

26 March 2009

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## **Chem-Bio News – S&T Edition**

**1. RAPID AND SIMPLE DETECTION OF CLOSTRIDIUM BOTULINUM TYPES A AND B BY LOOP-MEDIATED ISOTHERMAL AMPLIFICATION [LAMP]:** *“The LAMP is a sensitive, specific and rapid detection method for C. botulinum types A and B.”*

**2. ENHANCING TIME-SERIES DETECTION ALGORITHMS FOR AUTOMATED BIOSURVEILLANCE:** *“These enhanced methods may increase sensitivity without increasing the alert rate and may improve the ability to detect outbreaks by using automated surveillance system data.”*

**3. SENSITIVE POLYMERS SHOW DRUG DELIVERY PROMISE:** *“Chemists in the US have developed a three-component polymer that can respond to temperature, pH and the presence of a reducing agent. This means that when the polymer is made into micelles to encapsulate and deliver drugs, there are three different ways to release them where they are needed.”*

**4. REPLICATION-DEFICIENT EBOLAVIRUS AS A VACCINE CANDIDATE:** *“Our study demonstrates the potential of the Ebola{Delta} VP30 virus as a new vaccine platform.”*

**5. THE BEGINNING OF THE END FOR ELISA?:** *“A polymer-based test for proteins has proved sensitive, selective and much simpler than a traditional assay.”*

**6. STRUCTURE OF THE EBOLA VP35 INTERFERON INHIBITORY DOMAIN:** *“Our results suggest a structure-based model for dsRNA-mediated innate immune antagonism by Ebola VP35 and other similarly constructed viral antagonists.”*

**7. ROLE OF ANTHRAX TOXINS IN DISSEMINATION, DISEASE PROGRESSION, AND INDUCTION OF PROTECTIVE ADAPTIVE IMMUNITY IN THE MOUSE AEROSOL CHALLENGE MODEL:** *“Taken together, these studies indicate that anthrax toxins are required for dissemination of bacteria beyond the draining lymphoid tissue, leading to full virulence in the mouse aerosol challenge model, and that primary and anamnestic immune responses to toxin proteins provide protection against subsequent lethal challenge.”*

**8. DIFFERENT PATHOLOGIES BUT EQUAL LEVELS OF RESPONSIVENESS TO THE RECOMBINANT F1 AND V ANTIGEN VACCINE AND CIPROFLOXACIN IN A MURINE**

## **MODEL OF PLAGUE CAUSED BY SMALL- AND LARGE-PARTICLE AEROSOLS:**

*"Although there were major differences in pathogenesis, the recombinant F1 and V antigen vaccine and ciprofloxacin protected against plague infections caused by small-and large-particle aerosols."*

# **CB Daily Report**

## ***Chem-Bio News***

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### **RAPID AND SIMPLE DETECTION OF CLOSTRIDIUM BOTULINUM TYPES A AND B BY LOOP-MEDIATED ISOTHERMAL AMPLIFICATION [LAMP]**

Health & Medicine Week

March 30, 2009

"To develop a convenient and rapid detection method for toxigenic Clostridium botulinum types A and B using a loop-mediated isothermal amplification (LAMP) method. The LAMP primer sets for the type A or B botulinum neurotoxin gene, BoNT/A or BoNT/B, were designed."

"To determine the specificity of the LAMP assay, a total of 14 C. botulinum strains and 17 other Clostridium strains were tested. The assays for the BoNT/A or BoNT/B gene detected only type A or B C. botulinum strains, respectively, but not other types of C. botulinum or strains of other Clostridium species. Using purified chromosomal DNA, the sensitivity of LAMP for the BoNT/A or BoNT/B gene was 1 pg or 10 pg of DNA per assay, respectively. The assay times needed to detect 1 ng of DNA were only 23 and 22 min for types A and B, respectively. In food samples, the detection limit per reaction was one cell for type A and 10 cells for type B. The LAMP is a sensitive, specific and rapid detection method for C. botulinum types A and B."

The full article can be found at: (T. Sakuma, et. al., "Rapid and simple detection of Clostridium botulinum types A and B by loop-mediated isothermal amplification". Journal of Applied Microbiology, 2009; 106(4): 1252-9). Link not available.

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### **ENHANCING TIME-SERIES DETECTION ALGORITHMS FOR AUTOMATED BIOSURVEILLANCE**

By Jerome I. Tokars, Comments to Author Howard Burkom, Jian Xing, Roseanne English, Steven Bloom, Kenneth Cox, and Julie A. Pavlin

Emerging Infectious Diseases (US Centers for Disease Control and Prevention)

April 2009

"BioSense is a US national system that uses data from health information systems for automated disease surveillance. We studied 4 time-series algorithm modifications designed to improve sensitivity for detecting artificially added data. To test these modified algorithms,

we used reports of daily syndrome visits from 308 Department of Defense (DoD) facilities and 340 hospital emergency departments (EDs). At a constant alert rate of 1%, sensitivity was improved for both datasets by using a minimum standard deviation (SD) of 1.0, a 14–28 day baseline duration for calculating mean and SD, and an adjustment for total clinic visits as a surrogate denominator. Stratifying baseline days into weekdays versus weekends to account for day-of-week effects increased sensitivity for the DoD data but not for the ED data. These enhanced methods may increase sensitivity without increasing the alert rate and may improve the ability to detect outbreaks by using automated surveillance system data.”

The full article can be found at: <http://www.cdc.gov/eid/content/15/4/533.htm>

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## **SENSITIVE POLYMERS SHOW DRUG DELIVERY PROMISE**

By Lewis Brindley

Chemistry World (Royal Society of Chemistry – UK)

March 20, 2009

“Chemists in the US have developed a three-component polymer that can respond to temperature, pH and the presence of a reducing agent. This means that when the polymer is made into micelles to encapsulate and deliver drugs, there are three different ways to release them where they are needed.

Polymeric micelles are nano-sized particles made from clumps of polymer chains with both hydrophobic and hydrophilic ends. In aqueous solutions, the chains come together forming spheres with the hydrophobic end pointing inwards and the hydrophilic ends point outwards - trapping smaller molecules inside the structure.”

“The idea, he explains, is to develop a polymer that requires two or more stimuli to release its cargo. Since body chemistry is complex, many drug delivery systems are prone to 'leaking' - so a polymer that responds to multiple conditions would be highly effective. 'We are not sure whether this polymer itself will be a viable drug delivery vehicle,' Thayumanavan adds, but indicates that it is a step in the right direction.”

The full article can be found at: <http://www.rsc.org/chemistryworld/News/2009/March/20030901.asp>

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## **REPLICATION-DEFICIENT EBOLAVIRUS AS A VACCINE CANDIDATE**

By Peter Halfmann, Hideki Ebihara, Andrea Marzi, Yasuko Hatta, Shinji Watanabe, M. Suresh, Gabriele Neumann, Heinz Feldmann, and Yoshihiro Kawaoka

Journal of Virology

February 11, 2009

“Ebola virus causes severe hemorrhagic fever, with case fatality rates as high as 90%. Currently, no licensed vaccine is available against Ebola virus. We previously generated a replication-deficient, biologically contained Ebola virus, Ebola{Delta}VP30, which lacks the essential VP30 gene, grows only in cells stably expressing this gene product, and is genetically stable. Here, we evaluated the vaccine potential of Ebola{Delta}VP30. First, we demonstrated its safety in STAT-1-knockout mice, a susceptible animal model for Ebola virus infection. We then tested its protective efficacy in two animal models, mice and guinea pigs. Mice immunized twice with Ebola{Delta}VP30 were protected from a lethal infection of mouse-adapted Ebola virus. Virus titers in the serum of vaccinated mice were significantly lower than those in nonvaccinated mice. Protection of mice immunized with Ebola{Delta}VP30 was associated with a high antibody response to the Ebola virus glycoprotein and the generation of an Ebola virus NP-specific CD8+ T-cell response. Guinea pigs immunized twice with Ebola{Delta}VP30 were also protected from a lethal infection of guinea pig-adapted Ebola virus. Our study demonstrates the potential of the Ebola{Delta}VP30 virus as a new vaccine platform.”

The full article can be found at: <http://jvi.asm.org/cgi/content/abstract/83/8/3810>

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## **THE BEGINNING OF THE END FOR ELISA?**

By Freya Mearns

Chemical Biology (Royal Society of Chemistry – UK)

March 24, 2009

“A polymer-based test for proteins has proved sensitive, selective and much simpler than a traditional assay.

Proteins can act as markers for diseases, so it is important to be able to detect them easily and quickly. They are conventionally detected in clinics using immunoassays called enzyme-linked immunosorbent assays, or ELISAs. Now Jing Wang and Bin Liu from the National University of Singapore have developed a test for proteins that is simpler and faster to use.

Whilst ELISAs are sensitive they are time-consuming. The assays use antibodies on a solid substrate to bind the protein of interest so the test requires numerous surface modification and washing steps as well as detection. Wang and Liu's test uses aptamers instead of antibodies and protein detection occurs in solution rather than at a surface, which makes their assay quicker.”

The full article can be found at: [http://www.rsc.org/Publishing/Journals/cb/Volume/2009/5/beginning\\_of\\_the\\_end\\_for\\_ELISA.asp](http://www.rsc.org/Publishing/Journals/cb/Volume/2009/5/beginning_of_the_end_for_ELISA.asp)

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## **STRUCTURE OF THE EBOLA VP35 INTERFERON INHIBITORY DOMAIN**

Blood Weekly  
April 2, 2009

"The Ebola VP35 protein is multifunctional, acting as a component of the viral RNA polymerase complex, a viral assembly factor, and an inhibitor of host interferon (IFN) production."

"Mutation of select basic residues within the C-terminal half of VP35 abrogates its dsRNA-binding activity, impairs VP35-mediated IFN antagonism, and attenuates EBOV growth in vitro and in vivo. Because VP35 contributes to viral escape from host innate immunity and is required for EBOV virulence, understanding the structural basis for VP35 dsRNA binding, which correlates with suppression of IFN activity, is of high importance. Here, we report the structure of the C-terminal VP35 IFN inhibitory domain (IID) solved to a resolution of 1.4 angstrom and show that VP35 IID forms a unique fold. In the structure, we identify 2 basic residue clusters, one of which is important for dsRNA binding. The dsRNA binding cluster is centered on Arg-312, a highly conserved residue required for IFN inhibition. Mutation of residues within this cluster significantly changes the surface electrostatic potential and diminishes dsRNA binding activity. The high-resolution structure and the identification of the conserved dsRNA binding residue cluster provide opportunities for antiviral therapeutic design."

"Our results suggest a structure-based model for dsRNA-mediated innate immune antagonism by Ebola VP35 and other similarly constructed viral antagonists."

The full article can be found at: (D.W. Leung, et. al., "Structure of the Ebola VP35 interferon inhibitory domain". Proceedings of the National Academy of Sciences of the United States of America, 2009; 106(2):411-416). Link not available.

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## **ROLE OF ANTHRAX TOXINS IN DISSEMINATION, DISEASE PROGRESSION, AND INDUCTION OF PROTECTIVE ADAPTIVE IMMUNITY IN THE MOUSE AEROSOL CHALLENGE MODEL**

Health & Medicine Week  
March 30, 2009

"Anthrax toxins significantly contribute to anthrax disease pathogenesis, and mechanisms by which the toxins affect host cellular responses have been identified with purified toxins. However, the contribution of anthrax toxin proteins to dissemination, disease progression, and subsequent immunity after aerosol infection with spores has not been clearly elucidated."

"To better understand the role of anthrax toxins in pathogenesis in vivo and to investigate the contribution of antibody to toxin proteins in protection, we completed a series of in vivo experiments using a murine aerosol challenge model and a collection of in-frame deletion mutants lacking toxin components. Our data show that after aerosol exposure to *Bacillus anthracis* spores, anthrax lethal toxin was required for outgrowth of bacilli in the draining

lymph nodes and subsequent progression of infection beyond the lymph nodes to establish disseminated disease. After pulmonary exposure to anthrax spores, toxin expression was required for the development of protective immunity to a subsequent lethal challenge. However, immunoglobulin (immunoglobulin G) titers to toxin proteins, prior to secondary challenge, did not correlate with the protection observed upon secondary challenge with wild-type spores. A correlation was observed between survival after secondary challenge and rapid anamnestic responses directed against toxin proteins. Taken together, these studies indicate that anthrax toxins are required for dissemination of bacteria beyond the draining lymphoid tissue, leading to full virulence in the mouse aerosol challenge model, and that primary and anamnestic immune responses to toxin proteins provide protection against subsequent lethal challenge."

The full article can be found at: (C.L. Loving, et. al., "Role of Anthrax Toxins in Dissemination, Disease Progression, and Induction of Protective Adaptive Immunity in the Mouse Aerosol Challenge Model. *Infection and Immunity*", 2009; 77(1):255-265). Link not available.

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## **DIFFERENT PATHOLOGIES BUT EQUAL LEVELS OF RESPONSIVENESS TO THE RECOMBINANT F1 AND V ANTIGEN VACCINE AND CIPROFLOXACIN IN A MURINE MODEL OF PLAGUE CAUSED BY SMALL- AND LARGE-PARTICLE AEROSOLS**

Drug Week

April 3, 2009

"However, deliberate aerosol release of *Y. pestis* will generate both small and large inhalable particles. We report in this study that the pathogenesis patterns of plague infections caused by the deposition of 1- and 12-microm-particle aerosols of *Y. pestis* in the lower and upper respiratory tracts (URTs) of mice are different. The median lethal dose for 12-microm particles was 4.9-fold greater than that for 1-microm particles. The 12-microm-particle infection resulted in the degradation of the nasal mucosa and nasal-associated lymphoid tissue (NALT) plus cervical lymphadenopathy prior to bacteremic dissemination. Lung involvement was limited to secondary pneumonia. In contrast, the 1-microm-particle infection resulted in primary pneumonia; in 40% of mice, the involvement of NALT and cervical lymphadenopathy were observed, indicating entry via both URT lymphoid tissues and lungs. Despite bacterial deposition in the gastrointestinal tract, the involvement of Peyer's patches was not observed in either infection."

"Although there were major differences in pathogenesis, the recombinant F1 and V antigen vaccine and ciprofloxacin protected against plague infections caused by small- and large-particle aerosols."

The full article can be found at: (R.J. Thomas, et. al., "Different pathologies but equal levels of responsiveness to the recombinant F1 and V antigen vaccine and ciprofloxacin in a murine

model of plague caused by small- and large-particle aerosols". *Infection and Immunity*, 2009; 77(4): 1315-23). Link not available.

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