this technology. This ability can be demonstrated through experience and expertise in this or related areas of technology indicating the ability to contribute intellectually to ongoing research and development.

2. The demonstration of adequate resources to perform the research, development and commercialization of this technology (e.g. facilities, personnel and expertise) and accomplish objectives according to an appropriate timetable to be outlined in the CRADA Collaborator's proposal.

3. The willingness to commit best effort and demonstrated resources to the research, development and commercialization of this technology.

4. The demonstration of expertise in the commercial development, production, marketing and sales of products related to this area of technology.

5. The level of financial support the CRADA Collaborator will provide for CRADA-related Government activities.

6. The willingness to cooperate with the National Cancer Institute in the timely publication of research results.

7. The agreement to be bound by the appropriate DHHS regulations relating to human subjects, and all PHS policies relating to the use and care of laboratory animals.

8. The willingness to accept the legal provisions and language of the CRADA with only minor modifications, if any. These provisions govern the equitable distribution of patent rights to CRADA inventions. Generally, the rights of ownership are retained by the organization that is the employer of the inventor, with (1) the grant of a license for research and other Government purposes to the Government when the CRADA Collaborator's employee is the sole inventor, or (2) the grant of an option to elect an exclusive or nonexclusive license to the CRADA Collaborator when the Government employee is the sole inventor.

Dated: July 21, 1997.

Kathleen Sybert,

Acting Director, Office of Technology Development, National Cancer Institute, National Institutes of Health.

[FR Doc. 97–21148 Filed 8–8–97; 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 referenced below are owned by agencies 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 U.S. companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the issued U.S. patents and the U.S. patent applications referenced below may be obtained by contacting Carol Lavrich, Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057 ext. 287; fax: 301/402–0220; e-mail: CL21R@NIH.GOV. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: The National Institutes of Health is seeking licensees and/or CRADA collaborators for the further development, evaluation, and commercialization of nitric oxide (NO) compounds and subsequent drug delivery strategies for the treatment of a variety of medical disorders. Published elsewhere in this issue of the **Federal Register** is a notice describing the CRADA opportunities available from the National Cancer Institute for these NO technologies. A complete listing of these technologies may be found in the CRADA notice; abstracts for some of them appear below.

Complexes of Nitric Oxide With Polyamines

LK Keefer, JA Hrabie (NCI)

Serial No. 07/585,793 filed 20 Sep 90; U.S. Patent 5,155,137 issued 13 Oct 92

Novel complexes of nitric oxide and polyamines are potentially useful in treating a variety of clinical disorders. These nitric oxide/polyamine complexes release nitric oxide under physiological conditions in a sustained and controllable fashion and possess long-lived pharmacological effects.

Related cases: Serial No. 07/906,479 filed 30 Jun 92 (DIV), which issued as U.S. Patent 5,250,550 on 05 Oct 93; Serial No. 08/522,405 filed 02 Feb 96 (CIP of 07/906,479)

Oxygen Substituted Derivatives of Nucleophile-Nitric Oxide Adducts as Nitric Oxide Donor Products

LK Keefer, TM Dunams, JE Saavedra (NCI)

Serial No. 07/950,637 filed 23 Sep 92; U.S. Patent 5,366,997 issued 22 Nov 94

A novel class of compounds that release nitric oxide (NO) *in vivo* offers to improve the treatment of many clinical disorders. This new class of compounds is stable to acidic conditions of the stomach and in the blood stream but releases nitric oxide at sites of metabolic activation. Thus, they provide organ-selective NO release and can be advantageously administered orally.

Polymer-Bound Nitric Oxide/ Nucleophile Adduct Compositions, Pharmaceutical Compositions Incorporating Same, and Methods of Treating Biological Disorders

LK Keefer, JA Hrabie (NCI)

Serial No. 07/935,565 filed 24 Aug 92; U.S. Patent 5,405,919 issued 11 Apr 95

A polymeric composition capable of releasing nitric oxide including a polymer and a nitric oxide-releasing N_2O_2-functional group bound to the polymer; pharmaceutical compositions including the polymeric composition; and methods for treating biological disorders in which dosage with nitric oxide is beneficial. The compositions can be used as and/or incorporated into implants, injectables, condoms, prosthesis coatings, patches, and the like for use in a wide variety of medical applications.

Nitric Oxide-Releasing Compounds for the Sensitization of Hypoxic Cells in Radiation Therapy

JB Mitchell, MC Krishna, D Wink, JE Liebmann, A Russo (NCI)

Serial No. 08/319,888 filed 07 Oct 94; U.S. Patent 5,650,442 issued 22 Jul 97

A novel method has been developed for sensitizing oxygen-poor, or hypoxic, tumor cells, which will increase the effectiveness of radiation treatment. It has long been known that ionizing radiation is more effective in killing cancer cells if the cells are in an oxygen-rich environment; however, the farther tumor cells are away from the blood

supply, the more hypoxic they are and the more resistant they are to radiation therapy. Current methods for delivering oxygen to hypoxic cells have limitations because they are toxic to normal tissue, require oxygen for their activity, or have too short a half-life. This development overcomes such problems by employing a nitric oxide (NO)-containing compound that spontaneously releases NO under physiologic conditions without requiring oxygen. This compound—which has a relatively long half-life and is nontoxic to normal cells—has the dual advantages of being able to sensitize hypoxic tumor cells to ionizing radiation while protecting normal cells from the effects of radiation.

Use of Nitric Oxide-Releasing Agents for Reducing Metastasis Risk

RJ Korthuis, L Kong, LK Keefer (NCI)
Serial No. 08/344,341 filed 22 Nov 94

Metastasis, which involves the release of cancerous cells from a tumor into the circulatory or lymphatic system, is a major problem in tumor therapy. Current methods to prevent metastasis from occurring include chemotherapy and immunotherapy. However, chemotherapeutic methods currently in use employ inhibitors of nucleic acid or protein synthesis that cause serious side effects. This invention relates to the use of compounds that generate nitric oxide (NO) to reduce metastases. It is not known at the present whether NO in fact does reduce metastases, although it is known that tumor cells that synthesize NO appear to be less metastatic than those that do not. Specifically, the claims relate to a series of novel compounds that contain a nitric oxide-releasing N_2O_2-functional group. These compounds are useful for inhibiting tumor cell adherence at sites at risk.

Biopolymer-Bound Nitric Oxide-Releasing Compositions, Pharmaceutical Compositions Incorporating Same and Methods of Treating Biological Disorders Using Same

JE Saavedra, LK Keefer, PP Roller, M Akamatsu (NCI) Serial No. 08/344,157 filed 22 Nov 94; U.S. Patent 5,632,981 issued 27 May 97

Nitric oxide (NO) has recently been implicated in a variety of bioregulatory processes, including normal physiological control of blood pressure, macrophage-induced cytostasis and cytotoxicity, and neurotransmission. A number of compounds have been developed which are capable of delivering nitric oxide, including compounds which release nitric oxide upon being metabolized and compounds which release nitric oxide spontaneously in aqueous solution. Nitric oxide in its pure form, however, is a highly reactive gas having limited solubility in aqueous media. Nitric oxide, therefore, is difficult to introduce reliably into most biological systems without premature decomposition. The invention provides a polymeric-bound composition (biopolymer) capable of spontaneously releasing nitric oxide under physiological conditions. A biopolymer would include any biological polymer, such as peptides, polypeptides, proteins, oligonucleotides, and nucleic acids, including those that contain naturally occurring and/or nonnaturally occurring subunits. Specific examples include antibodies or fragments thereof and peptide hormones, proteins, and growth factors for which the target cell type has a high population of receptors.

Incorporation of N_2O_2 Functional Group Into Polymeric Drug Delivery Systems for Treatment of Impotence

LK Keefer (NCI), JE Saavedra (NCI), M Hanamoto (Vivus), PC Doherty (Vivus), V Place (Vivus)
Serial No. 08/419,044 filed 10 Apr 95

Impotence is a major problem in the urology clinic with approximately 10–20 million men with moderate to severe forms of erectile dysfunction. This invention relates to a method of treating impotency in males through the use of nitric oxide-releasing agents. As nitric oxide is a mediator of penile erection, this method comprises the administration of a nitric oxide-releasing agent which is capable of providing a penile erection-inducing amount of nitric oxide to the male animal and which includes a nitric oxide-releasing functional group. Thus the invention provides a method of administering nitric oxide by using: compounds comprising nitric oxide-releasing functional groups, polymers to which a nitric oxide-releasing functional group is bound, as well as a nitric oxide delivery means for use in the method which delivers such a compound or polymer. The delivery means may be biodegradable or nonbiodegradable. The invention provides a method in which the nitric-oxide releasing agent provides nitric oxide to the penis of an impotent male animal in sufficient quantity to create a penile erection.

Polysaccharide-Bound Nitric Oxide/ Nucleophile Adducts

DJ Smith, D Chakravarthy, LK Keefer (NCI)
Serial No. 08/419,424 filed 10 Apr 95

The present invention relates to compositions comprising a number of nitric oxide/nucleophile adducts capable of releasing nitric oxide in a physiological environment, pharmaceutical compositions comprising such nitric oxide/ nucleophile adduct compositions, and methods of their use to treat biological disorders for which the administration of nitric oxide is indicated. The spontaneous generation of nitric oxide by these compounds has proven advantageous for many applications in which only one tissue is to be targeted among the many that could be affected by systemic administration. The invention details the compounds which eventually provides a composition capable of releasing nitric oxide which includes a nitric oxide-releasing N_2O_2 functional group bound to a polymer, specifically a polysaccharide. This permits modulation of the time course of nitric oxide release in a controllable way as well as limiting nitric oxide exposure to selected sites within the body through the use of incorporating the N_2O_2 functional group into a variety of polymeric matrices. It also provides a pharmaceutical composition which includes a pharmaceutically acceptable carrier and a polymer, specifically a polysaccharide, having a nitric oxide-releasing N_2O_2 functional group bound to the polymer. The invention provides for a method of treatment of disorders which comprises administering a composition comprising a polymer and a nitric oxide-releasing N_2O_2 functional group bound to the polymer in an amount sufficient to release a therapeutically effective amount of nitric oxide.

N-Substituted Piperazine NONOates

LK Keefer, JE Saavedra, JA Hrabie (NCI)
Serial No. 08/475,732 filed 07 Jun 95

A frequent problem in nitric oxide research is the delivery of nitric oxide to a specific organ or cell type needed without adversely affecting other nitric oxide sensitive parts of the body. This invention overcomes this problem by the synthesis of a number of N-substituted piperazine NONOate compounds which are potent nitric oxide releasing compounds without activation at physiological pH. The invention's N-substituted piperazine NONOates, when tagged to polypeptides and proteins, can become an effective tissue-selective potent nitric oxide releasing protein. Thus, the invention may achieve specific cellular interactions unique to the proteins to be adducted allowing for exquisite

targeting even though the adduct is systemically administered and nitric oxide release is spontaneous.

Selective Prevention of Organ Injury in Sepsis and Shock Using Selective Release of Nitric Oxide in Vulnerable Organs

JF Saavedra, TR Billiar, LK Keefer (NCI)
Serial No. 08/509,558 filed 31 Jul 95

The invention provides a method of treating mammalian tissue which is injured or is at risk of injury during sepsis or shock, including septic shock, hemorrhagic stock, and cardiogenic shock. In the suggested method, nitric oxide is delivered to target tissue or cells in a controlled and predictable manner through the administration of a nitric oxide containing compound (diazeniumdiolate) which is protected from the systemic release of nitric oxide under physiological conditions, and/or that is concentrated in at risk organs before releasing its nitric oxide. The diazeniumdiolate is capable of releasing at the targeted tissue a therapeutically effective amount of nitric oxide, sufficient to protect tissue from sepsis or shock-induced injury.

O^2-aryl Substituted Diazeniumdiolates

JE Saavedra, A Srinivasan, LK Keefer (NCI)
Serial No. 60/026,816 filed 27 Sep 96

Diazeniumdiolates, wherein the N^1 position is substituted by an organic moiety and the O^2-oxygen is bound to a substituted or unsubstituted aromatic group, are provided. The O^2-aryl diazeniumdiolates are stable with respect to the hydrolytic generation of nitric oxide in neutral to acidic solutions. These novel compounds generate nitric oxide in basic or nucleophilic environments or microenvironments. Also provided are compositions, including pharmaceutical compositions, comprising such compounds and methods of using such compounds.

Encapsulated and Non-Encapsulated Nitric Oxide Generators Used as Antimicrobial Agents

SJ Green, LK Keefer (NCI)
Serial No. 08/428,632 filed 24 Apr 95

This invention relates to compositions capable of releasing nitric oxide and therapeutic methods of use thereof for the treatment of microorganism-related disease states. The composition comprises one or more nitric oxide generators, preferably encapsulated in vesicles, such as liposomes. The compositions are used therapeutically by administration to humans and animals via different routes for the treatment of infectious diseases caused by pathogenic microbes.

Dated: August 4, 1997.

Barbara M. McGarey,

Deputy Director, Office of Technology Transfer.

[FR Doc. 97–21149 Filed 8–8–97; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of Exclusive License: New Brefeldin a Derivatives

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

ACTION: Notice.

SUMMARY: This is notice in accordance with 35 U.S.C. 209(c)(1) and 37 CFR 404.7(a)(1)(i) that the National Institutes of Health (NIH), Department of Health and Human Services, is contemplating the grant of an exclusive world-wide license to practice the inventions embodied in U.S. Patent Application Serial Number 08/267,525, entitled ''New Brefeldin A Derivatives And Their Utility In The Treatment Of Cancer,'' and corresponding U.S. and foreign patent applications to Allelix Biopharmaceuticals, Inc. of Mississauga, Ontario, Canada. The patent rights of the NIH inventors in these inventions have been assigned to the United States of America.

DATES: Only written comments and/or applications for a license which are received by NIH on or before October 10, 1997, will be considered.

ADDRESSES: Requests for copies of the patent applications, inquiries, comments and other materials relating to the contemplated licenses should be directed to: Raphe Kantor, Ph.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; Telephone: (301) 496–7056 ext. 247; Facsimile: (301) 402–0220. A signed Confidentiality Agreement will be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: This invention relates to a new class of compounds which can be characterized as breveldin A derivatives, e.g., 4-O-(N,N-dimethylglycyl) breveldin A; 7-O-(N-N-dimethylglycyl) breveldin A. These breveldin A analogs are more water soluble than the parent compound. These analogs appear to have reduced toxicities which limited the clinical utility of the parent compound. These compounds exhibit activity against a wide variety of cancers, including colon cancer, melanoma, leukemia, ovarian, prostate, breast and renal tumors. However, recently performed toxicity studies on one breveldin A analog (breflate) found that it still retained an unacceptable toxicity profile.

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

Applications for a license filed in response to this notice will be treated as objections to the grant of the contemplated licenses. 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: August 1, 1997.

Barbara M. McGarey,

Deputy Director, Office of Technology Transfer.

[FR Doc. 97–21093 Filed 8–8–97; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of Exclusive License: Diagnostic Methods Derived From the Human Metastasis Suppressor Gene KAI1

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 404.7(a)(1)(i) that the National Institutes of Health, Department of Health and Human Services, is contemplating the grant of an exclusive world-wide license to practice the inventions embodied in U.S. Patent Applications SN 08/430,225 and corresponding foreign patent applications entitled, ''Diagnostic Methods and Gene Therapy Using Reagents Derived From the Human Metastasis Suppressor Gene KAI1'' to Centocor, Inc. of Malvern, PA. The patent rights in these inventions have been assigned to the United States of