Licensing Contact: Norbert Pontzer; (301) 435–5502; *pontzern@mail.nih.gov*

The simple diatomic molecule nitric oxide (NO) is known to play a diverse and complex role in cellular physiology. NCI scientists have previously produced a number of nucleophile/nitric oxide adducts (diazeniumdiolates) that spontaneously dissociate at physiological pH to release nitric oxide by stable first order kinetics. These compounds are finding diverse therapeutic uses as pharmacological agents. Growing evidence suggests that redox related forms of NO such as nitroxyl (HNO) also have a rich pharmacological potential and may complement that of NO. The present invention provides compounds that release both NO and HNO under physiological conditions, compositions comprising those compounds and methods of using the compounds alone and in conjunction with medical devices such as stents to treat disease. Included among the compositions claimed is a glycosylated prodrug derivative that can be cleaved to active form by β–D-glucosidase (J. Am. Chem. Soc. 2004, 126, 12880–12887).

A Method With Increased Yield for Production of Polysaccharide-Protein Conjugate Vaccines Using Hydrazide Chemistry

Che-Hung Robert Lee and Carl Frasch (FDA), U.S. Provisional Application No. 60/493,389 filed 06 Aug 2003 (DHHS Reference No. E–301–2003/0–US–01)

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

Current methods for synthesis and manufacturing of polysaccharide-protein conjugate vaccines employ conjugation reactions with low efficiency (about twenty percent). This means that up to eighty percent of the added activated polysaccharide (PS) is lost. In addition, inclusion of a chromatographic process for purification of the conjugates from unconjugated PS is required.

The present invention utilizes the characteristic chemical property of hydrazide groups on one reactant to react with aldehyde groups or cyanate esters on the other reactant with an improved conjugate yield of at least sixty percent. With this conjugation efficiency the leftover unconjugated protein and polysaccharide would not need to be removed and thus the purification process of the conjugate product can be limited to diafiltration to remove the by-products of small molecules. The new conjugation reaction can be carried out within one or two days with reactant concentrations between 1 and 25 mg/mL at PS/protein ratios from 1:2 to 3:1, at temperatures between 4 and 40 degrees Centigrade, and in a pH range of 5.5 to 7.4, optimal conditions varying from PS to PS.

Therefore, this invention can reduce the cost of conjugate vaccine manufacture.

Dated: November 24, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–26596 Filed 12–2–04; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of Exclusive License: Dendrimer Based MRI Contrast Agents

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 worldwide license to practice the invention embodied in:

E–151–2002 ''Methods for Functional Kidney Imaging Using Dendrimer Conjugate Agents,'' U.S. Patent App. Serial No. 10/229,316 and International Patent Application No. PCT/US02/27297;

E–240–2001 ''Macromolecular Imaging Agents for Liver Imaging,'' U.S. Patent App. Serial No. 10/481,706, International Patent Application No. PCT/US02/20118, European Patent Application 02752092.3;

E–338–2003 ''Method for Imaging the Lymphatic Systems Using Dendrimer-Based Contrast Agents,'' U.S. Patent App. Serial No. 10/756,948;

E–317–2004 ''Synthetic Metal Ion Chelating Amino Acid Suitable for Use in Solid Phase Peptide Synthesis.'' Filed October 4, 2004 (Serial Number to be determined);

to Dendritic NanoTechnologies, Inc., a Delaware corporation having its principle place of business in Mount Pleasant, Michigan. The United States of America is the assignee to the patent rights of the above inventions.

The contemplated exclusive license may be granted in the field of use of MRI imaging contrast agents.

DATES: Only written comments and/or applications for a license received by the NIH Office of Technology Transfer on or before February 1, 2005 will be considered.

ADDRESSES: Requests for a copy of the patent application, inquiries, comments and other materials relating to the contemplated license should be directed to: Michael A. Shmilovich, Esq., Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852–3804; Telephone: (301) 435–5019; Facsimile: (301) 402–0220; E-mail: *shmilovm@mail.nih.gov.* A signed confidentiality nondisclosure agreement will be required to receive copies of the patent applications.

SUPPLEMENTARY INFORMATION: The patent applications intended for licensure disclose and/or cover the following:

E–151–2002—Methods for Functional Kidney Imaging Using Dendrimer Conjugate Agents

The invention is a method for functional kidney imaging using small dendrimer-based MRI contrast agents that transiently accumulate in renal tubules. The accumulation enables visualization of renal structure and function, permitting assessment of structural and functional damage to the kidneys. Six small dendrimer-based MRI contrast agents have been synthesized, and their pharmacokinetics, whole body retention and renal MRI images were evaluated in mice. Surprisingly, despite having unequal renal clearance properties, all of the dendrimer agents clearly visualized the renal anatomy and proximal straight tubules of the mice better than Gd-[DTPA]-dimeglumine. Dendrimer conjugate contrast agents prepared from PAMAM–G2D, DAB–G3D and DAB–G2D dendrimers were excreted rapidly and may be acceptable for use in clinical applications.

E–240–2001—Macromolecular Imaging Agents for Liver Imaging

The invention is a macromolecular imaging agent comprising a polyalkylenimine dendrimer conjugated to a metal chelate that has been shown to be an excellent agent for imaging liver micrometastases as small as about 0.3 mm in a magnetic resonance image of the human liver. In a particular embodiment, the imaging agent is a diaminobutane-core polypropylenimine dendrimer having surface amino groups conjugated to gadolinium metal chelates. The invention makes possible the earlier detection of metastatic disease, leading to earlier application of a therapeutic regime and an improved prognosis. Accordingly, the method of

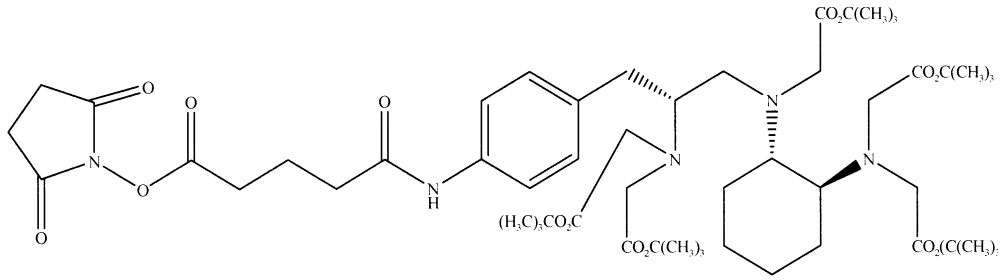
using the imaging agent in the detection of metastatic disease in the liver is also within the scope of the invention.

E–338–2003—Method for Imaging the Lymphatic Systems Using Dendrimer-Based Contrast Agents

The invention is a 4D method of Magnetic Resonance lymphography using a 240kD contract agent based on generation-6 polyamidoamine dendrimer (G6). The use of the G6 contrast agent greatly enhances visualization of lymphatics and node drainage associated with mammary tumors and further aids in the diagnosis of metastatic breast cancer. After direct injection of the G6 contrast agent into mice, lymphatics and nodes were visualized in both spontaneous (HER2 transgenic mouse) and xenografted (PT–18) breast tumors to metastatic lymph nodes. The conventional clinically approved MRI contract agent, Gd-[DTPA]-dimeglumine (<1kD) was unable (in murine models) to depict lymphatics when used in conjunction with the same imaging system. The invention provides a novel method of using a known contrast agent to visualize lymphatic drainage that has not been previously reported.

E–317–2004—Synthetic Metal Ion Chelating Amino Acid Suitable for Use in Solid Phase Peptide Synthesis

The invention is metal chelators, metal chelator-targeting moiety complexes, metal chelator-targeting moiety-metal conjugates, kits, and methods of preparing them. These chelators are useful in diagnosing and/or treatment of cancer and thrombosis. The metal chelators may be used in conventional synthetic methods to form targeting moieties (*e.g.*, peptides, proteins, and Starburst polyamidoamine dendrimers (PAMAM), capable of conjugating diagnostic and/or therapeutic metals. The formulae for two such chelators is shown below:



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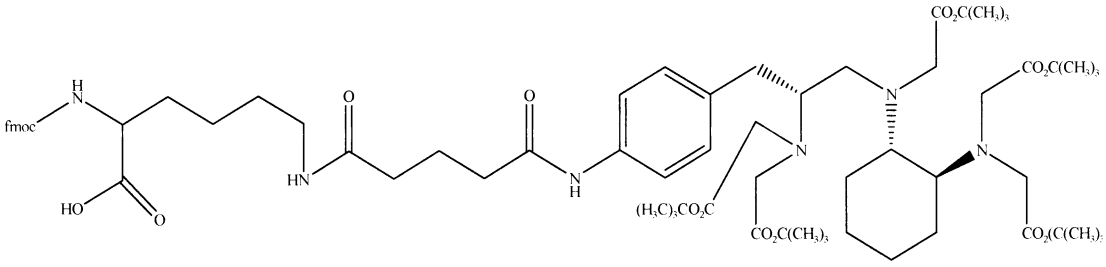

II

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.

Properly filed competing applications for a license filed in response to this notice will be treated as objections to the contemplated license. Comments and objections submitted in response 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: November 24, 2004.

Steven M. Ferguson,

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

[FR Doc. 04–26595 Filed 12–2–04; 8:45 am]

BILLING CODE 4140–01–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program; National Institute of Environmental Health Sciences (NIEHS); National Institutes of Health (NIH) Notice of Additional Data and Analyses for the Assessment of the Current Validation Status of In Vitro Testing Methods for Identifying Potential Ocular Irritants

Summary

The National Toxicology Program (NTP) Interagency Center for the