigen Receptors That Deliver 4-1BB-Mediated Costimulatory Signals" 2003 *Blood* 102(11); abstract #223.
 Carpenito et al., "Control of large, established tumor xenografts with genetically retargeted human T cells containing CD28 and CD137 domains." 2009, *Proc Natl Acad Sci U S A* 106:3360-3365.
 Davila et al., "B Cell Aplasia in a Patient with Relapsed B Cell Acute Lymphoblastic Leukemia Following Re-Induction and Consolidation with Autologous T Cells Genetically Targeted to the CD19 Antigen." 2010 ASH Meeting Abstract No. 3268, presented Dec. 6, 2010 (poster abstract).
 Davila et al., "T Cells Genetically Targeted to CD19 Eradicate B-All in a Novel Syngeneic Mouse Disease Model." 2010 ASH Meeting Abstract No. 171, presented Dec. 6, 2010 (poster abstract).
 Dohner et al., "p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias." 1995, *Blood*, 85: 1580-9.
 Dropulic et al., "Gene-based immunotherapy for human immunodeficiency virus infection and acquired immunodeficiency syndrome." 2006, *Human Gene Therapy*, 17: 577-88.
 Dull et al., "A third-generation lentivirus vector with a conditional packaging system." 1998, *J Virol*, 72: 8463-71.
 Eshhar et al., "Specific activation and targeting of cytotoxic lymphocytes through chimeric single chains consisting of antibody-binding domains and the Y or ζ subunits of the immunoglobulin and T-cell receptors." 1993, *Proc Natl Acad Sci USA* 90:720-724.
 Finney et al., "Activation of resting human primary T cells with chimeric receptors: costimulation from CD28, inducible costimulator, CD134, and CD137 (4-1BB) in series with signals from the TCR zeta chain." 2004, *J. Immunol* 172:104-113.
 Finney et al., "Chimeric receptors providing both primary and costimulatory signaling in T cells from a single gene product." 1998, *J Immunol* 161:2791-2797.
 Friedmann-Morvinski et al., "Redirected primary T cells harboring a chimeric receptor require costimulation for their antigen-specific activation." 2005, *Blood* 105:3087-3093.
 Geiger and Jyothi, "Development and application of receptor-modified T lymphocytes for adoptive immunotherapy." 2001, *Transfusion Medicine Reviews*, 15(1): 21-34.

(56)

References Cited

OTHER PUBLICATIONS

- Geiger et al., "Integrated src kinase and costimulatory activity enhances signal transduction through single-chain chimeric receptors in T lymphocytes." 2001, *Blood* 98(8):2364-71.
- Gilham et al., "Primary Polyclonal Human T lymphocytes targeted to carcino-embryonic antigens and neural cell adhesion molecule tumor antigens by CD3 ζ -based chimeric immune receptors." 2001, *J. Immunology*, 25(2): 139-151.
- Gong et al., "Cancer patient T cells genetically targeted to prostate-specific membrane antigen specifically lyse prostate cancer cells and release cytokines in response to prostate-specific membrane antigen." 1999, *Neoplasia*, 1(2): 123-127.
- Gribben et al., "Stem cell transplantation for indolent lymphoma and chronic lymphocytic leukemia." 2011, *Biol Blood Marrow Transplant*, 17: Suppl:S63-S70.
- Griffin et al., "Development and application of surface-linked single chain antibodies against T-cell antigens." 2001, *J. Immunological Methods*, 248: 77-90.
- Gross and Eshhar, 1992, "Endowing T cells with antibody specificity using chimeric T cell receptors." 1992, *FASEB J.* 6: 3370-3378.
- Hallek et al., "Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute—Working Group 1996 guidelines." 2008, *Blood* 111(12):5446-5456.
- Hekele et al., "Growth retardation of tumors by adoptive transfer of cytotoxic T lymphocytes reprogrammed by CD44v6-specific scFv:zeta-chimera." 1996, *Int J Cancer* 68:232-238.
- Ho et al., "Adoptive Immunotherapy: Engineering T cell responses as biological weapons for tumor mass destruction." 2003, *Cancer Cell* 3:431-437.
- Hollyman et al., "Manufacturing Validation of Biologically Functional T Cells Targeted to CD19 Antigen for Autologous Adoptive Cell Therapy." *J. Immunother.*, 2009, pp. 169-180, vol. 32, No. 2.
- Homback et al., "The Recombinant T Cell Receptor Strategy: Insights into Structure and Function of Recombinant Immunoreceptors on the Way Towards an Optimal Receptor Design for Cellular Immunotherapy," 2002 *Current Gene Therapy* 2:211-226.
- Imai et al., "Chimeric receptors with 4-1BB signaling capacity provoke potent cytotoxicity against acute lymphoblastic leukemia." 2004, *Leukemia* 18(4):676-684.
- Imai et al., 2005, Genetic modification of primary natural killer cells overcomes inhibitory signals and induces specific killing of leukemic cells. *Blood*, 106:376-383.
- International Search Report for PCT/US2011/064191 dated May 1, 2012.
- Irving & Weiss, "The cytoplasmic domain of the T cell receptor zeta chain is sufficient to couple to receptor-associated signal transduction pathways." 1991, *Cell* 64:891-901.
- Jena et al., "Redirecting T-cell specificity by introducing a tumor-specific chimeric antigen receptor." 2010, *Blood*, 116: 1035-44.
- Jensen et al., "Antitransgene Rejection Responses Contribute to Attenuated Persistence of Adoptively Transferred CD20/CD19-Specific Chimeric Antigen Receptor Redirected T Cells in Humans." 2010 *Biol Blood Marrow Transplant* 16:1245-1256.
- Johnson et al., "Gene therapy with human and mouse T-cell receptors mediates cancer regression and targets normal tissues expressing cognate antigen." 2009, *Blood*, 114: 535-46.
- June et al., "Engineering lymphocyte subsets: tools, trials and tribulations." 2009, *Nat Rev Immunol*, 9: 704-16.
- Kalos, et al., "T Cells with Chimeric Antigen Receptors Have Potent Antitumor Effects and Can Establish Memory in Patients with Advanced Leukemia." 2011, *Sci Transl Med* 3(95):95ra73.
- Kershaw et al., "A phase I study on adoptive immunotherapy using gene-modified T cells for ovarian cancer." 2006, *Clin Cancer Res* 12:6106-6115.
- Kim et al., "Human 4-1BB regulates CD28 co-stimulation to promote Th1 cell responses." 1998, *Eur J Immunol* 28:881-890.
- Kochenderfer et al., "Construction and Pre-clinical Evaluation of an Anti-CD19 Chimeric Antigen Receptor." 2009, *J Immunother* 32(7):689-702.
- Kochenderfer, et al., "A Phase I Clinical Trial of Treatment of B-Cell Malignancies with Autologous Anti-CD19-CAR-Transduced T Cells." 2010 ASH Meeting Abstract No. 2865, presented Dec. 5, 2010 (poster abstract).
- Kochenderfer, et al., "Adoptive transfer of syngeneic T cells transduced with a chimeric antigen receptor that recognizes murine CD19 can eradicate lymphoma and normal B cells." 2010, *Blood*, 116(9):3875-3886.
- Kochenderfer, et al., "Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically-engineered to recognize CD19." 2010, *Blood* 116:4099-4102.
- Kochenderfer, et al., "Novel Antigen-Specific Expansion of T Cells Transduced with a CD19 Chimeric Antigen Receptor." 2010 ASH Meeting Abstract No. 3262, presented Dec. 6, 2010 (poster abstract).
- Kohn, et al., "CARs on track in the clinic." 2011, *Molecular Ther* 19(3):432-438.
- Krause et al., "Antigen-dependent CD28 signaling selectively enhances survival and proliferation in genetically modified activated human primary T lymphocytes." 1998, *J. Exp. Med.*, 188(4): 619-626.
- Lamanna et al., "Pentostatin, cyclophosphamide, and rituximab is an active, well-tolerated regimen for patients with previously treated chronic lymphocytic leukemia." 2006, *J Clin Oncol*, 24: 1575-81.
- Lamers et al., "Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against carbonic anhydrase IX: first clinical experience." 2006, *J Clin Oncol* 24:e20-e22.
- Laport et al., "Adoptive transfer of costimulated T cells induces lymphocytosis in patients with relapsed/refractory non-Hodgkin lymphoma following CD34+-selected hematopoietic cell transplantation." 2003, *Blood* 102: 2004-2013.
- Lee et al., "In vivo inhibition of human CD19-targeted effector T cells by natural T regulatory cells in a xenotransplant murine model of B cell malignancy." 2011, *Cancer Res* 71:2871-2881.
- Letourneur & Klausner, "T-cell and basophil activation through the cytoplasmic tail of T-cell-receptor zeta family proteins." 1991, *Proc Natl Acad Sci U S A* 88:8905-8909.
- Levine et al., "Gene transfer in humans using a conditionally replicating lentiviral vector." 2006, *Proc Natl Acad Sci U S A* 103:17372-17377.
- Macallan et al., "Measurement and modeling of human T cell kinetics." 2003, *Eur J Immunol*, 33: 2316-26.
- Maher et al., "Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRzeta/CD28 receptor." 2002, *Nat Biotechnol* 20(1):70-5.
- McGuinness, et al., "Anti-tumor activity of human T cells expressing the CC49-zeta chimeric immune receptor." 1999, *Hum.Gene Ther* 10:165-173.
- Milone et al., "Chimeric receptors containing CD137 signal transduction domains mediate enhanced survival of T cells and increased antileukemic efficacy in vivo." 2009, *Mol Ther* 17(8):1453-64.
- Molina, "A decade of rituximab: improving survival outcomes in non-Hodgkin's lymphoma." 2008, *Ann Rev Med*, 59: 237-50.
- Morgan et al., "Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2." 2010, *Mol Ther*, 18: 843-51.
- Moritz & Groner, "A spacer region between the single chain antibody- and the CD3 zeta-chain domain of chimeric T cell receptor components is required for efficient ligand binding and signaling activity," 1995, *Gene Therapy*, 2:539-546.
- Moritz et al., "Cytotoxic T lymphocytes with a grafted recognition specificity for ERBB2-expressing tumor cells" 1994, *Proc. Natl. Acad. Sci.* 91:4318-4322.
- Naldini et al., "In vivo gene delivery and stable transduction of nondividing cells by a lentiviral vector." 1996, *Science*, 272: 263-7.

(56)

References Cited

OTHER PUBLICATIONS

- Nicholson, et al., "Constructions and Characterization of a Functional CD19 Specific Single Chain Fv Fragment for Immunotherapy of B Lineage Leukemia and Lymphoma." *Mol. Immunol.*, 1997, pp. 1157-1165, vol. 34, No. 16-17.
- Ochoa et al., *Immune Defects in T Cells From Cancer Patients, Parallels in Infectious Diseases, from: Cancer Immunotherapy at the Crossroads: how tumors evade immunity and what can be done (current clinical oncology)*, edited by James H. Finke, Ronald M. Bukowski., 2004 edition.
- Park and Brentjens, "Adoptive Immunotherapy for B-cell Malignancies with Autologous chimeric Antigen Receptor Modified Tumor Targeted T Cells." 2010, *Discov Med* 9(47):277-288.
- Park et al., "Adoptive transfer of chimeric antigen receptor redirected cytolytic T lymphocyte clones in patients with neuroblastoma." 2007, *Mol Ther* 15:825-833.
- Patel et al., "Impact of chimeric immune receptor extracellular protein domains on T cell function." 1998, *Gene Therapy*, 6: 412-419.
- Porter et al. "A phase I trial of donor lymphocyte infusions expanded and activated ex vivo via CD3/CD28 costimulation." 2006, *Blood*, 107:1325-31.
- Porter et al., *Chimeric Antigen Receptor Therapy for B-cell Malignancies*. 2011, *J Cancer* 2:331-332.
- Porter, "Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia." 2011 *New England J Med* 365(8):725-733.
- Pule et al., "Virus-specific T cells engineered to coexpress tumor-specific receptors: persistence and antitumor activity in individuals with neuroblastoma." 2008, *Nat Med* 14:1264-1270.
- Rapoport et al., "Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer." 2005, *Nat Med* 11:1230-1237.
- Roederer, "T-cell dynamics of immunodeficiency." 1995, *Nat Med*, 1: 621-7.
- Romeo & Seed, "Cellular immunity to HIV activated by CD4 fused to T cell or Fc receptor polypeptides." 1991, *Cell* 64:1037-1046.
- Sabbagh et al., "TNF family ligands define niches for T cell memory." 2007, *Trends Immunol* 28:333-339.
- Sadelain et al., "Targeting tumours with genetically enhanced T lymphocytes." 2003, *Nat Rev Cancer* 3(1):35-45.
- Sadelain et al., "The promise and potential pitfalls of chimeric antigen receptors." 2009, *Curr Opin Immunol*, 21: 215-23.
- Savoldo et al., "CD28 costimulation improves expansion and persistence of chimeric antigen receptor-modified T cells in lymphoma patients." 2011, *J Clin Invest* 121(5):1822-6.
- Sebestyen, et al., "Human TCR that incorporate CD3zeta induce highly preferred pairing between TCRalpha and beta chains following gene transfer." 2008, *J Immunol*, 2008, 180(11):7736-46.
- Song, et al. "CD27 costimulation augments the survival and anti-tumor activity of redirected human T cells in vivo." 2011 *Blood* 119:696-706.
- Sorror et al., "Outcomes after allogeneic hematopoietic cell transplantation with nonmyeloablative or myeloablative conditioning regimens for treatment of lymphoma and chronic lymphocytic leukemia." 2008, *Blood*, 111: 446-52.
- Tammana Syam et al., "4-1BB and CD28 signaling plays a synergistic role in redirecting umbilical cord blood T cells against B-cell malignancies." 2010 *Human Gene Therapy* 21:75-86.
- Till et al., "Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells." 2008, *Blood*, 112, 2261-2271.
- Uckun, et al., "Detailed studies on expression and function of CD19 surface determinant by using B43 monoclonal antibody and the clinical potential of anti-CD19 immunotoxins." 1988, *Blood*, 71:13-29.
- Vinay and Kwon, "Role of 4-1BB in immune responses." 1998, *Seminars in Immunology*, 10:481-489.
- Willemsen et al., "Genetic Engineering of T Cell Specificity for Immunotherapy of Cancer." 2003, *Human Immunology*, 64: 56-68.
- Zufferey et al., "Multiply attenuated lentiviral vector achieves efficient gene delivery in vivo." 1997, *Nature Biotechnology* 15:871-875.
- Chinese Patent Application No. 201180067173.X—Office Action dated Oct. 22, 2014.
- Chinese Patent Application No. 201180067173.X—Second Office Action dated Jul. 10, 2015.
- Colombia Patent Application No. 13-137636—Colombian resolution No. 8176 dated Feb. 27, 2015.
- Colombia Patent Application No. 13-137636—English translation of Office Action of Sep. 5, 2014.
- Cuba Patent Application No. 2013/0079 Office Action of Apr. 1, 2014.
- Cuba Patent Application No. 2013/0079 Office Action of Oct. 28, 2014.
- Eurasian Region Patent Application No. 201390847/28 Office Action dated Mar. 11, 2015.
- European Patent Appl 11846757.0 European Search Report of Dec. 2, 2014.
- European Patent Application No. 11846757.0—Office Action dated Aug. 17, 2015.
- Guatemala Patent Application No. A-2013-150—English translation of Observer's comments of Sep. 17, 2014.
- Japanese Patent Application No. 2013-543380—Office Action dated Oct. 15, 2015.
- Mexican Patent Application No. MX/a/2013/006570—Office Action dated Oct. 9, 2015.
- New Zealand Patent Application No. 612512—First Exam Report of Nov. 20, 2013.
- Thailand Patent Application No. 1301003120—Office Action of Jul. 2014.
- U.S. Appl. No. 14/107,302—Final Office Action of Mar. 31, 2015.
- U.S. Appl. No. 14/107,302—non-final Office Action of Sep. 30, 2014.
- U.S. Appl. No. 14/567,426—non-final Office Action of Jan. 16, 2015.
- U.S. Appl. No. 14/568,195—non-final Office Action of Jan. 30, 2015.
- U.S. Appl. No. 14/568,569—non-final Office Action of Jan. 15, 2015.
- U.S. Appl. No. 13/992,622—non-final Office Action of Jun. 19, 2015.
- U.S. Appl. No. 13/992,622—Final Office Action of Jan. 5, 2016.
- U.S. Appl. No. 14/465,952—non-final Office Action of Nov. 20, 2014.
- U.S. Appl. No. 13/938,923—Final Office Action mailed Mar. 28, 2014.
- U.S. Appl. No. 13/938,923—Final Office Action mailed Oct. 8, 2014.
- U.S. Appl. No. 13/938,923—non-final Office Action of Sep. 19, 2013.
- U.S. Appl. No. 13/938,947—Final Office Action of Sep. 11, 2014.
- U.S. Appl. No. 13/938,947—non-final Office Action of Dec. 16, 2013.
- U.S. Appl. No. 14/466,096—non-final Office Action of Oct. 8, 2014.
- Colombian Patent Application No. 15-80428—Office Action issued Dec. 23, 2015.
- Colombian Patent Application No.—No. 13-137536—Office Action issued Nov. 23, 2015.
- Eurasian Patent Application No. 201390847—Office Action issued Feb. 14, 2016.
- U.S. Appl. No. 13/992,622—Final Office Action issued Jan. 5, 2016.
- U.S. Appl. No. 14/996,953—non-final Office Action issued Feb. 22, 2016.
- "Genetically Engineered Lymphocyte Therapy in Treating Patients with B-Cell Leukemia or Lymphoma That is Resistant or Refractory to Chemotherapy" *ClinicalTrials.gov Identifier NCT01029366*; Retrieved from the internet on Jan. 29, 2016. Found at <https://www.clinicaltrials.gov/ct2/show/NCT01029366?term=NCT01029366&rank=1>.
- "Pilot Study for Patients with Chemotherapy Resistant or Refractory CD19 Leukemia and Lymphoma (CART-19)" *ClinicalTrials*.

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