Computer-Based Model for Identification and Characterization of Non-Competitive Inhibitors of Nicotinic Acetylcholine Receptors and Related Ligand-Gated Ion Channel Receptors

I. W. Wainer *et al.* (NIA). U.S. Patent Application No. 10/411,206 filed 11 Apr 2003 (DHHS Reference No. E–158–2003/0-US–01); PCT Application No. PCT/US04/10978 filed 09 Apr 2004 (DHHS Reference No. E–158–2003/1-PCT–01); U.S. Patent Application No. 10/820,809 filed 09 Apr 2004 (DHHS Reference No. E–158–2003/1-US–02).

Licensing Contact: Cristina Thalhammer-Reyero; (301) 435–4507; *thalhamc@mail.nih.gov.*

This invention relates to a computer system for generating molecular models of ligand-gated ion channels and in particular, molecular models of the inner lumen of a ligand-gated ion channel and associated binding pockets. It further relates to a computer system simulating interaction of the computer-based model of the ligand-gated channel and non-competitive inhibitor compounds for identification and characterization of non-competitive inhibitors and to inhibitor compounds so discovered. It also includes methods for treating various disorders related to ligand-gated ion channel receptor function, and provides a way to examine compounds for ''off-target'' activity that may cause undesirable side effects to a desired target activity or that may represent a new therapeutic activity for a known compound.

Ligand gated ion channels (LGICs) are currently very important targets for drug discovery in the pharmaceutical industry. The superfamily is separated into the nicotinic receptor superfamily (muscular and neuronal nicotinic, GABA-A and-C, glycine and 5-HT3 receptors), the excitatory amino acid superfamily (glutamate, aspartate and kainate receptors) and the ATP purinergic ligand gated ion channels. These families only differ in the number of transmembrane domains found in each subunit (nicotinic–4 transmembrane domains, excitatory amino acid receptors–3 transmembrane domains, ATP purinergic LGICs–2 transmembrane domains). In particular, the nicotinic acetylcholine receptors control the fast permeation of cations through the postsynaptic cell membrane, and are key targets in drug discovery for a number of diseases, including Alzheimer's and Parkinson's disease.

Modulators of Nuclear Hormone Receptor Activity: Novel Compounds, Diverse Applications for Infectious Diseases, Including Anthrax (*B. anthracis*)

E. M. Sternberg (NIMH), J. I. Webster (NIMH), L. H. Tonelli (NIMH), S. H. Leppla (NIAID), and M. Maoyeri (NIAID). U.S. Provisional Application No. 60/416,222 filed 04 Oct 2002 (DHHS Reference No. E–247–2002/0-US–01); U.S. Provisional Application No. 60/419,454 filed 18 Oct 2002 (DHHS Reference No. E–348–2003/0-US–01); PCT Application No. PCT/US03/31406 filed 03 Oct 2003 (DHHS Reference No. E–247–2002/1-PCT–01).

Licensing Contact: Peter Soukas; (301) 435–4646; *soukasp@mail.nih.gov.*

Technology summary and benefits: Nuclear hormones such as glucocorticoids dampen inflammatory responses, and thus provide protection to mammals against inflammatory disease and septic shock. The Anthrax lethal factor represses nuclear hormone receptor activity, and thus may contribute to the infectious agent causing even more damage to the host. This observation can be exploited to find new means of studying and interfering with the normal function of nuclear hormone receptors. Scientists at NIH have shown that under the appropriate conditions, these molecules can be used to modulate the activity of various nuclear hormone receptors. Identifying useful agents that modify these important receptors can provide relief in several human disorders such as inflammation, autoimmune disorders, arthritis, malignancies, shock and hypertension.

Long-term potential applications: This invention provides novel agents that can interfere with the action of nuclear hormone receptors. It is well known that malfunction or overdrive of these receptors can lead to a number of diseases such as enhanced inflammation; worse sequelae of infection including shock; diabetes; hypertension and steroid resistance. Hence a means of controlling or fine-tuning the activity of these receptors can be of great benefit. Current means of affecting steroid receptor activity are accompanied by undesirable side-effects. Since the conditions for which these treatments are sought tend to be chronic, there is a critical need for safer drugs that will have manageable side-effects.

Uniqueness or innovativeness of technology: The observation that the lethal factor from Anthrax has a striking effect on the activity of nuclear hormone receptors opens up new routes to controlling their activity. The means of action of this repressor is sufficiently different from known modulators of hormone receptors (*i.e.* the classical antagonists). For instance, the repression of receptor activity is non-competitive, and does not affect hormone binding or DNA binding. Also, the efficacy of nuclear hormone receptor repression by Anthrax lethal factor is sufficiently high that the pharmacological effect of this molecule is seen at vanishingly small concentrations. Taken together, these attributes may satisfy some of the golden rules of drug development such as the uniqueness or novelty of the agent's structure, a low threshold for activity, high level of sophistication and knowledge in the field of enquiry, and the leeway to further refine the molecule by rational means.

Stage of Development: In vitro studies have been completed, and a limited number of animal studies have been carried out.

Dated: August 16, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–19300 Filed 8–23–04; 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.

Methods of Use of Nitrite Therapy

M. Gladwin (CC), R. Cannon (NHLBI), A. Schechter (NIDDK), C. Hunter (CC), R. Pluta (NINDS), E. Oldfield (NINDS), D. Kim-Shapiro (EM), R. Patel (EM), D. Lefer (EM), G. Power (EM). U.S. Patent Application 60/484,959 filed 09 July 2003 (DHHS Reference No. E–254–2003/0–US–01). U.S. Patent Application 60/511,244 filed 14 Oct 2003 (DHHS Reference No. E–254–2003/1–US–01). PCT Applications filed 09 July 2004 (DHHS Reference Nos. E–254–2003/2–PCT–01 and E–254–2003/3–PCT–01).

Licensing Contact: Susan Carson; (301) 435–5020; *carsonsu@mail.nih.gov.*

Different therapeutic classes of compounds that are able to increase blood flow and act as vasodilators have been used to treat a wide variety of disease indications including cardiovascular and respiratory diseases. Endothelium-derived factors, such as nitric oxide (NO), play a crucial role in the maintenance of vascular homeostasis, and NO-enhancing compounds have been administered alone or in combination with an approved pharmaceutical agent in order to provide an effective therapeutic treatment. Many of these therapies are very costly and there remains a strong need for an affordable treatment. Recent scientific work by the inventors provided evidence that the anion nitrite represents a circulating and tissue storage form of nitric oxide whose bioactivation is mediated by the nitrite reductase activity of deoxyhemoglobin [Nature Medicine 2003 9(12):1498–1505].

NIH scientists and their collaborators have now shown that low, physiological and non-toxic concentrations of sodium nitrite are able to increase blood flow and produce vasodilation by infused and nebulised routes of administration. Proof of concept data has been obtained in animal models for myocardial and hepatic ischemia and reperfusion injury, in a neonate lamb model for neonatal pulmonary hypertension, and in a primate model for prevention of delayed cerebral vasospasm following sub-arachnoid hemorrhage. The implications of these results point to the use of nitrite as a potential cost-effective platform therapy for a wide variety of disease indications characterized broadly by constricted blood flow or tissue hypoxia. Available for licensing are method of use claims for nitrite salt formulations directed to conditions associated with high blood pressure, decreased blood flow or hemolytic disease (E–254–2003/2) and for the treatment of specific conditions such as pulmonary hypertension, cerebral artery vasospasm and hepatic, cardiac or brain ischemia-reperfusion injury (E–254–2003/3).

Dated: August 14, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–19301 Filed 8–23–04; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institutes; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the National Cancer Institute Director's Consumer Liaison Group.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: National Cancer Institute Director's Consumer Liaison Group, NCI's Director's Consumer Liaison Group.

Date: September 13–15, 2004.

Time: 10 a.m. to 4 p.m.

Agenda: Open; Review of DCLG Working Group; Dep Dir Panel; NCI Orientation; Cancer Survivorship, Reducing Cancer Health Disparities; Discussion with NCI Director/Next Steps; Update for NCI Director; Director's Remarks/Discussion; Recognition of Former DCLG Members; Facilitating Dialogue.

Place: Holiday Inn Select, 8120 Wisconsin Avenue, Bethesda, MD 20814.

Contact Person: Nancy Caliman, Executive Secretary, Office of Liaison Activities, National Institutes of Health, National Cancer Institute, 6116 Executive Boulevard, Suite 220, MSC8324, Bethesda, MD 20892, (301) 496–0307, *calimann@mail.nih.gov.*

Any interested person may file written comments with the committee by forwarding the statement to the Contact Person listed on this notice. The statement should include the name, address, telephone number and when applicable, the business or professional affiliation of the interested person.

Information is also available on the Institute's/Center's home page: *http://deainfo.nci.nih.gov/advisory/dclg/dclg.htm,* where an agenda and any additional information for the meeting will be posted when available.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: August 16, 2004.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–19295 Filed 8–23–04; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Eye Institute; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Eye Institute Special Emphasis Panel, Review of Nanomedicine Roadmap.

Date: September 1–2, 2004.

Time: 7:30 p.m. to 5 p.m.

Agenda: To review and evaluate grant applications.

Place: Double Tree Rockville, 1750 Rockville Pike, Rockville, MD 20852.

Contact Person: Richard S. Fisher, PhD, Scientific Review Administrator, National Eye Institute, Division of Extramural Research, 5635 Fishers Lane, Bethesda, MD 20892, (301) 451–2020, *rfisher@nei.nih.gov.*

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

(Catalogue of Federal Domestic Assistance Program Nos. 93.867, Vision Research, National Institutes of Health, HHS)

Dated: August 16, 2004.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–19292 Filed 8–23–04; 8:45 am]

BILLING CODE 4140–01–M