Novel Cyclic Polyamines That Release Nitric Oxide in a Biphasic Manner

David Waterhouse et al. (NCI).
DHHS Reference No. E–189–2002/0 filed 07 May 2002.
Licensing Contact: Norbert Pontzer; 301/435–5502; e-mail: *np59n@nih.gov.*

Nitric oxide (NO), a simple diatomic molecule, plays a diverse and complex role in cellular physiology. Although medical research is rapidly discovering potential therapeutic uses for NO, the exogenous administration of gaseous NO is not feasible because of low solubility in physiological buffers, widespread pharmacological actions and a short half-life in the body. NCI scientists have previously produced a number of nucleophile/nitric oxide adducts (diazeniumdiolates) that spontaneously dissociate at physiological pH to release nitric oxide (NO) by stable first order kinetics. These compounds allow for the localized action of NO by, for example, having NO released from biocompatible medical devices coated with the NO-releasing compounds or polymers. The half-life of NO release from currently available compounds and polymers can vary from minutes to many hours under physiological conditions. However, it could be useful to have an initial high rate of NO release followed by a subsequent slower longer term release from a single compound. These inventors have now discovered polydiazeniumdiolated materials that, as single crystals compounds, provide the multiple multiphasic NO release necessary to accomplish that goal. They also provide medical uses of these compounds such as treatment of infection, inhibition of tumor cell growth, conjugation to antibodies, treatment of ischemia/repurfusion injury, attachment to polymers, and medical substrates such as stents coated with these compounds.

Dated: March 11, 2003.

Steven M. Ferguson,

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

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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 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 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.

Lepirudin Adsorbed to Catheter

McDonald Horne (CC)
DHHS Reference No. E–295–02/0
Licensing Contact: Michael Shmilovich; 301/435–5018; *shmilovichm@od.nih.gov.*

The invention is a method for preventing venous access device (VAD) thrombosis by coating the VAD catheter with lepirudin, which has been found to be readily adsorbed by the silicone rubber of the VADs, and is expected to have good retention properties. VADs typically remain in place for weeks or months and sometimes cause clotting (thrombosis) of the veins. Accordingly, the simple technique of soaking a silicone catheter in lepirudin before venous insertion is the gist of the invention. Chronically ill patients who must be catheterized for long periods of time will benefit particularly from this technique which promises to reduce swelling and pain associated with VAD-induced thrombosis.

Peptide Inhibitors of Yersinia Phosphatase (YopH) as Potential Treatments Against Plague

Terrence Burke, Jr., et al. (NCI)
DHHS Reference No. E–263–2002
Licensing Contact: Cristina Thalhammer-Reyero; 301/435–4507; *thalhamc@od.nih.gov.*

This invention pertains to compounds, i.e., peptides or pro-drugs thereof, which are useful as inhibitors of phosphotyrosine phosphatases, and in particular, as inhibitors of the Yersinia phosphatase (YopH). The invention also provides pharmaceutical compositions and a method of inhibiting the YopH enzyme as well as a method of treating plague or Black Death. The compounds may be useful as anti-bioterrorism agents, and are potentially important for therapeutic development because they may facilitate bioavailablility, given the low ionic charge of the inhibitors.

The bacterium Yersinia pestis causes bubonic, pneumonic and septicemic plague, and it is considered as a potential bioterrorism agent. Within Yersinia is a 70 kb virulence plasmid, which encodes for a system of secreted proteins, called ''Yops'', which act either as intracellular effectors or as translocators. Yersinia's Yop system represents the archetype for one of the major virulence mechanisms in various pathogenic bacteria, referred to as type III, where extracellular bacteria that are in close contact with a eukaryotic cell deliver bacterial proteins into the cytosol of the cell. Other animal pathogens with related systems include the genera Salmonella, Shigella, Pseudomonas, Chlamydia, and Bortedella, as well as E. coli.

One such effector protein, YopH, is a protein-tyrosine phosphatase (PTP) with a C-terminal catalytic domain that is essential to Yersinia's virulence, playing an antiphagocytic role by dephosphorylating focal adhesion proteins. The phosphatase activity of YopH is required for bacterial pathogenesis. This invention relates to the use of tripeptides as inhibitors of YopH, and therefore as potential treatments of plague. More in particular, the inventors have discovered that certain structural features are required to be present on those peptides in order to be inhibitory against Yersinia's YopH.

A Varicella-Zoster Virus Vaccine Mutant That Is Markedly Impaired for Latent Infection

Jeffrey Cohen (NIAID), Edward Cox (FDA), Lesley Pesnicak (NIAID)
DHHS Reference No. E–250–02/0 filed 05 Nov 2002
Licensing Contact: Peter Soukas; 301/435–4646; *soukasp@od.nih.gov.*

Chickenpox is caused by acute infection with varicella-zoster virus (VZV). The virus spreads throughout the body and enters cells of the nervous system. Latent infection occurs and the virus establishes itself in dorsal root and cranial nerve ganglia. The latent virus subsequently can reactivate and present as zoster (shingles). The current varicella-zoster virus vaccine (Oka strain) is highly effective to protect against varicella (chickenpox), but establishes a latent infection in the central nervous system and can reactivate to cause shingles. This invention relates to a mutated form of

the current Oka vaccine strain that it is markedly impaired for establishing latency. This virus may be a safer vaccine than the currently available vaccine.

Recombinant of Respiratory Syncytial Virus (RSV) Expressing Green and/or Red Fluorescent Protein

Mark Peeples (Rush Presbyterian-St. Luke's Medical Center) and Peter Collins (NIAID)
DHHS Reference No. E–038–2002/0 (Research Materials)
Licensing Contact: Susan Ano; 301/435–5515; *anos@od.nih.gov.*

The biological materials RSV expressing green and/or red fluorescent proteins are available for licensing as research tools for antiviral drug screening or for studying infection and replication of the virus in real time in cultured cells. RSV is the most important viral respiratory pathogen in infants and thus is a major target for development of antiviral agents. The fluorescent protein markers allow rapid quantification of the extent of virus infection and are easily used in conjunction with common apparatuses such as 96-well plates and fluorescence plate readers.

These viruses are produced by the reverse genetic system as described in U.S. patent 6,264,957 (issued July 24, 2001) to Dr. Peter Collins of the NIAID. This reverse genetic system is also available for licensing (DHHS Ref. E–187–1995/1), including all of the plasmids necessary to make the recombinant viruses.

This research has been described, in part, in Hallak et al., Virology 271:264–275, 2000; Zhang et al., J. Virol. 76:5654–5666, 2002; Techaarpornkul et al., Virology 294:296–304, 2002.

HIV–1 Reverse Transcriptase Expression Systems

Dr. Stephen Hughes et al. (NCI)
DHHS Reference No. E–034–91/0
Licensing Contact: Sally Hu; 301/435–5606; *hus@od.nih.gov.*

This invention describes a series of HIV–1 reverse transcriptase (RT)-based products:

(a) HIV–1 RT (66 kDa) and HIV–2 RT (68 kDa) expression plasmids. These lead to the production of homodomeric forms of these proteins.

(b) Inducible expression plasmid p66his-prot producing large amounts of HIV–1 RT (p66) and small amounts of HIV–1 protease. This leads to the production of a p66/p51 heterodimeric form of the protein. A version of this plasmid is available with 6x his tail on p66 to simplify purification of the heterodimer. Expression plasmids for wild-type RT and for numerous mutated RT, including most of the common drug resistant mutants, are available. Mutated RT forms: AZT–21; HIV–2 (His); L74V; P236L; L100I; K103N; V106A; E138K; V181I; M184V; Y188L.

(c) HIV–1 RT with a substitution C280S and a double mutant C38V/C280S that are less susceptible to oxidation than the wild-type enzyme. These mutant HIV–1 RTs have enzymatic properties that are similar to wild-type HIV–1 RT.

Those RT expression plasmids might be used both in biological and medical research such as to study various properties of the enzyme, to determine which domains of the enzyme are the most promising for directing anti-RT reagents against, and to screen RT inhibitors *in vitro.* The HIV–1 Reverse Transcriptase Expression plasmids subject of this report are available for licensing via biological material licenses (BML).

Dated: March 11, 2003.

Steven M. Ferguson,

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

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IL–21 Critically Regulates Immunoglobulin Production

Warren J. Leonard, Katsutoshi Ozaki, and Rosanne Spolski (NHLBI)
U.S. Provisional Patent Application 60/393,215 filed 01 Jul 2002
Licensing Contact: Brenda Hefti; 301/435–4632; *heftib@od.nih.gov.*

The invention includes a mouse in which the IL–21 receptor gene is disrupted by homologous recombination, the disruption being sufficient to prevent expression of the IL–21 receptor and thus to inhibit the action of IL–21. The invention also includes a mouse in which both the IL–21 receptor gene and the IL–4 gene are simultaneously disrupted in fashions being sufficient to inhibit the action of IL–21 and the production of IL–4. In a homozygous state, these mutations produce a mouse that has diminished B cell function.

This invention also relates to the use of agents that inhibit the interaction of IL–21 with the IL–21 receptor to modulate an immune response. This invention may be used to alter B cell activity, to treat a subject with Job's disorder, to treat an allergic reaction in a subject, or prevent an allergic reaction in a subject.

Grafting of a Murine Antibody Onto a Human Framework

S. Rybak, J. Krauss, M. Arndt, and A. Martin (NCI)
U.S. Provisional Patent Application 60/390,033 filed 17 June 2002
Licensing Contact: Brenda Hefti; 301/435–4632; *heftib@od.nih.gov.*

This invention relates to humanization of antibodies specifically providing novel biophysically stable human framework sequences that can be used to humanize antibody single chain Fv (scFv) fragments. An exemplary RFB4 humanized scFv antibody was constructed using the new sequences. The novel sequences were obtained after stringent panning of a human phage display library on (irrelevant) antigen. These antibody variable domain frameworks were subsequently used as human acceptor scaffolds for grafting the murine antibody specificity. The general approach described here differs from other humanization procedures wherein appropriate human acceptor scaffolds are selected from either antibodies with solved crystal structures or (germline) sequence databases. In the current invention, human acceptor frameworks were first pre-selected for