

15 October 2009

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

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Chem-Bio News – S&T Edition

1. POTENT NEUTRALIZATION OF ANTHRAX EDEMA TOXIN BY A HUMANIZED MONOCLONAL ANTIBODY THAT COMPETES WITH CALMODULIN FOR EDEMA FACTOR BINDING: *"This anti-EF neutralizing mAb could potentially be used alone or with an anti-PA mAb in the emergency prophylaxis and treatment of anthrax infection."*

2. ANTIBODY PROTECTION AGAINST BOTULINUM NEUROTOXIN INTOXICATION IN MICE: *"The timing of antibody rescue in the mouse intoxication models revealed windows of opportunity for antibody therapeutic treatment that correlated well with the biologic half-life of the toxin in the serum."*

3. INVESTIGATION OF NEW DOMINANT-NEGATIVE INHIBITORS OF ANTHRAX PROTECTIVE ANTIGEN MUTANTS FOR USE IN THERAPY AND VACCINATION: *"Thus, PA DNI mutants, such as F427D and F427N mutants, may serve in the development of novel therapeutic agents and vaccines to fight B. anthracis infections."*

4. CA-074ME PROTECTION AGAINST ANTHRAX LETHAL TOXIN: *"We present results suggesting that LMP may be involved in the activation of the NLRP1b inflammasome."*

5. LOW PH REGULATES THE PRODUCTION OF DEOXYNIVALENOL BY FUSARIUM GRAMINEARUM: *"A combination of low pH and amines results in significantly enhanced expression of the TRI5 gene and increased DON [deoxynivalenol] production during axenic growth."*

6. NANOTECHNOLOGY SENSOR DETECTS LIVING BACTERIA AT ULTRALOW CONCENTRATIONS: *"In their effort to develop a fast, sensitive, selective, inexpensive, and easy-to-use method for detecting and quantifying pathogenic bacterial cells, researchers in Spain have now demonstrated a carbon nanotube based potentiometric biosensor for selectively detecting one single colony-forming unit of the bacterium Salmonella Typhi in close to real time."*

7. FEDBIZOPPS NOTICES FROM DTRA: *"The Transformational Medical Technologies Initiatives (TMTI), Defense Threat Reduction Agency (DTRA), has requested that the Chemical, Biological, Radiological and Nuclear Defense Information Analysis Center (CBRNIAAC) inform potentially interested parties about the following FedBizOpps postings."*

8. RESEARCHERS PRESENT NOVEL ENVIRONMENTAL DISINFECTION TECHNOLOGY: *"In a study presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), researchers presented information about a mobile, automated UV device to decontaminate hospital rooms at the Cleveland Veterans Affairs (VA) Medical Center in Ohio and analyzed its ability to remove troublesome bacteria, including C. difficile spores. The device, known as Tru-D, uses reflected UVC germicidal energy to decontaminate air and surfaces, including those in primary shadows. Tru-D is manufactured by Lumalier in Memphis, Tenn."*

9. COPPER'S ANTIMICROBIAL PROPERTIES MAY CHANGE HOSPITAL DESIGN: *"Antimicrobial copper alloys may soon make their way into healthcare facilities. The Copper Development Association (CDA) will exhibit antimicrobial door hardware and hospital accessories made of various copper alloys at the Healthcare Design 2009 Conference in Orlando, Fla. next month."*

CB Daily Report

POTENT NEUTRALIZATION OF ANTHRAX EDEMA TOXIN BY A HUMANIZED MONOCLONAL ANTIBODY THAT COMPETES WITH CALMODULIN FOR EDEMA FACTOR BINDING

Medical Letter on the CDC & FDA

October 18, 2009

"This study describes the isolation and characterization of a neutralizing monoclonal antibody (mAb) against anthrax edema factor, EF13D. EF13D neutralized edema toxin (ET)-mediated cyclic AMP (cAMP) responses in cells and protected mice from both ET-induced footpad edema and systemic ET-mediated lethality."

"The antibody epitope was mapped to domain IV of EF. The mAb was able to compete with calmodulin (CaM) for EF binding and displaced CaM from EF-CaM complexes. EF-mAb binding affinity (0.05-0.12 nM) was 50- to 130-fold higher than that reported for EF-CaM."

"This anti-EF neutralizing mAb could potentially be used alone or with an anti-PA mAb in the emergency prophylaxis and treatment of anthrax infection."

The full article can be found at: (Z.C. Chen, et. al., "Potent neutralization of anthrax edema toxin by a humanized monoclonal antibody that competes with calmodulin for edema factor binding". Proceedings of the National Academy of Sciences of the United States of America, 2009;106(32):13487-13492).

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ANTIBODY PROTECTION AGAINST BOTULINUM NEUROTOXIN INTOXICATION IN MICE

Drug Week

October 9, 2009

"A sensitive immunoassay for detecting BoNT serotype A (BoNT/A), based on monoclonal antibodies (MAbs) F1-2 and F1-40, has been developed and used in complex matrices. The epitope for F1-2 has been mapped to the heavy chain of BoNT/A, and the epitope of F1-40 has been mapped to the light chain. The ability of these MAbs to provide therapeutic protection against BoNT/A intoxication in mouse intravenous and oral intoxication models was tested. High dosages of individual MAbs protected mice well both pre-and postexposure to BoNT/A holotoxin. A combination therapy consisting of antibodies against both the light and heavy chains of the toxin, however, significantly increased protection, even at a lower MAb dosage. An in vitro peptide assay for measuring toxin activity showed that pretreatment of toxin with these MAbs did not block catalytic activity but instead blocked toxin entry into primary and cultured neuronal cells. The timing of antibody rescue in the mouse intoxication models revealed windows of opportunity for antibody therapeutic treatment that correlated well with the biologic half-life of the toxin in the serum."

The full article can be found at: (L.W. Cheng, et. al., "Antibody protection against botulinum neurotoxin intoxication in mice". Infection and Immunity, 2009;77(10):4305-13). Link not available.

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INVESTIGATION OF NEW DOMINANT-NEGATIVE INHIBITORS OF ANTHRAX PROTECTIVE ANTIGEN MUTANTS FOR USE IN THERAPY AND VACCINATION

Medical Letter on the CDC & FDA

October 11, 2009

"Phenylalanine-427 (F427) is crucial for PA function. This study was designed to discover potential novel therapeutic agents and vaccines for anthrax. This was done by screening PA mutants that were mutated

at the F427 residue for a dominant-negative inhibitory (DNI) phenotype which was nontoxic but inhibited the toxicity of the wild-type LeTx. For this, PA residue F427 was first mutated to each of the other 19 naturally occurring amino acids. The cytotoxicity and DNI phenotypes of the mutated PA proteins were tested in the presence of 1 microg/ml LF in RAW264.7 cells and were shown to be dependent on the individual amino acid replacements. A total of 16 nontoxic mutants with various levels of DNI activity were identified in vitro. Among them, F427D and F427N mutants had the highest DNI activities in RAW264.7 cells. Both mutants inhibited LeTx intoxication in mice in a dose-dependent way. Furthermore, they induced a Th2-predominant immune response and protected mice against a challenge with five 50% lethal doses of LeTx. The protection was correlated mainly with a low level of interleukin-1 beta (IL-1 beta) and with high levels of PA-specific immunoglobulin G1, IL-6, and tumor necrosis factor alpha."

"Thus, PA DNI mutants, such as F427D and F427N mutants, may serve in the development of novel therapeutic agents and vaccines to fight B. anthracis infections."

The full article can be found at: (S. Cao, et. al., "Investigation of new dominant-negative inhibitors of anthrax protective antigen mutants for use in therapy and vaccination". *Infection and Immunity*, 2009;77(10):4679-87). Link not available.

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CA-074ME PROTECTION AGAINST ANTHRAX LETHAL TOXIN

Preventive Medicine Week

October 11, 2009

"Anthrax lethal toxin (LT) activates the NLRP1b (NALP1b) inflammasome and caspase-1 in macrophages from certain inbred mouse strains, but the mechanism by which this occurs is poorly understood. We report here that similar to several NLRP3 (NALP3, cryopyrin)-activating stimuli, LT activation of the NLRP1b inflammasome involves lysosomal membrane permeabilization (LMP) and subsequent cytoplasmic cathepsin B activity."

"CA-074Me, a potent cathepsin B inhibitor, protects LT-sensitive macrophages from cell death and prevents the activation of caspase-1. RNA interference knockdown of cathepsin B expression, however, cannot prevent LT-mediated cell death, suggesting that CA-074Me may also act on other cellular proteases released during LMP. CA-074Me appears to function downstream of LT translocation to the cytosol (as assessed by mitogen-activated protein kinase kinase cleavage), K(+) effluxes, and proteasome activity. The initial increase in cytoplasmic activity of cathepsin B occurs at the same time or shortly before caspase-1 activation but precedes a larger-scale lysosomal destabilization correlated closely with cytolysis."

"We present results suggesting that LMP may be involved in the activation of the NLRP1b inflammasome."

The full article can be found at: (Z.L. Newman, et. al., "CA-074Me protection against anthrax lethal toxin". *Infection and Immunity*, 2009;77(10):4327-36). Link not available.

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LOW PH REGULATES THE PRODUCTION OF DEOXYNIVALENOL BY FUSARIUM GRAMINEARUM

Life Science Weekly

October 13, 2009

"Fusarium graminearum, which causes the globally important head blight disease of wheat, is responsible for the production of the harmful mycotoxin deoxynivalenol (DON) in infected grain. The production of DON by F. graminearum occurs at much higher levels during infection than during axenic growth, and it is therefore important to understand how DON production is regulated in the fungus."

"Recently, we have identified amines as potent inducers of in vitro DON production in *F. graminearum*. Although amines strongly induced expression of the key DON biosynthesis gene TRI5 and DON production to levels equivalent to those observed during infection, the timing of this induction suggested that other factors are also likely to be important for the regulation of DON biosynthesis. Here we demonstrate that low extracellular pH both promotes and is required for DON production in *F. graminearum*. A combination of low pH and amines results in significantly enhanced expression of the TRI5 gene and increased DON production during axenic growth."

The full article can be found at: (D.M. Gardiner, et. al., "Low pH regulates the production of deoxynivalenol by *Fusarium graminearum*". *Microbiology*, 2009;155(Pt 9):3149-56). Link not available.
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NANOTECHNOLOGY SENSOR DETECTS LIVING BACTERIA AT ULTRALOW CONCENTRATIONS

By Michael Berger
Nanowerk.com
October 05, 2009

"In their effort to develop a fast, sensitive, selective, inexpensive, and easy-to-use method for detecting and quantifying pathogenic bacterial cells, researchers in Spain have now demonstrated a carbon nanotube based potentiometric biosensor for selectively detecting one single colony-forming unit of the bacterium *Salmonella Typhi* in close to real time."

"According to F. Xavier Rius, a professor at the Rovira i Virgili University in Tarragona, Spain, who heads the Chemometrics, Qualimetrics and Nanosensors Group, "the most important strength of this biosensor is that simple positive/negative tests can be carried out in real zero-tolerance conditions and without cross reaction with other types of bacteria. The ease with which measurements are taken in potentiometric analysis opens the door to greater simplicity in microbiological analysis."

To build their sensor, the Spanish team linked carboxylated single-walled carbon nanotubes (SWCNT) to an aptamer. Aptamers are not only highly suitable receptors for the selective and high-proficiency detection of a wide range of molecular targets, including bacteria, they have also shown to self-assemble on carbon nanotubes. This hybrid nanomaterials has already been demonstrated as effective nanobiosensors"

("Detection and Titer Estimation of *Escherichia coli* Using Aptamer-Functionalized Single-Walled Carbon-Nanotube Field-Effect Transistors").

The full article can be found at: <http://www.nanowerk.com/spotlight/spotid=12906.php>
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FEDBIZOPPS NOTICES FROM DTRA

DTRA through CBRNIAC
October 09, 2009

The Transformational Medical Technologies Initiatives (TMTI), Defense Threat Reduction Agency (DTRA), has requested that the Chemical, Biological, Radiological and Nuclear Defense Information Analysis Center (CBRNIAC) inform potentially interested parties about the following FedBizOpps postings.

Database for Animal Model Development RFI:
https://www.fbo.gov/index?s=opportunity&mode=form&id=3702d686279b74e1ffe2b3d8bd861fe8&tab=core&_cview=0

Host Response as a Medical Countermeasure RFI:
<https://www.fbo.gov/index?>

s=opportunity&mode=form&id=735c0cbfed7119a711a7f435b4273fbe&tab=core&_cview=0

Clinical Data to Support Licensure Under Animal Rule RFI:

[https://www.fbo.gov/index?](https://www.fbo.gov/index?s=opportunity&mode=form&id=cb5f3507e45a6c6e6089e73f844dbf37&tab=core&_cview=0)

s=opportunity&mode=form&id=cb5f3507e45a6c6e6089e73f844dbf37&tab=core&_cview=0

Identification of Host Pathways and Targets for Biodefense RFI:

[https://www.fbo.gov/index?](https://www.fbo.gov/index?s=opportunity&mode=form&id=240ce8a8808f8d80d9b59c8ddcdb63c5&tab=core&_cview=0)

s=opportunity&mode=form&id=240ce8a8808f8d80d9b59c8ddcdb63c5&tab=core&_cview=0

Discovery of Therapeutic Countermeasures RFI:

[https://www.fbo.gov/index?](https://www.fbo.gov/index?s=opportunity&mode=form&id=481837838d8a66c0821923fe38aaa77c&tab=core&_cview=0)

s=opportunity&mode=form&id=481837838d8a66c0821923fe38aaa77c&tab=core&_cview=0

Pre-solicitation notice – Treatment of Hemorrhagic Fever Viruses:

[https://www.fbo.gov/index?](https://www.fbo.gov/index?s=opportunity&mode=form&id=f6a3ee8d0f4e93bcc402442c1e0ce492&tab=core&_cview=0)

s=opportunity&mode=form&id=f6a3ee8d0f4e93bcc402442c1e0ce492&tab=core&_cview=0

Link not available.

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RESEARCHERS PRESENT NOVEL ENVIRONMENTAL DISINFECTION TECHNOLOGY

Infection Control Today Magazine

October 12, 2009

“In a study presented at the 49th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), researchers presented information about a mobile, automated UV device to decontaminate hospital rooms at the Cleveland Veterans Affairs (VA) Medical Center in Ohio and analyzed its ability to remove troublesome bacteria, including *C. difficile* spores. The device, known as Tru-D, uses reflected UVC germicidal energy to decontaminate air and surfaces, including those in primary shadows. Tru-D is manufactured by Lumalier in Memphis, Tenn.

Curtis Donskey, MD, chair of the Infection Control Committee at the Cleveland VA Medical Center, concluded that Tru-D is a "novel method for cleaning hospital rooms...easy to use...and more effective than standard disinfection for removing hardy bacteria. The Tru-D device was able to decontaminate all surfaces in 40 hospital rooms, including hard-to-clean surfaces such as the undersides of tables." Eighteen percent of sites under the edges of bedside tables were still contaminated with MRSA after routine hospital cleaning, versus 0 percent after Tru-D use. Research revealed that disinfection with Tru-D reduced the frequency of positive MRSA and VRE cultures by 89 percent.

"*C. difficile* spores are especially challenging for hospital staff," Donskey said. On inoculated surfaces, application of Tru-D using the "spore" setting consistently reduced recovery of *C. difficile* spores and MRSA by greater than 2-3 logs. Similar VRE reduction was achieved in about half the time using a lower dose setting. "The UV device is computerized and can assess how much is needed for decontamination by measuring the reflected UV radiation from surfaces in the room," stated Donskey. "It's inexpensive to operate and requires no cleaning supplies." After viewing results, Donskey requested the purchase of several Tru-D units for the Cleveland VA Medical Center."

The full article can be found at: <http://www.infectioncontroltoday.com/hotnews/novel-disinfection-technology.html>

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COPPER'S ANTIMICROBIAL PROPERTIES MAY CHANGE HOSPITAL DESIGN

Infection Control Today Magazine

October 13, 2009

“Antimicrobial copper alloys may soon make their way into healthcare facilities. The Copper Development Association (CDA) will exhibit antimicrobial door hardware and hospital accessories made of various copper alloys at the Healthcare Design 2009 Conference in Orlando, Fla. next month.”

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“CDA will showcase a 2-foot wide by 6-foot long table containing a backsplash and a front apron made of untreated copper alloys: copper-nickel, nickel-silver and phosphor bronze. The table’s legs will also be made of nickel silver. An IV stand made of copper-nickel with a nickel-silver finish will be featured in CDA’s booth. A standard 3-foot by 7-foot commercial door containing antimicrobial hardware, including a lockset made of Eco-Brass, nickel silver and copper nickel kick plates and push/pull handles, will also be on display.”

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/antimicrobial-properties-of-copper.html>

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