Activation of Recombinant Diphtheria Toxin Fusion Proteins by Specific Proteases Highly Expressed on the Surface of Tumor Cells

Stephen Leppla, Shi-Hui Liu, Manuel Osorio, and Jennifer Avallone (NIDCR)

U.S. Provisional Application No. 60/468,577 filed 06 May 2003 (DHHS Reference No. E–331–2002/0–US–01)

PCT Application No. PCT/US04/01430 filed 06 May 2004 (DHHS Reference No. E–331–2002/0–PCT–02)

Licensing Contact: Brenda Hefti; (301) 435–4632; *heftib@mail.nih.gov.*

This invention relates to diphtheria toxin fusion proteins comprising a diphtheria toxin (DT) cell-killing component and a cell-binding component such as granulocyte macrophage colony-stimulating factor (GM–CSF), interleukin 2 (IL–2), or epidermal growth factor (EGF). Receptors for the latter three materials are present on many types of cancer cells; therefore, these fusion proteins bind preferentially to these cancer cells. A key feature is that these toxins are altered so as to require activation by a cell-surface protease that is overexpressed on many types of cancers. Examples of such proteases include matrix metalloproteinases and urokinase plasminogen activator. Consequently, these novel cytotoxins kill tumors expressing receptors for either GM–CSF, IL–2, or EGF along with the cell-surface protease. Because killing requires the presence of both a receptor and a cancer-cell enriched protease, and few normal tissues contain both, there is less toxicity to normal cells. Thus, a larger amount of the agent may be used for cancer therapy without inducing side effects. In other words, these cytotoxins have a higher therapeutic index than toxins that are targeted to cells using a single strategy.

BASE, a New Cancer Gene, and Uses Thereof

Ira Pastan, Kristi Egland, James Vincent, Byungkook Lee, and Robert Strausberg (NCI)

PCT Application No. PCT/US03/39476 filed 10 Dec 2003 (DHHS Reference No. E–321–2002/0–PCT–02)

Licensing Contact: Brenda Hefti; (301) 435–4632; *heftib@mail.nih.gov*

The present invention identifies a new gene expressed in breast cancers. The gene undergoes alternative splicing, and is expressed as one of two polypeptides. Both splice variants appear to be secreted proteins, and therefore good potential therapeutic targets. The patent application claims BASE polypeptides, nucleic acids, gene therapy and vaccine uses, and antibodies. This novel gene target might be useful as a breast cancer marker for diagnostics, or as a target for breast cancer therapeutics.

Applications for the HMGN1 Pathway

Michael Bustin (NCI)

U.S. Provisional Patent Application No. 60/455,728 filed 17 Mar 2003 (DHHS Reference No. E–208–2002/0–US–01)

PCT Application No. PCT/US04/08060 filed 17 Mar 2004, which published as WO 2004/083398 on 30 Sep 2004 (DHHS Reference No. E–208–2002/0–PCT–02)

Licensing Contact: Brenda Hefti; (301) 435–4632; *heftib@mail.nih.gov*

HMGN1 is a protein that binds to nucleosomes, changes chromatin structure and affects transcription, and the expression of this protein changes during differentiation. Mice lacking this protein have increased growth capacity of several skin components, including epidermis, epidermal appendages, and dermis. Conceivably, this change could be related to an alteration of stem cell differentiation or to cell cycling events. The current invention relates to interference with this pathway, which might lead to increased stem cell differentiation and increased hair cycling and growth in humans as well. This invention might be useful to increase hair growth, enhance wound healing for epidermal and dermal wounds, and enhance stem cell populations for tissue regeneration, gene targeting, or gene therapeutic indications.

Dated: December 20, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–28684 Filed 12–30–04; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of an Exclusive License: ''Vasostatin as Marrow Protectant'' and ''Use of Calreticulin and Calreticulin Fragments To Inhibit Endothelial Cell Growth and Angiogenesis and Suppress Tumor Growth''

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

ACTION: Notice.

SUMMARY: This notice, in accordance with 35 U.S.C. 209(c)(1) and 37 CFR part 404.7(a)(1)(i), announces that the Department of Health and Human Services is contemplating the grant of an exclusive license to practice the inventions embodied in U.S. Patent No. 6,596,690 B2 entitled ''Vasostatin as Marrow Protectant'' (DHHS Reference E–230–2000/0); U.S. Patent Application No. 09/807,148 filed April 5, 2001, entitled ''Use of Calreticulin and Calreticulin fragments to inhibit endothelial cell growth and angiogenesis and suppress tumor growth'' (DHHS Reference E–082–1998/0–US–03); PCT Application No. PCT/US99/23240 filed October 5, 1999 entitled ''Use of Calreticulin and Calreticulin fragments to inhibit endothelial cell growth and angiogenesis and suppress tumor growth'' (DHHS Reference E–082–1998/0–PCT–02); to BioAccelerate, Inc., a venture capital group controlling the following twelve companies: Bioenvision, Enhance Biotech, Evolve Oncology, CNS Thera, Innova Lifestyle, Inncardio, Anvira, Neuro Bioscience, Biocardio, Oncbio, Innovative Oncology and Genar Oncology. The patent rights in these inventions have been assigned to the United States of America.

The prospective exclusive license territory may be worldwide and the field of use may be limited to development and sale of a pharmaceutical product useful in protecting bone marrow stem cells from the toxic effects of chemotherapy and radiotherapy.

DATES: Only written comments and/or license applications which are received by the National Institutes of Health on or before March 4, 2005 will be considered.

ADDRESSES: Requests for copies of the patent and/or patent applications, inquiries, comments and other materials relating to the contemplated exclusive license should be directed to: Mojdeh Bahar, J.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852–3804. Telephone: (301) 435–2950; Facsimile: (301) 402–0220; E-mail: *baharm@od.nih.gov*.

SUPPLEMENTARY INFORMATION: The technology claimed in the aforementioned patents is based on the discovery of the calreticulin N-domain (vasostatin) and the three previously uncharacterized properties of calreticulin. First, calreticulin N-domain is shown to stimulate the proliferation and survival in vitro of hematopoietic cells in the presence of previously identified growth factors. Second, Vasostatin is shown to protect

hematopoietic cells in vitro from toxicity induced by a variety of chemotherapeutic agents. Third, Vasostatin is shown to protect a subject from toxicity to the hematopoietic system induced by chemotherapy or irradiation.

The prospective exclusive license will be royalty-bearing and will comply with the terms and conditions of 35 U.S.C. 209 and 37 CFR part 404.7. The prospective exclusive license may be granted unless within sixty (60) days from the date of this published notice, the NIH receives written evidence and argument that establish that the grant of the license would not be consistent with the requirements of 35 U.S.C. 209 and 37 CFR part 404.7.

Applications for a license in the field of use filed in response to this notice will be treated as objections to the grant of the contemplated exclusive license. Comments and objections submitted to this notice will not be made available for public inspection and, to the extent permitted by law, will not be released under the Freedom of Information Act, 5 U.S.C. 552.

Dated: December 20, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–28686 Filed 12–30–04; 8:45 am]

BILLING CODE 4140–01–P

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.

Novel Compounds and Methods for Treating Alzheimer's and Related Diseases

Nigel H. Greig *et al.* (NIA)
U.S. Provisional Application filed 22 Oct 2004 (DHHS Reference No. E–172–2004/0–US–01)
Licensing Contact: Norbert Pontzer; (301) 435–5502; *pontzern@mail.nih.gov.*

The brain cholinergic system is thought to play an important role in learning and memory. The loss of cholinergic neurons early in the course of Alzheimer's Disease may thus be an etiological factor in the cognitive decline that is the hallmark of that disease. Therefore, potentiating cholinergic transmission has been the main pharmacological approach for the treatment of AD patients. Inhibition of acetylcholinesterase (AChE) or butyrylcholinesterase (BChE) enhances cholinergic transmission by reducing enzymatic degradation of acetylcholine.

AChE inhibitors are now used clinically to help restore cognitive function in AD patients. However the therapeutic index for inhibition of AChE is quite low. Drugs with this mechanism of action have to have the proper pharmacodynamic properties to achieve even a marginally useful clinical effect without unacceptable side effects. The presence of BChE in brain tissue makes this enzyme another possible target for increasing the activity of the cholinergic system.

The present invention provides a series of novel and potent tricyclic compounds that have a range of selectivity for inhibiting AchE, as compared to BchE, and possess neuroprotective activity in cell culture models. Also provided are methods of using these compounds to treat a number of different medical conditions such as Alzheimer's Disease, mild cognitive impairment, and other dementia-related disorders.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Novel Methods for Reducing Inflammation and Treating Diseases such as Parkinson's and Alzheimer's Disease

Jau-Shyong Hong *et al.* (NIEHS)
U.S. Provisional Application No. 60/570,566 filed 12 May 2004 (DHHS Reference No. E–130–2004/0–US–01)
Licensing Contact: Norbert Pontzer; (301) 435–5502; *pontzern@mail.nih.gov.*

Activated microglia mediate inflammation in the CNS by secreting various cytokines and free radicals that could damage neurons. Brains from patients with Parkinson disease show microglia reaction, and previous studies by this laboratory show microglia activation leads to inflammation mediated dopaminergic degeneration. Thus identification of drugs that reduce microglia activation could prevent or reverse neuronal degeneration in Parkinson's Disease, Alzheimer's Disease, ischemia and other degenerative CNS disorders.

Considerable research has shown the ability of various peptides to attenuate microglia activation and prevent neuronal degeneration *in vitro* with a bi-modal dose response curve. These peptides demonstrate maximum effects at femto-molar and micro-molar concentrations. These inventors have now discovered small-peptide and non-peptide molecules that also inhibit microglia and prevent neuronal degeneration with the same bi-modal dose response curve. The non-peptide compounds have also been shown to prevent dopamine neuronal degeneration in animal models. The present invention provides compositions and methods for inhibiting inflammatory mechanisms and treating inflammation-related condition by administering ultra-low (femto-molar) doses of at least one compound of the invention. These compounds include morphinans, opioid peptides, and the tripeptide GGF.

In addition to licensing, the technology is available for further development through collaborative research with the inventors via a Cooperative Research and Development Agreement (CRADA).

Multi-Domain Amphipathic Helical Peptides and Methods of Their Use

Alan Remaley *et al.* (NHLBI)
U.S. Provisional Application filed 15 Oct 2004 (DHHS Reference No. E–114–2004/0–US–01)
Licensing Contact: Fatima Sayyid; (301) 435–4521; *sayyidf@mail.nih.gov.*

Mutations in the ABCA1 transporter lead to diseases characterized by the accumulation of excess cellular cholesterol, low levels of HDL and an increased risk for cardiovascular disease. Currently, there are a wide variety of treatments for dyslipidemia, which include, but are not limited to,