

25 March 2010

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Chem-Bio News - S&T Edition

1. MOLECULAR SMALLPOX VACCINE DELIVERED BY ALPHAVIRUS REPLICONS ELICITS PROTECTIVE IMMUNITY IN MICE AND NON-HUMAN PRIMATES:

"These findings revealed that a single-boost VRP smallpox vaccine shows promise as a safe alternative to the currently licensed live-vaccinia virus smallpox vaccine."

2. 40 PERCENT OF SURFACE DISINFECTANTS INEFFECTIVE IN ELIMINATING VIRUSES THAT CAUSE GASTROENTERITIS:

"Some 40 percent of commercial disinfectants used to clean surfaces are believed to be ineffective in eliminating noroviruses, a group of viruses responsible for more than half of all foodborne gastroenteritis outbreaks. According to a recent study published by Université Laval researchers in the Journal of Food Protection, only bleach-based disinfectants drastically reduce the concentration of these viruses."

3. C. DIFF SURPASSING MRSA INFECTIONS IN COMMUNITY HOSPITALS: *"This is not a nuisance disease," said Daniel Sexton, MD, director of the Duke Infection Control Outreach Network (DICON). "A small percentage of patients with C. difficile may die, despite treatment. Also, it is likely that the routine use of alcohol-containing hand cleansers to prevent infections from MRSA does not simultaneously prevent infections due to C. difficile."*

4. COLORIMETRIC DIPSTICK FOR ASSAY OF ORGANOPHOSPHATE PESTICIDES AND NERVE AGENTS REPRESENTED BY PARAOXON, SARIN AND VX: *"The achieved limit of detection was $5 \times 10^{-8}M$ for paraoxon-ethyl and $5 \times 10^{-9}M$ for sarin and VX."*

5. THE EL TOR BIOTYPE OF VIBRIO CHOLERAE EXHIBITS A GROWTH ADVANTAGE IN THE STATIONARY PHASE IN MIXED CULTURES WITH THE CLASSICAL BIOTYPE: *"The growth advantage of the El Tor biotype was also observed in vivo using the ligated rabbit ileal loop and infant mouse animal models."*

6. N-TERMINAL EXTENSION OF THE CHOLERA TOXIN A1-CHAIN CAUSES RAPID DEGRADATION AFTER RETROTRANSLOCATION FROM ENDOPLASMIC RETICULUM TO CYTOSOL: *"The loss of toxicity is explained by rapid degradation by the proteasome after retrotranslocation to the cytosol."*

7. THE NEBRASKA EXPERIENCE IN BIOCONTAINMENT PATIENT CARE: *"Priorities, unit management, challenges, and lessons learned will be shared to guide others in establishing similar infrastructure."*

8. EXTRACTION OF CHEMICAL IMPURITIES FOR FORENSIC INVESTIGATIONS: A CASE STUDY FOR INDOOR RELEASES OF A SARIN SURROGATE: *"Five chemical impurities that were present in DMMP - dimethyl phosphate, trimethyl ester phosphoric acid, ethyl methyl methylphosphonate, O,O,S-trimethyl ester phosphorothioic acid, and biphenyl were detected on the PWB and were utilized to determine the source/supplier of the DMMP."*

9. THE EFFECT OF CARBON NANOTUBES ON DRUG DELIVERY IN AN ELECTRO-SENSITIVE TRANSDERMAL DRUG DELIVERY SYSTEM: *"The amount of released drug was effectively increased with higher applied electric voltages. These results were attributed to the excellent electrical conductivity of the carbon additive."*

10. NOVEL MICROENCAPSULATION OF POTENTIAL DRUGS WITH LOW MOLECULAR WEIGHT AND HIGH HYDROPHILICITY: *"This proposed method has successfully used to prepare batches of microspheres having different encapsulation efficiencies and its potential applications have been demonstrated accordingly."*

CB Daily Report

Chem-Bio News

MOLECULAR SMALLPOX VACCINE DELIVERED BY ALPHAVIRUS REPLICONS ELICITS PROTECTIVE IMMUNITY IN MICE AND NON-HUMAN PRIMATES

Health Risk Factor Week

March 23, 2010

"Naturally occurring smallpox was eradicated as a result of successful vaccination campaigns during the 1960s and 1970s. Because of its highly contagious nature and high mortality rate, smallpox has significant potential as a biological weapon."

"Unfortunately, the current vaccine for orthopoxviruses is contraindicated for large portions of the population. Thus, there is a need for new, safe, and effective orthopoxvirus vaccines. Alphavirus replicon vectors, derived from strains of Venezuelan equine encephalitis virus, are being used to develop alternatives to the current smallpox vaccine. Here, we demonstrated that virus-like replicon particles (VRPs) expressing the vaccinia virus A33R, B5R, A27L, and L1R genes elicited protective immunity in mice comparable to vaccination with live-vaccinia virus. Furthermore, cynomolgus macaques vaccinated with a combination of the four poxvirus VRPs (4pox-VRP) developed antibody responses to each antigen. These antibody responses were able to neutralize and inhibit the spread of both vaccinia virus and monkeypox virus. Macaques vaccinated with 4pox-VRP, flu HA VRP (negative control), or live-vaccinia virus (positive control) were challenged intravenously with 5×10^6 pfu of monkeypox virus 1 month after the second VRP vaccination. Four of the six negative control animals succumbed to monkeypox and the remaining two animals demonstrated either

severe or grave disease. Importantly, all 10 macaques vaccinated with the 4pox-VRP vaccine survived without developing severe disease."

"These findings revealed that a single-boost VRP smallpox vaccine shows promise as a safe alternative to the currently licensed live-vaccinia virus smallpox vaccine."

The full article can be found at: (J.W. Hooper, et. al., "Molecular smallpox vaccine delivered by alphavirus replicons elicits protective immunity in mice and non-human primates". Vaccine, 2009;28(2):494-511). Link not available.

40 PERCENT OF SURFACE DISINFECTANTS INEFFECTIVE IN ELIMINATING VIRUSES THAT CAUSE GASTROENTERITIS

Infection Control Today Magazine
March 17, 2010

"Some 40 percent of commercial disinfectants used to clean surfaces are believed to be ineffective in eliminating noroviruses, a group of viruses responsible for more than half of all foodborne gastroenteritis outbreaks. According to a recent study published by Université Laval researchers in the Journal of Food Protection, only bleach-based disinfectants drastically reduce the concentration of these viruses."

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"The team of researchers led by Julie Jean, professor at the Faculty of Agriculture and Food Sciences, tested the efficacy of three major categories of household disinfectants in eliminating noroviruses: bleach-based products, alcohol-based products, and quaternary ammonium-based products.

Lab tests showed that five minutes of contact with a bleach-based disinfectant reduced the concentration of noroviruses on a stainless steel surface by a factor of 1,000. Alcohol- and quaternary ammonium-based products proved 100 times less effective.

"Our results are of particular concern considering that some 40 percent of the commercial surface disinfectants on the market are alcohol or ammonium based," stressed Jean, who is also a researcher at the Institute of Nutraceuticals and Functional Foods (INAF).

Julie Jean's team also discovered that it takes only 10 minutes for human noroviruses to firmly latch on to a stainless steel surface. "Once attached, these viruses can survive for weeks and potentially contaminate anyone who touches them. And it's highly probable that our findings on stainless steel surfaces also apply to other materials," Jean added."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/surface-disinfectants-efficacy-noroviruses.html>

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C. DIFF SURPASSING MRSA INFECTIONS IN COMMUNITY HOSPITALS

Infection Control Today Magazine

March 22, 2010

“We found that MRSA infections have declined steadily since 2005, but *C. difficile* infections have increased since 2007,” said Becky Miller, MD, an infectious diseases fellow at Duke University Medical Center.

C. difficile is a multi-drug resistant bacterium that causes diarrhea and in some cases life-threatening inflammation of the colon. The infections are currently treated with one of two antibiotics. But relapses are common and occur in one-quarter of patients despite treatment, according to Miller.

“This is not a nuisance disease,” said Daniel Sexton, MD, director of the Duke Infection Control Outreach Network (DICON). “A small percentage of patients with *C. difficile* may die, despite treatment. Also, it is likely that the routine use of alcohol-containing hand cleansers to prevent infections from MRSA does not simultaneously prevent infections due to *C. difficile*.”

The full article can be found at: <http://www.infectioncontroltoday.com/hotnews/c-diff-surpassing-mrsa-infections.html>

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COLORIMETRIC DIPSTICK FOR ASSAY OF ORGANOPHOSPHATE PESTICIDES AND NERVE AGENTS REPRESENTED BY PARAOXON, SARIN AND VX

Drug Week

April 2, 2010

“A dipstick for fast assay of nerve agents and organophosphate pesticides was developed. Indicator pH papers were used as detectors.”

“The principle of the assay is based on enzymatic hydrolysis of acetylcholine into acetic acid and choline by acetylcholinesterase. Acidification of the reaction medium due to accumulation of acetic acid was visible. The colour changed from dark red to yellow as the pH indicator recognized pH shift. Presence of an organophosphate pesticide or a nerve agent results in irreversible inhibition of acetylcholinesterase intercepted on the dipstick. The inhibition stops the enzymatic reaction. The inhibition appears as no change of the medium pH. Three compounds were assayed: paraoxon-ethyl as representative organophosphate pesticides and nerve agents sarin and VX. The achieved limit of detection was 5×10^{-8} M for paraoxon-ethyl and 5×10^{-9} M for sarin and VX. Dipsticks were found stable for at least one month.”

The full article can be found at: (M. Pohanka, et. al., “Colorimetric dipstick for assay of organophosphate pesticides and nerve agents represented by paraoxon, sarin and VX”.

Talanta, 2010;81(1-2):621-4). Link not available.

ANALYST NOTE: The lead author's contact information is given as: "University of Defense, Centre of Advanced Studies, Faculty of Military Health Sciences, Hradec Kralove, Czech Republic.

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THE EL TOR BIOTYPE OF VIBRIO CHOLERAE EXHIBITS A GROWTH ADVANTAGE IN THE STATIONARY PHASE IN MIXED CULTURES WITH THE CLASSICAL BIOTYPE

Health Risk Factor Week

March 23, 2010

"Vibrio cholerae strains of the O1 serogroup that typically cause epidemic cholera can be classified into two biotypes, classical and El Tor. The El Tor biotype emerged in 1961 and subsequently displaced the classical biotype as a cause of cholera throughout the world."

"In this study we demonstrate that when strains of the El Tor and classical biotypes were cocultured in standard LB medium, the El Tor strains clearly had a competitive growth advantage over the classical biotype starting from the late stationary phase and could eventually take over the population. The classical biotype produces extracellular protease(s) in the stationary phase, and the amounts of amino acids and small peptides in the late stationary and death phase culture filtrates of the classical biotype were higher than those in the corresponding culture filtrates of the El Tor biotype. The El Tor biotype cells could utilize the amino acids more efficiently than the classical biotype under the alkaline pH of the stationary phase cultures but not in medium buffered to neutral pH."

"The growth advantage of the El Tor biotype was also observed in vivo using the ligated rabbit ileal loop and infant mouse animal models."

The full article can be found at: (S. Pradhan, et. al., "The El Tor Biotype of Vibrio cholerae Exhibits a Growth Advantage in the Stationary Phase in Mixed Cultures with the Classical Biotype". Journal of Bacteriology, 2010;192(4):955-963). Link not available.

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N-TERMINAL EXTENSION OF THE CHOLERA TOXIN A1-CHAIN CAUSES RAPID DEGRADATION AFTER RETROTRANSLOCATION FROM ENDOPLASMIC RETICULUM TO CYTOSOL

Hospital Business Week

March 28, 2010

"Cholera toxin travels from the plasma membrane to the endoplasmic reticulum of host cells, where a portion of the toxin, the A1-chain, is unfolded and targeted to a protein-conducting channel for retrotranslocation to the cytosol. Unlike most retrotranslocation

substrates, the A1-chain escapes degradation by the proteasome and refolds in the cytosol to induce disease."

"How this occurs remains poorly understood. Here, we show that an unstructured peptide appended to the N terminus of the A1-chain renders the toxin functionally inactive. Cleavage of the peptide extension prior to cell entry rescues toxin half-life and function. The loss of toxicity is explained by rapid degradation by the proteasome after retrotranslocation to the cytosol. Degradation of the mutant toxin does not follow the N-end rule but depends on the two Lys residues at positions 4 and 17 of the native A1-chain, consistent with polyubiquitination at these sites."

"Thus, retrotranslocation and refolding of the wild-type A1-chain must proceed in a way that protects these Lys residues from attack by E3 ligases."

The full article can be found at: (N.L. Wernick, et. al., "N-terminal extension of the cholera toxin A1-chain causes rapid degradation after retrotranslocation from endoplasmic reticulum to cytosol". *Journal of Biological Chemistry*, 2010;285(9):6145-52). Link not available.

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THE NEBRASKA EXPERIENCE IN BIOCONTAINMENT PATIENT CARE

Health Risk Factor Week

March 23, 2010

Early access to a biocontainment patient care unit (BPCU) for isolation during a bioterrorism or public health emergency event along with appropriate use of epidemiological and therapeutic interventions in the community may dramatically impact the size and severity of a disease outbreak (Smith et al., 2006). As emerging infectious agents, pandemics, resistant organisms, and terrorism continue to threaten human life; health care and emergency care providers must be empowered to work with nurses and other professionals in public health to plan for the consequences. This article describes the evolution of Nebraska's BPCU strategy for public health preparedness in the face of a biological threat."

"Priorities, unit management, challenges, and lessons learned will be shared to guide others in establishing similar infrastructure."

The full article can be found at: (E.L. Beam, et. al., "The Nebraska Experience in Biocontainment Patient Care". *Public Health Nursing*, 2010;27(2):140-147). Link not available.

ANALYST NOTE:

"The Biocontainment Unit at The Nebraska Medical Center is currently one of 3 units in the United States equipped to safely care for anyone exposed to a highly contagious and dangerous disease. It is a joint project involving The Nebraska Medical Center, Nebraska Health and Human Services, and the University of Nebraska Medical Center."

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"The Biocontainment Unit at The Nebraska Medical Center has ten beds and can receive patients from anywhere in the country, and is equipped with many safety features. Examples include special air handling systems to ensure that micro-organisms do not spread beyond the patient rooms, with high level filtration and ultraviolet light for additional protection. A dunk tank for laboratory specimens and a pass-through autoclave help assure that hazardous infections are contained. Hepa-filtered individual isolation units, are available for safe transport and transfer of an infected patient to the unit."

Further information on the Biocontainment Unit can be found at: <http://www.nebraskamed.com/Services/BiocontainmentUnit/Default.aspx>

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EXTRACTION OF CHEMICAL IMPURITIES FOR FORENSIC INVESTIGATIONS: A CASE STUDY FOR INDOOR RELEASES OF A SARIN SURROGATE

Energy & Ecology

April 2, 2010

"A solvent extraction approach was developed and examined for extraction of targeted organophosphorus compounds as well as nerve agent simulants from painted wallboard (PWB). Painted wallboard was chosen as a substrate due to its presence as large surface area media in an indoor environment that is applicable to a chemical agent release scenario."

"Three different solvent systems were examined with a 1:1 methylene chloride: acetone mixture having the most robust and consistent extraction for four target organophosphorus compounds [dimethyl methyl phosphonate (DMMP), diethyl methyl phosphonate (DEMP), diethyl methyl phosphonothioate (DEMPT), and diisopropyl methyl phosphonate (DIMP)]. An average extraction efficiency of approximately 60% was obtained for these four compounds. The extraction approach was further demonstrated by extracting and detecting the chemical impurities present in neat DMMP that was vapor deposited onto painted wallboard tickets as a simulant to an agent release."

The researchers concluded: "Five chemical impurities that were present in DMMP - dimethyl phosphate, trimethyl ester phosphoric acid, ethyl methyl methylphosphonate, O,O,S-trimethyl ester phosphorothioic acid, and biphenyl were detected on the PWB and were utilized to determine the source/supplier of the DMMP."

The full article can be found at: (J.H. Wahl, et. al., "Extraction of chemical impurities for forensic investigations: A case study for indoor releases of a sarin surrogate". Building and Environment, 2010; 45(5):1339-1345). Link not available.

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THE EFFECT OF CARBON NANOTUBES ON DRUG DELIVERY IN AN ELECTRO-SENSITIVE TRANSDERMAL DRUG DELIVERY SYSTEM

Drug Week

March 26, 2010

"An electro-sensitive transdermal drug delivery system was prepared by the electrospinning method to control drug release. A semi-interpenetrating polymer network was prepared as the matrix with polyethylene oxide and pentaerythritol triacrylate polymers."

"Multi-walled carbon nanotubes were used as an additive to increase the electrical sensitivity. The release experiment was carried out under different electric voltage conditions. Carbon nanotubes were observed in the middle of the electrospun fibers by SEM and TEM. The amount of released drug was effectively increased with higher applied electric voltages. These results were attributed to the excellent electrical conductivity of the carbon additive. The suggested mechanism of drug release involves polyethylene oxide of the semi-interpenetrating polymer network being dissolved under the effects of carbon nanotubes, thereby releasing the drug."

The full article can be found at: (J.S. Im, et. al., "The effect of carbon nanotubes on drug delivery in an electro-sensitive transdermal drug delivery system". *Biomaterials*, 2010; 31 (6):1414-9). Link not available.

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NOVEL MICROENCAPSULATION OF POTENTIAL DRUGS WITH LOW MOLECULAR WEIGHT AND HIGH HYDROPHILICITY

Drug Week

March 19, 2010

"Microencapsulation of drugs into solid biodegradable polymeric microspheres via solvent evaporation technique remains challenging especially with those having low molecular weight and high hydrophilicity nature. This paper presents an efficient encapsulation protocol for this group of drugs, demonstrated using hydrogen peroxide as a model compound that is encapsulated into poly(lactic-co-glycolic acid) microspheres."

"Hydrogen peroxide can be employed as antiseptic agent or its decomposed form into oxygen can be useful in various pharmaceutical applications. The new encapsulation technique was developed based on the modification of conventional double emulsion and solvent evaporation protocol with a backward concentration gradient of hydrogen peroxide. This was achieved by adding and controlling the concentration of hydrogen peroxide at the continuous phase during the solidification stage of the microspheres. Parameters involved in the production and the formulation aspect were optimized to achieve the best protocol having controlled efficiency of encapsulation that is simple, safe, practical, and economical. Evaluation on the encapsulation efficiency and the release profile has been made indirectly by monitoring the dissolved oxygen level of the solution where the microspheres were incubated. Morphology of the microspheres was investigated using scanning electron microscopy."

"This proposed method has successfully used to prepare batches of microspheres having different encapsulation efficiencies and its potential applications have been demonstrated accordingly."

The full article can be found at: (S.M. Ng, et. al., "Novel microencapsulation of potential drugs with low molecular weight and high hydrophilicity: Hydrogen peroxide as a candidate compound". International Journal of Pharmaceutics, 2010;384(1-2):120-127). Link not available.

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Steve Tesko: Steve.Tesko@anser.org

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