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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, HHS

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. 209 and 37 CFR Part 404 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.

FOR FURTHER INFORMATION: 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.

SUPPLEMENTARY INFORMATION: Technology descriptions follow.

Vaccine for Protection Against *Shigella sonnei* Disease

Description of Technology: Shigellosis is a global human health problem.

Transmission usually occurs by contaminated food and water or through person-to-person contact. The bacterium is highly infectious by the oral route, and ingestion of as few as 10 organisms can cause an infection in volunteers. An estimated 200 million people worldwide suffer from shigellosis, with more than 650,000 associated deaths annually. A recent CDC estimate indicates the occurrence of over 440,000 annual shigellosis cases in the United States alone, approximately eighty percent (80%) of which are caused by *Shigella sonnei*. *Shigella sonnei* is more active in developed countries. *Shigella* infections are typically treated with a course of antibiotics. However, due to the emergence of multidrug resistant *Shigella* strains, a safe and effective vaccine is highly desirable. No vaccines against *Shigella* infection currently exist. Immunity to *Shigellae* is mediated largely by immune responses directed against the serotype specific O-polysaccharide. Claimed in the invention are compositions and methods for inducing an immunoprotective response against *S. sonnei*. Specifically, an attenuated bacteria capable of expressing an *S. sonnei* antigen comprised of the *S. sonnei* form I O-polysaccharide expressed from the *S. sonnei* rfb/rfc gene cluster is claimed. The inventors have shown that the claimed vaccine compositions showed one hundred percent (100%) protection against parenteral challenge with virulent *S. sonnei* in mice.

Potential Commercial Applications:

- Shigella/Typhoid vaccine for travelers, military
- Shigella/Typhoid vaccine for developing countries
- Shigella/Typhoid diagnostics

Competitive Advantages:

- Low cost of production
- Temperature stable formulation
- Safety/efficacy of Ty21a established in humans

Development Stage: In vivo data available (animal)

Inventors: Dennis J. Kopecko (FDA), De Qi Xu (NIDCR), John O. Cisar
(NICHD)

Publication: Kopecko DJ, et al. Molecular cloning and characterization of genes for Shigella sonnei form I O polysaccharide: proposed biosynthetic pathway and stable expression in a live salmonella vaccine vector. Infect Immun. 2002 Aug;70(8):4414-23. [PMID: 12117952]

Intellectual Property: HHS Reference No. E-210-2001/0 -

- US Patent No. 7,541,043 issued 02 Jun 2009
- US Patent No. 8,071,084 issued 06 Dec 2011
- US Patent No. 8,337,832 issued 25 Dec 2012
- US Patent Application No. 13/686,299 filed 27 Nov 2012

Licensing Contact: Peter A. Soukas; 301-435-4646; soukasp@mail.nih.gov

Live Oral Shigella dysenteriae Vaccine

Description of Technology: This application claims a *Salmonella typhi* Ty21a construct comprising a *Shigella dysenteriae* O-specific polysaccharide (O-Ps) inserted into the *Salmonella typhi* Ty21a chromosome, where heterologous *Shigella dysenteriae* serotype 1 O-antigen is stably expressed together with homologous *Salmonella typhi* O-antigen. The constructs of this invention elicit immune protection against virulent *Shigella dysenteriae* challenge, as well as *Salmonella typhi* challenge. Also claimed in this application are methods of making the constructs of this invention and methods for inducing an immune response.

Shigella cause millions of cases of dysentery every year, which result in about seven hundred thousand deaths worldwide. *Shigella dysenteriae* serotype 1, one of about forty serotypes of *Shigella*, causes a more severe disease with a much higher mortality rate than other serotypes. There are no licensed vaccines available for protection against *Shigella*. The fact that many isolates exhibit multiple antibiotic resistance complicates the management of dysentery infections.

Potential Commercial Applications:

- One component of a multivalent anti-shigellosis vaccine under development.
- *Shigella* vaccines, therapeutics and diagnostics.

Competitive Advantages:

- Vector is well-characterized.
- Simple manufacturing process.
- Potential low-cost vaccine.
- Oral vaccine - avoids need for needles.

- Temperature-stable formulation allows for vaccine distribution without refrigeration.

Development Stage:

- In vitro data available
- In vivo data available (animal)

Inventors: Dennis J. Kopecko and De Qi Xu (FDA/CBER)

Publication: Xu DQ, et al. Core-linked LPS expression of *Shigella dysenteriae* serotype 1 O-antigen in live *Salmonella typhi* vaccine vector Ty21a: preclinical evidence of immunogenicity and protection. *Vaccine*. 2007 Aug 14;25(33):6167-75. [PMID 17629369]

Intellectual Property: HHS Reference No. E-214-2004/0 -

- US Patent No. 8,071,113 issued 06 Dec 2011
- US Patent No. 8,337,831 issued 25 Dec 2012
- US Patent No. 8,790,635 issued 29 Jul 2014
- US Patent Application No. 14/145,104 filed 31 Dec 2013 (allowed)
- Various international patent applications pending

Licensing Contact: Peter A. Soukas; 301-435-4646; soukasp@mail.nih.gov

Oral Shigellosis Vaccine

Description of Technology: This application claims a *Salmonella typhi* Ty21a construct comprising a *Shigella sonnei* O-antigen biosynthetic gene region inserted into the *Salmonella typhi* Ty21a chromosome, where heterologous *Shigella sonnei* form 1 O-antigen is stably expressed together with homologous *Salmonella typhi* O-antigen. The

constructs of this invention elicit immune protection against virulent *Shigella sonnei* challenge, as well as *Salmonella* Typhi challenge. Also claimed in this application are methods of recombineering a large antigenic gene region into a bacterial chromosome.

Bacillary dysentery and enteric fevers continue to be important causes of morbidity in both developed and developing nations. *Shigella* cause greater than one hundred and fifty million cases of dysentery and enteric fever occurs in greater than twenty-seven million people annually. Currently, there is no licensed vaccine to prevent the occurrence of *shigellosis*. Increasing multiple resistance in *Shigella* commonly thwarts local therapies.

Potential Commercial Applications:

- One component of a multivalent Shigellosis vaccine under development

- Research tool

Competitive Advantages:

- Low cost production

- Lower cost vaccine

- Oral vaccine - no needles required

- Temperature-stable manufacturing process - avoids need for refrigeration during

vaccine distribution

Development Stage:

- In vitro data available

- In vivo data available (animal)

Inventors: Dennis J. Kopecko and Madushini N. Dharmasena (FDA/CBER)

Publication: Dharmasena MN, et al. Stable expression of *Shigella sonnei* form I O-polysaccharide genes recombineered into the chromosome of live *Salmonella* oral vaccine vector Ty21a. *Int J Med Microbiol.*2013 Apr;303(3):105-13. [PMID 23474241]

Intellectual Property: HHS Reference No. E-168-2012/0 -

- US Provisional Application No. 61/701,939 filed 17 Sep 2012
- PCT Application No. PCT/US2013/059980 filed 16 Sep 2013, which published as WO 2014/043637 on 20 Mar 2014

Licensing Contact: Peter A. Soukas; 301-435-4646; soukasp@mail.nih.gov

Acid-Resistant, Attenuated Microbial Vector for Improved Oral Delivery of Multiple Targeted Antigens

Description of Technology: Ty21a, the licensed oral live, attenuated bacterial vaccine for *Salmonella typhi* (the causative agent of typhoid fever), has been engineered to stably express a variety of target LPS (lipopolysaccharides) and protein antigens to protect against shigellosis, anthrax, and plague. Ty21a induces mucosal, humoral, and cellular immunity and can be utilized as a multivalent vaccine vector that is inexpensive to produce. *Salmonella* species encode inducible acid tolerance, but this genus does not survive well below pH 4. *Shigella* and enterohemorrhagic *E. coli* isolates have more effective acid resistance systems than *Salmonella* and can survive an extreme acid challenge of pH 1-2 (the acidity of the human stomach when full).

This application claims an engineered Ty21a vector that can survive a very low pH for two to three hours (i.e., normal transit time through a full stomach), allowing for a final delivery format for Ty21a as a rapidly dissolvable wafer, instead of the large bullet-

size enteric-coated capsule, which small children cannot swallow. This formulation enhances the ability of the immunogenic composition and/or vaccine to stimulate immune responses sublingually and throughout the intestinal tract.

Potential Commercial Applications:

- Shigella vaccines
- Biodefense vaccines
- Diagnostics

Competitive Advantages:

- Ease of manufacture
- Inexpensive to manufacture
- Ease of administration
- Known live attenuated bacterial vector

Development Stage:

- In vitro data available
- In vivo data available (animal)

Inventors: Madushini N. Dharmasena and Dennis J. Kopecko (FDA/CBER)

Intellectual Property: HHS Reference No. E-535-2013/0 -

- US Provisional Application No. 61/862,815 filed 06 Aug 2013
- PCT Application No. PCT/US2014/049933 filed 06 Aug 2014

Licensing Contact: Peter A. Soukas; 301-435-4646; soukasp@mail.nih.gov

Attenuated Salmonella as a Delivery System for siRNA-Based Tumor Therapy

Description of Technology: This technology comprises live, attenuated *Salmonella* strains as a delivery system for small interfering double-stranded RNA (siRNA)-based tumor therapy. The inventors' data provide the first convincing evidence that *Salmonella* can be used for delivering plasmid-based siRNAs into tumors growing in vivo. Claimed in the related patent application are methods of inhibiting the growth or reducing the volume of solid cancer tumors using the si-RNA constructs directed against genes that promote tumor survival and cancer cell growth. The Stat3-siRNAs carried by an attenuated *S. typhimurium* described in the application exhibit tumor suppressive effects not only on the growth of the primary tumor but also on the development of metastases, suggesting that an appropriate attenuated *S. typhimurium* combined with the RNA interference (RNAi) approach may offer a clinically feasible method for cancer therapy.

Potential Commercial Applications:

- Development of live attenuated bacterial cancer vaccines, cancer therapeutics and diagnostics.
- Developing/developed world vaccine.

Competitive Advantages:

- Low cost of production
- Vaccine vector safety/efficacy in humans established

Development Status: In vivo data available (animal)

Inventors: Dennis J. Kopecko (FDA), De Qi Xu (FDA), Ling Zhang (Jilin University), Xuejian Zhao (Jilin University), Jiadi Hu (University of Maryland)

Publications:

1. Zhang L, et al. Intratumoral delivery and suppression of prostate tumor growth by attenuated *Salmonella enterica* serovar typhimurium carrying plasmid-based small interfering RNAs. *Cancer Res.* 2007 Jun 15;67(12):5859-64. [PMID 17575154]

2. Zhang L, et al. Effects of plasmid-based Stat3-specific short hairpin RNA and GRIM-19 on PC-3M tumor cell growth. *Clin Cancer Res.* 2008 Jan 15;14(2):559-68. [PMID 18223232]

Intellectual Property: HHS Reference No. E-278-2007/0 -

- PCT Application No. PCT/US2007/074272 filed 27 Jul 2007, which published as WO 2008/091375 on 31 Jul 2008

- US Patent Application No. 12/374,916 filed 23 Jan 2009

- International Application No. 200610017045.5 filed in China 27 Jul 2006

Licensing Contact: Peter A. Soukas; 301-435-4616; soukasp@mail.nih.gov

DNA Promoters and Anthrax Vaccines

Description of Technology: Currently, the only licensed vaccine against anthrax in the United States is AVA BioThrax®, which, although efficacious, suffers from several limitations. This vaccine requires six injectable doses over 18 months to stimulate protective immunity, requires a cold chain for storage, and in many cases has been associated with adverse effects.

This application claims a modified *B. anthracis* protective antigen (PA) gene for optimal expression and stability, linked it to an inducible promoter for maximal expression in the host, and fused to the secretion signal of the *Escherichia coli* alpha-hemolysin protein (HlyA) on a low-copy-number plasmid. This plasmid was introduced

into the licensed typhoid vaccine strain, *Salmonella enterica* serovar Typhi strain Ty21a, and was found to be genetically stable. Immunization of mice with three vaccine doses elicited a strong PA-specific serum immunoglobulin G response with a geometric mean titer of 30,000 (range, 5,800 to 157,000) and lethal-toxin-neutralizing titers greater than 16,000. Vaccinated mice demonstrated 100% protection against a lethal intranasal challenge with aerosolized spores of *B. anthracis* 7702.

Potential Commercial Applications: Anthrax vaccines, therapeutics and diagnostics.

Competitive Advantages:

- Vector is well-characterized.
- Simple manufacturing process.
- Potential low-cost vaccine.
- Oral vaccine - avoids needles and can be administered rapidly during emergencies.
- Temperature-stable manufacturing allows for vaccine distribution without refrigeration.

Development Stage:

- In vitro data available
- In vivo data available (animal)

Inventors: Dennis J. Kopecko, Siba Bhattacharyya, Milan Blake (all of FDA/CBER)

Publication: Osorio M, et al. Anthrax protective antigen delivered by Salmonella enterica serovar Typhi Ty21a protects mice from a lethal anthrax spore challenge. *Infect Immun.* 2009 Apr;77(4):1475-82. [PMID 19179420]

Intellectual Property: HHS Reference No. E-344-2003/1 -

- US Patent No. 7,758,855 issued 20 Jul 2010
- US Patent No. 8,247,225 issued 21 Aug 2012
- US Patent No. 8,709,813 issued 29 Apr 2014
- US Patent Application No. 14/185,353 filed 20 Feb 2014
- Various international patents issued

Licensing Contact: Peter A. Soukas; 301-435-4646; soukasp@mail.nih.gov

Typhoid-Plague Bivalent Vaccine

Description of Technology: *Yersinia pestis* (*Y. pestis*) bacteria is the causative agent of plague, typically transmitted from animals to humans by the bite of an infected flea. *Y. pestis* infection of the lungs leads to pneumonic plague, which is highly contagious and generally fatal. *Y. pestis* is a potential bioterrorist threat agent for which no vaccine yet exists.

This invention claims the generation and development of a candidate oral vaccine against plague. The vaccine consists of a synthetic gene construct that expresses a *Y. pestis* F1-V fusion antigen linked to a secretion signal, resulting in the production of large amounts of the F1-V antigen. The F1-V synthetic gene fusion is housed within Ty21a, an attenuated typhoid fever strain that is licensed for human use as a live oral bacterial vaccine. Ty21a serves as a carrier to deliver the F1-V fusion antigens of the plague

bacteria; the combined F1-V fusion in the Ty21a carrier has been shown to stimulate a robust immune response in mice. The possibility of combining the oral plague vaccine of this invention with FDA's candidate oral anthrax vaccine exists and would result in an easy-to-administer oral delivery system to streamline administration of the vaccine to large numbers of recipients in emergency situations.

Potential Commercial Applications: Plague vaccines, therapeutics and diagnostics.

Competitive Advantages:

- Vector is well-characterized.
- Simple manufacturing process.
- Potential low-cost vaccine.

Development Stage:

- In vitro data available
- In vivo data available (animal)

Inventors: Dennis J. Kopecko, Manuel A. Osorio, Monica R. Foote (all of FDA/CBER)

Intellectual Property: HHS Reference No. E-105-2011/0 -

- US Provisional Application No. 61/650,676 filed 23 May 2012
- PCT Application No. PCT/US2013/042240 filed 22 May 2013, which published as WO 2013/177291 on 28 Nov 2013

Related Technologies: HHS Reference No. E-344-2003/1-

- US Patent No. 7,758,855 issued 20 Jul 2010
- US Patent No. 8,247,225 issued 21 Aug 2012

- US Patent No. 8,709,813 issued 29 Apr 2014
- US Patent Application No. 14/185,353 filed 20 Feb 2014
- Various international patents issued

Licensing Contact: Peter A. Soukas; 301-435-4616; soukasp@mail.nih.gov

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