

### Novel Cyclic Polyamines That Release Nitric Oxide in a Biphasic Manner

David Waterhouse et al. (NCI).  
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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 (diazoniumdiolates) 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 polydiazoniumdiolated 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/reperfusion injury, attachment to polymers, and medical substrates such as stents coated with these compounds.

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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

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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

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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 bioavailability, 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 *Bordetella*, 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

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DHHS Reference No. E-250-02/0 filed 05 Nov 2002  
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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