DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

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

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.

2-Amino-O^4-Substituted Pteridines and Their Use as Inactivators of O^6-Alkylguanine-DNA Alkyltransferase

Robert C. Moschel *et al.* (NCI)

DHHS Reference No. E–274–2003/0–US–01 filed 06 Jan 2004

Licensing Contact: George Pipia; 301/435–5560; *pipiag@mail.nih.gov*

This invention is directed to 2-amino-O^4-benzylpteridine derivatives targeted for use in cancer treatment in combination with chemotherapeutic agents such as 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU) or temozolomide. The derivatives of the present invention inactivate the O^6-alkylguanine-DNA-alkyltransferase repair protein and thus enhance activity of such chemotherapeutic agents. Examples of these derivatives have advantages over the earlier O^6-benzylguanine compounds from this research group. Some compounds of the current invention are more water soluble compared to O^6-benzylguanine and they exhibit greater specificity for inactivating O^6-alkylguanine-DNA-alkyltransferase in certain tumor cells, compared to normal cells.

Interference With *c-maf* Function in Multiple Myeloma Retards Tumor Adherence and Progression and Decreases Expression of Integrin β7, C-C Chemokine Receptor 1, and Cyclin D2

Louis Staudt *et al.* (NCI)

DHHS Reference No. E–173–2003/0-PCT–01 filed 17 Oct 2003

Licensing Contact: Catherine Joyce; 301/435–5031; e-mail: *joycec@mail.nih.gov*

Multiple myeloma (MM) is an incurable malignancy of the plasma cell that accounts for 20% of all hematologic malignancies. It has been shown that there are recurrent genetic lesions associated with the disease. One of the recurrent lesions, occurring in approximately 5–10% of the cases, is a translocation involving the *c-maf* gene which results in overexpression of the *c-maf* gene.

Unexpectedly, the inventors have found that overexpression of the *c-maf* gene is more frequent than the occurrence of the genetic lesion, with approximately 50% of MM samples showing overexpression of *c-maf*. Additionally, the inventors have shown that the interference with *c-maf* function markedly decreases expression of integrin β7, C-C chemokine receptor1, and cyclin D2. The inventors have also demonstrated that decreased expression of integrin β7 markedly decreases the ability of tumor cells to bind to bone marrow stroma and that the proliferation of myeloma cells was slowed significantly by the inhibition of *c-maf* expression. Therefore, *c-maf* appears to play a central role in regulating the proliferation and survival of tumor cells in MM.

The above-mentioned invention is available for licensing on an exclusive or a non-exclusive basis.

Glioma-Selective Polypeptides, Alone or Coupled to a Therapeutic/Diagnostic Agent, Compositions Comprising Same, and Uses Thereof

Howard A. Fine (NCI), Benjamin Purow (CC)

U.S. Provisional Application No. 60/509,737 filed 08 Oct 2003 (DHHS Reference No. E–244–2002/0–US–01)

Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@mail.nih.gov*

Primary brain tumors are an important cause of cancer mortality in the U.S., representing the leading cause of cancer-related death in children and the fourth leading cause of cancer-related death in young adults. Progress in the treatment of these tumors has been slow, since the demonstration of more than 20 years ago that fractionated radiotherapy could significantly extend survival. Although improved neurosurgical techniques have lessened the morbidity of extensive resections, the impact of such procedures on the overall survival of patients with the most malignant gliomas remains modest, at best, given the diffuse infiltrative nature of the tumor. Chemotherapy recently has been demonstrated to have some activity for specific subtypes of malignant gliomas, such as oligodendrogliomas and anaplastic astrocytomas. The effectiveness, however, of standard chemotherapy for the most common and malignant of the gliomas, glioblastoma, is marginal at best. Clearly, novel therapeutic approaches and novel drug targets are needed. In view of the foregoing, it is an object of the present invention to provide new agents and compositions that can be used in the diagnosis and treatment of glioma. This and other objects and advantages of the present invention, as well as additional inventive features, will be apparent from the detailed description provided in the patent application.

The present invention relates to glioma-selective polypeptides, which can be used alone or coupled to a therapeutic or diagnostic agent, in the diagnosis and therapy of glioma. Also provided by the present invention is a composition comprising the above-described polypeptide, desirably coupled to a diagnostic agent or a therapeutic agent, and a carrier.

Additionally, a method of diagnosing glioma in an animal is provided. The method comprises administering to the animal a polypeptide coupled to a diagnostic agent as described above, or a composition comprising same and a carrier therefore, and assaying for the presence of the diagnostic agent in the central nervous system (CNS). The presence of the diagnostic agent in the CNS is indicative of the presence of glioma in the animal.

A method of inhibiting the proliferation of a glioma cell in an animal having a glioma is also provided. The method comprises administering to the animal in an amount sufficient to inhibit the proliferation of the glioma cell in the animal a polypeptide coupled to a therapeutic agent as described above, or a composition comprising the same and a carrier, whereupon the proliferation of the glioma cell in the animal is inhibited.

Brother of the Regulator of Imprinted Sites (BORIS)

Victor Lobanenkov *et al.* (NIAID)

U.S. Provisional Application No. 60/358,889 filed 22 Feb 2002 (DHHS Reference No. E–227–2001/0–US–01);

PCT Application No. PCT/US03/05186 filed 21 Feb 2003 (DHHS Reference No. E–227–2001/0–PCT–02)

Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@mail.nih.gov*

The subject application discloses an isolated or purified nucleic acid molecule consisting essentially of a nucleotide sequence encoding a human or a non-human BORIS, or a fragment of either of the foregoing; an isolated or purified nucleic acid molecule consisting essentially of a nucleotide sequence that is complementary to a nucleotide sequence encoding a human or a non-human BORIS, or a fragment of either of the following; a vector comprising such an isolated or purified polypeptide molecule consisting essentially of an amino acid sequence encoding a human or a non-human BORIS, or a fragment or either of the foregoing; a cell line that produces a monoclonal antibody that is specific for an aforementioned isolated or purified polypeptide molecule; and the monoclonal antibody produced by the cell line; methods of diagnosing a cancer or a predisposition to a cancer in a male or female mammal; a method of prognosticating a cancer in a mammal; a method of assessing the effectiveness of treatment of a cancer in a mammal; a method of treating a mammal prophylactically or therapeutically for a cancer; and a composition comprising a carrier and an inhibitor of BORIS.

Use of IL–13 Inhibitors To Prevent Tumor Recurrence

Jay Berzofsky *et al.* (NCI).

PCT Application No. PCT/US01/51339 filed 22 Oct 2001 (DHHS Reference No. E–037–2001/1–PCT–02).

Licensing Contact: Catherine Joyce; 301/435–5031; e-mail: *joycec@mail.nih.gov*

This invention relates to the discovery of a role for IL–13 in the down-regulation of tumor immunosurveillance. Using a mouse model in which tumors show a growth-regression-recurrence pattern, the mechanisms for down-regulation of cytotoxic T lymphocyte-mediated tumor immunosurveillance was investigated. It was discovered that interleukin 4 receptor (IL–4R) knockout mice, and downstream signal transducer and activator of transcription 6 (STAT6) knockout mice, but not IL–4 knockout mice, resisted tumor recurrence. Thus, IL–13, the only other cytokine that uses the IL–4R-STAT6 pathway, was discovered to have a role in the down-regulation of tumor immunosurveillance. The use of an IL–13 inhibitor confirmed these results.

Additionally, loss of natural killer T cells (NKT cells) in CD1 knockout mice resulted in decreased IL–13 production and resistance to recurrence. Therefore, NKT cells and IL–13, possibly produced by NKT cells and signaling through the IL–4R-STAT6 pathway, are necessary for down-regulation of tumor immunosurveillance. Thus, the inventors have discovered a method of inhibiting tumor growth which comprises the administration of an IL–13 inhibitor. This invention is described in PCT application, PCT Publication No. WO 02/055100.

This technology is available for licensing on a non-exclusive basis.

Interleukin-2 Stimulated T-Lymphocyte Cell Death for the Treatment of Autoimmune Diseases, Allergic Disorders and Graft Rejection

Michael J. Lenardo (NIAID).

U.S. Patent 6,083,503 issued 07 Jul 2000 (DHHS Reference No. E–137–1991/0–US–03); U.S. Patent 5,989,546 issued 23 Nov 1999 (DHHS Reference No. E–137–1991/0–US–04).

Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@mail.nih.gov*

T-cell apoptosis induced by administration of IL–2 and antigen offers an important new treatment for allergic disorders, which are due to the effects of antigen-activated T-cells. Antigen-activated T-cells cause the release of harmful lymphokines and the production of immunoglobulin E by B cells. Presently available methods for treating allergies have limitations because they are nonspecific in their action and have side effects and limited efficacy. IL–2 and antigen stimulates the programmed death of only antigen-specific T-cells while leaving the rest of the patient's T-cells and other immune cells intact. This invention is also useful in treating HIV. Both fields of use, allergies and HIV, are available for licensing.

Interleukin-4 Stimulated T-Lymphocyte Cell Death for the Treatment of Autoimmune Diseases, Allergic Disorders and Graft Rejection

Michael J. Lenardo, Stefen A. Boehme, Jeffrey Critchfield (NIAID).

U.S. Patent 5,935,575 issued 10 Aug 1999 (DHHS Reference No. E–151–1992/0–US–11).

Licensing Contact: Matthew Kiser; 301/435–5236; *kiserm@mail.nih.gov*

The discovery that interleukin-4 (IL–4) predisposes T lymphocytes to programmed cell death (apoptosis) allows for a novel method of therapeutic intervention in diseases caused by the action of IL–4-responsive T cells. Specifically, the therapy induces the death of a subpopulation of T lymphocytes that are capable of causing disease. Current therapies may cause general death or suppression of immune responses involving T-cells, severely comprising a patient's immune system. This treatment affects only the subset of T cells that react with a specified antigen, thereby leaving a patients immune system uncompromised. This invention is useful in treating allergies and HIV complications. Both fields are available for licensing.

Dated: February 9, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–3526 Filed 2–18–04; 8:45 am]

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SPATIAL for Altering Cell Proliferation

Ronald E. Gress, Francis A. Flomerfelt (NCI).

PCT Application No. PCT/US03/36874 filed 18 Nov 2003 (DHHS Reference No. E–177–2003/0–PCT–01).

Licensing Contact: Fatima Sayyid; (301) 435–4521; *sayyidf@mail.nih.gov.*