Dated: June 21, 2011.

Sarah L. Glavin,

Deputy Director, Office of Science Policy, Analysis and Communications, National Institute of Child Health and Human Development.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, HHS.

ACTION: Notice.

SUMMARY: The inventions listed below are owned by an agency of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of Federally-funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301–496–7057; fax: 301–402–0220. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Breakthrough Immunotherapy for Brain Cancer: Epidermal Growth Factor Receptor Variant III Chimeric Antigen Receptors

Description of Technology: Scientists at the National Institutes of Health (NIH) have developed chimeric antigen receptors (CARs) with high affinity for the epidermal growth factor receptor variant III (EGFRvIII) to use as a promising immunotherapy for aggressive brain cancer (glioblastoma) as well as several other malignancies. CARs are hybrid proteins consisting of the portion of an antibody that recognizes a cancer antigen, in this case human monoclonal antibody 139 which recognizes EGFRvIII, fused to protein signaling domains that serve to activate the CAR-expressing cell. Human cells that express CARs, most notably T cells, can recognize specific tumor antigens in an MHC-unrestricted manner with high reactivity and mediate an immune response that promotes robust tumor cell elimination.

Advantages

- EGFRvIII CAR immunotherapy is a breakthrough treatment for glioblastomas, a cancer with no other effective treatment option.
- EGFRvIII CARs can cross the blood-brain barrier, are expected to target only tumor cells, and thus, generate fewer side effects than other brain cancer treatment approaches.
- With the advent of Provenge®, personalized immunotherapy is becoming more widely accepted as a viable cancer treatment option.

Applications

- Immunotherapeutics to treat and/or prevent the recurrence of a variety of cancers that overexpress human EGFRvIII, primarily glioblastoma multiforme (GBM). About half of GBM tumor cells express the EGFRvIII antigen. Other cancers that overexpress EGFRvIII include breast, ovarian, prostate, bladder, colorectal, non-small cell lung carcinomas, and head and neck squamous cell carcinomas.
- A personalized cancer treatment strategy for patients whose tumor cells express EGFRvIII whereby the patient's own T cells are isolated, engineered to express the EGFRvIII specific CAR, and re-infused into the patient to attack the tumor.

EGFRvIII is a rare antigen in that is highly expressed by tumor cells, but not expressed by other cells in the body. This cancer antigen is expressed on nearly 50% of GBM tumor cells and also in other tumor types, such as other nervous system cancers and head and neck cancers. There exist very few, if any, effective treatments for GBM, so the expected clinical benefit of an anti-EGFRvIII CAR to patients is expected to be a therapeutic breakthrough for treatment of this cancer. These CARs are expected to combine high affinity recognition of EGFRvIII provided by the antibody portion with the target cell killing activity of cytotoxic T cells. Infusion of these EGFRvIII-specific CARs into patients could prove to be a powerful new immunotherapeutic tool for treating brain cancers, a type of cancer with a long-felt need for breakthrough therapeutics.

Development Status: This technology could soon be ready for clinical development. A clinical protocol to utilize an EGFRvIII CAR to treat GBM is currently under review at NIH.

Inventors: Richard A. Morgan and Steven A. Rosenberg (NCI).

Patent Status: U.S. Provisional Application No. 61/473,409 filed April 8, 2011 (HHS Reference No. E–148–2011/0–US–01).

Related Technologies

- E–269–2010/0—U.S. Provisional Application No. 61/384,931 filed September 21, 2010.
- E–236–2010/0—U.S. Provisional Application No. 61/405,931 filed October 22, 2010.
- E–205–2009/0—PCT Application No. PCT/US2010/048701 filed September 14, 2010, which published as WO2011/041093 on April 7, 2011.

Relevant Publications

1. Weber R, *et al.* U.S. Patent No. 7,628,986 issued December 8, 2009 entitled ''Antibodies Directed to the Deletion Mutants of Epidermal Growth Factor Receptor and Uses Thereof''.
2. Carter B.S., *et al.* U.S. Patent Application No. 12/444,090 filed April 2, 2009 entitled ''Chimeric T–Cell Receptors and T–Cells Targeting EGFRvIII on Tumors''.
3. Bullian SS, *et al.* Genetically engineered T cells to target EGFRvIII expressing glioblastoma. *J Neurooncol.* 2009 Sept;94(3):373–382. [PMID: 19387557].
4. Ohno M, *et al.* Retrovirally engineered T-cell based immunotherapy targeting type III variant epidermal growth factor receptor, a glioma-associated antigen. *Cancer Sci.* 2010 Dec;101(12):2518–2524. [PMID: 20880333].

Licensing Status: Available for licensing.

Licensing Contact: Samuel E. Bish, PhD; 301–435–5282; *bishse@mail.nih.gov*.

Collaborative Research Opportunity: The National Cancer Institute, Surgery Branch, is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize cell-based immunotherapies targeting EGFRvIII expressing cancers. Please contact John Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

An Improved Anti-Mesothelin Immunotoxin for Treatment of Mesothelioma, Lung Cancer, Ovarian Cancer and Pancreatic Cancer

Description of Technology: Mesothelin is a cell surface glycoprotein that is highly expressed in many cancers (*e.g.,* malignant mesothelioma, lung cancer, ovarian cancer, and pancreatic cancer). Because of its differential expression, mesothelin is an excellent

target for the selective killing of cancer cells. For instance, anti-mesothelin monoclonal antibodies can carry cellular toxins specifically to mesothelin-expressing cancer cells, resulting in their selective killing while healthy, essential cells remain unharmed.

A high affinity anti-mesothelin antibody (SS1) was previously combined with a functional fragment of *Pseudomonas* Exotoxin A (PE), producing the immunotoxin SS1P. SS1P selectively killed mesothelin-expressing cancer cells, suggesting it could be an excellent therapeutic agent. Unfortunately, PE-based immunotoxins can lose therapeutic efficacy following multiple administrations, due to the formation of neutralizing antibodies against the PE portion of the molecule. As a result, less immunogenic variants of PE have been created in order to develop immunotoxins that do not induce the formation of neutralizing antibodies.

Improved PE variants have been created which lack lysosomal protease sites, a dominant T-cell epitope (PE–LR), and several major B-cell epitopes (PE–LR/8M). Although these new PE variants demonstrate efficient cell killing activity when used in combination with certain antibodies, their activity when using SS1 as the targeting agent (SS1–LR and SS1–LR/8M) was less impressive. Fortunately, the inventors surprisingly discovered that the addition of a small linker peptide within these immunotoxins was able to restore their cell killing activity to the level of SS1P.

These new SS1-targeted immunotoxins (*e.g.,* SS1–LR/GGS and SS1–LR/GGS/8M) have the cell-killing activity of SS1P, but are less likely to generate neutralizing antibodies. As a result, these immunotoxins are considered to be very promising prospects for treating patients suffering from mesothelin-expressing cancers.

Applications

- Treatment of mesothelin expressing cancers, including mesothelioma, pancreatic cancer, ovarian cancer and lung adenocarcinoma.
- Treatment in combination with standard chemotherapy.
- Diagnostic agent for the detection of mesothelin-expressing cancers.

Advantages

- Immunotoxins are highly selective for cancer cells, reducing side-effects due to the non-specific killing of essential, healthy cells.
- Less immunogenic PE variants increase the efficacy of the immunotoxin by reducing the formation and action of neutralizing antibodies.
- PE variants include the removal of both B-cell and T-cell epitopes.
- Use of a small linker peptide offers an unexpected advantage of strong cell-killing activity with reduced immunogenicity.

Development Status: Preclinical stage of development for anti-mesothelin immunotoxins; immunotoxins directed to other targets have some clinical data to demonstrate proof-of-concept

Inventors: Ira Pastan (NCI) *et al.*

Patent Status

- U.S. provisional patent application 61/483,531 (HHS technology E–117–2011/0–US–01).
- U.S. provisional patent application 61/495,085 (HHS technology E–174–2011/0–US–01).

For More Information

- U.S. Patent 7,081,518 (HHS technology E–139–1999/0–US–07).
- U.S. Patent Publication US 20090142341 A1 (HHS technology E–262–2005/0–US–06).
- U.S. Patent Publication US 20100215656 A1 (HHS technology E–292–2007/0–US–06).
- PCT Publication WO 2011/032022 (HHS technology E–269–2009/0–PCT–02).

Licensing Status: Available for licensing.

Licensing Contact: David A. Lambertson, PhD; 301–435–4632; *lambertsond@mail.nih.gov.*

Efficient Production of Functional Recombinant Human Neonatal Receptor (FcRn) Proteins

Description of Technology: Human monoclonal antibodies are becoming common therapeutics for numerous diseases, including rheumatoid arthritis, multiple sclerosis, and several different types of cancers. To improve their half-life, antibodies are engineered to have a high affinity to the Fc receptor (FcRn). This requires a reliable method to produce high yields of functional FcRn which comprises a 1:1 molar ratio of the alpha to the beta chain. Unfortunately, current methods can be difficult to implement and are not very efficient in producing functional FcRns with the 1:1 molar ratio of the alpha to the beta chain. Thus, there is a strong need for quick and economical methods of producing functional FcRn to aid in antibody development and the improvement of existing antibody therapeutics.

This technology describes a new and efficient method for producing functional human FcRn at a 1:1 molar ratio of the alpha to the beta chain. The uniqueness of this invention is that the expression of both the beta and the alpha chains is under the control of a single promoter and the correct 1:1 molar folding of the two chains is facilitated by the intermediate flexible linker. The method is easy to scale up for producing large quantities of highly pure FcRn. Further, the inventors have recently developed a stable cell line for large scale production.

Benefits: Improving the half-life of existing monoclonal antibodies as well as monoclonal antibodies still in development.

Advantages

- Efficient method of producing high yields of functional human FcRn at a 1:1 molar ratio of the alpha to the beta chain.
- Stable cell line also available.

Market: The monoclonal antibodies market generated over $40 billion in sales for therapeutic uses last year and is expected to grow significantly over the next several years.

Publications: Feng Y, Gong R, Dimitrov D.S. Design, expression and characterization of a soluble single-chain functional human neonatal Fc receptor. Protein Expr Purif. 2011 Mar 29, E-pub ahead of print. [PMID: 21453773]

Inventors: Dimiter S. Dimitrov and Yang Feng (NCI).

Patent Status: HHS Reference No. E–296–2010/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for licensing.

Licensing Contact: Whitney A. Hastings; 301–451–7337; *hastingw@mail.nih.gov.*

Immunocompetent Mouse Model for Tracking Cancer Progression

Description of Technology: The technology is a transgenic mouse model tolerized to firefly Luciferase (ffLuc)- and enhanced green fluorescent protein (eGFP)-labeled tissue whilst maintaining normal immune function. Luc and eGFP are the most frequently used bioimaging markers to track cancer progression in pre-clinical mouse models. As these markers are immunogenic, their reporter activity becomes diminished over time and so their use has largely been limited to immunodeficient mice. However, immune function is crucial for tumor development and progression, making the use of immunocompetent mice more desirable.

The immunocompetent mouse model described in this invention was

generated using the rat growth hormone gene promoter (rGH) to target ffLuc-eGFP fusion gene expression to the pituitary gland, restricting any resulting interfering reporter signal within the head. This allows the tracking of cancer progression throughout the body, where the reporter activity of introduced ffLuc/eGFP-labeled tumors is maintained, despite normal immune function. These immunocompetent rGH-ffLuc-eGFP transgenic mice can be used as hosts in cancer models, allowing long-term in vivo monitoring of the progression of ffLuc/eGFP-labeled tumor cells in the body, which may lead to more clinically relevant insights into cancer progression, metastases and response to therapies.

Applications

- In vivo model for studying tumor progression and testing anti-cancer therapeutics using ffLuc or eGFP labeling for bioimaging.
- Since rGH-ffLuc-eGFP is also a growth hormone-responsive reporter, these rGH–Luc-GFP mice may also be used to screen growth-hormone stimulating drugs for treating Achondroplasia (dwarf syndrome) or as a test for illegal performance-enhancing drugs.

Advantages

- This technology represents a more clinically relevant in vivo model of cancer progression for testing anti-cancer therapeutics.
- This immunocompetent mouse model is more desirable as a pre-clinical model over the currently used immunodeficient mouse models as immune function is crucial for tumor development and progression.

Development Status

- Early-stage.
- Pre-clinical.
- In vitro data available.
- In vivo data available (animal).

Inventors: Chi-Ping Day and Glenn Merlino (NCI).

Relevant Publications

1. Day C.P., *et al.* Preclinical therapeutic response of residual metastatic disease is distinct from its primary tumor of origin. *Int J Cancer.* 2011 Feb 10, doi: 10.1002/ijc.25978. [Epub ahead of print].

2. Day C.P., *et al.* Lentivirus-mediated bifunctional cell labeling for in vivo melanoma study. *Pigment Cell Melanoma Res.* 2009 Jun;22(3):283–295. [PMID: 19175523].

3. Luque R.M., *et al.* Reporter expression, induced by a growth hormone promoter-driven Cre recombinase (rGHp-Cre) transgene, questions the developmental relationship between somatotropes and lactotropes in the adult mouse pituitary gland. *Endocrinology.* 2007 May;148(5):1946–1953. [PMID: 17289844].

4. Latta-Mahieu M., *et al.* Gene transfer of a chimeric trans-activator is immunogenic and results in short-lived transgene expression. *Hum Gene Ther.* 2002 Sep 1;13(13):1611–1620. [PMID: 12228016].

5. Stripecke R., *et al.* Immune response to green fluorescent protein: implications for gene therapy. *Gene Ther.* 1999 Jul;6(7):1305–1312. [PMID: 10455440].

6. Liao C.P., *et al.* Mouse models of prostate adenocarcinoma with the capacity to monitor spontaneous carcinogenesis by bioluminescence or fluorescence. *Cancer Res.* 2007 Aug 1;67(15):7525–7533. [PMID: 17671224].

Patent Status: HHS Reference No. E–173–2010/0—Research Tool. Patent protection is not being pursued for this technology.

Licensing Status: Available for licensing.

Licensing Contact: Sabarni K. Chatterjee, PhD; 301–435–5587; *chatterjeesa@mail.nih.gov.*

Collaborative Research Opportunity: The National Cancer Institute Center for Cancer Research is seeking statements of capability or interest from parties interested in collaborative research to further develop, evaluate, or commercialize immunocompetent rGH-ffLuc-eGFP transgenic mice. Please contact John Hewes, PhD at 301–435–3121 or *hewesj@mail.nih.gov* for more information.

Dated: July 1, 2011.

Richard U. Rodriguez,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 2011–17228 Filed 7–7–11; 8:45 am]

BILLING CODE 4140–01–P

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Mouse Model and Derived Cells That Hypersecrete Leukemia Inhibitory Factor (LIF)

Description of Technology: Embryonic stem cells (ESCs) are pluripotent cells that can be cultured indefinitely, and maintain their capability to differentiate into all cell lineages. To maintain these cells as well as various types of related induced stem cells and progenitor cells in culture, Mouse Embryonic Fibroblasts (MEFs) are routinely used as feeder cells, largely to serve as a source of Leukemia Inhibitory Factor (LIF). ESCs can also be cultured without feeders if the medium is supplemented with recombinant LIF and other factors. However, these methods of culturing ESCs suffer from certain drawbacks, such as limited proliferation capacity and variability of primary MEFs. Therefore, finding improved conditions that maintain ESC pluripotency is an area of great interest.

Scientists at NIEHS have now developed a knock-in (KI) mouse model in which LIF is overproduced from its endogenous locus because of increased stability of its mRNA. MEFs and presumably other cells derived from the homozygous mice hypersecrete LIF protein; lesser degrees of overexpression would be expected from heterozygous mice. These mice can be used to study LIF function, including how LIF contributes to various physiological and pathological states. Cells derived from these mice can be used to culture ESCs, as well as other progenitor cells. Cells or genetic material derived from these mice can also be used as sources of LIF for isolation and purification.

Applications

- Maintenance of ESCs and progenitor cells.
- *In vivo,* cellular and cell-free sources of LIF.
- Sources of LIF for isolation and purification.
- Studies of LIF function in mice, such as contribution of LIF to tumor growth.

Inventors: Dr. Perry Blackshear (NIEHS), *et al.*