

11 September 2008

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 Supplement

1. AN ALTERNATIVE APPROACH TO COMBINATION VACCINES: INTRADERMAL ADMINISTRATION OF ISOLATED COMPONENTS FOR CONTROL OF ANTHRAX, BOTULISM, PLAGUE AND STAPHYLOCOCCAL TOXIC SHOCK:

"Our results demonstrated that the physical separation of vaccines both in the syringe and at the site of administration did not adversely affect the biological activity of each component."

2. MY CORONA! NOVEL SPECTROSCOPIC TECHNIQUE COULD REVOLUTIONIZE CHEMICAL ANALYSIS:

"In comparison to LIBS [laser-induced breakdown spectroscopy], the researchers found that the observed spectra are 1) of better quality 2) have significantly smaller analytical volumes and 3) are accomplished using drastically simpler, smaller and less expensive equipment and materials. Furthermore, OES [optical emission spectroscopy] can be performed remotely, using nanorods and nanotubes dispersed in fluid."

3. APPLICATION OF A MICROCOIL PROBE HEAD IN NMR ANALYSIS OF CHEMICALS RELATED TO THE CHEMICAL WEAPONS CONVENTION:

"Furthermore, a 2D H-1-C-13 fast-HMOC spectrum with sufficient quality was possible to measure in 5 h. The microcoil probe head demonstrated a considerable sensitivity improvement and reduction of measurement times for the NMR spectroscopy in identification of chemicals related to the Chemical Weapons Convention."

4. DUAL-PROBE REAL-TIME PCR ASSAY FOR DETECTION OF VARIOLA OR OTHER ORTHOPOXVIRUSES WITH DRIED REAGENTS:

"Furthermore, the implementation of dried reagents in real-time PCR assays is an important step towards simplifying such assays and allowing their use in areas where cold storage is not easily accessible."

5. MODELING THE INCUBATION PERIOD OF INHALATIONAL ANTHRAX:

"The resulting incubation period distribution and the dose dependence of the median incubation period are in good agreement with human data from the 1979 accidental atmospheric anthrax release in Sverdlovsk, Russia, and limited nonhuman primate data."

6. AN IMMUNOCHROMATOGRAPHIC ASSAY TO DETECT REDUCED LEVEL OF

LAMININ-5 GAMMA2 IN SULFUR MUSTARD-EXPOSED NORMAL HUMAN EPIDERMAL

KERATINOCYTES: *"This method may serve as a rapid SM-exposure diagnostic/screening procedure that could be applied directly to skin extracts of individuals who have supposedly been exposed to SM [sulfur mustard]."*

7. TOWARD SINGLE MOLECULE DETECTION OF STAPHYLOCOCCAL ENTEROTOXIN B

[SEB]: MOBILE SANDWICH IMMUNOASSAY ON GLIDING MICROTUBULES: *"This study demonstrates the kinesin/MT-mediated capture, transport, and detection of the biowarfare agent SEB in a microfluidic format."*

8. CLONING AND DEVELOPMENT OF SYNTHETIC INTERNAL AMPLIFICATION CONTROL [IAC] FOR BACILLUS ANTHRACIS REAL-TIME POLYMERASE CHAIN

REACTION ASSAYS: *"The IAC, in conjunction with target system, should decrease the rate of false-positive and false-negative results in real-time PCR assays."*

9. KILLING BACTERIA ISN'T ENOUGH TO RESTORE IMMUNE FUNCTION AFTER

INFECTION: *"A bacterial molecule that initially signals to animals that they have been invaded must be wiped out by a special enzyme before an infected animal can regain full health, researchers at UT Southwestern Medical Center have found."*

10. SYNTHESIS OF BIOINORGANIC ANTIMICROBIAL PEPTIDE NANOPARTICLES

WITH POTENTIAL THERAPEUTIC PROPERTIES: *"The resultant antimicrobial peptide nanoparticles retain biocidal activity, protect the peptide from proteolytic degradation, and facilitate a continuous release of the antibiotic over time."*

11. SCIENTISTS FORM ALLIANCE TO DEVELOP NANOTOXICOLOGY PROTOCOLS:

"A team of materials scientists and toxicologists announced the formation of a new international research alliance to establish protocols for reproducible toxicological testing of nanomaterials in both cultured cells and animals."

12. LOW COST GRAPHITE ALTERNATIVE TO FABRICATING NANOTECHNOLOGY

BIOSENSORS: *"Now, for the first time, scientists have tested nanometal decorated graphene (actually graphite nanoplatelets, a thickness of 10 nm would contain approximately 30 graphene sheets, considering an interlayer spacing of 0.335 nm) in biosensor application."*

13. INTRINSIC CURVATURE ASSOCIATED WITH THE COORDINATELY REGULATED ANTHRAX TOXIN GENE PROMOTERS:

"These findings suggest that the structural topology of the DNA plays an important role in the control of anthrax toxin gene expression."

14. INHIBITING THE SPREAD OF SUPERBUGS:

"UK chemists have found a small molecule with the potential to overcome one of the most serious problems facing the healthcare profession today - the spread of the deadly infection MRSA [Methicillin-resistant Staphylococcus aureus]."

CB Daily Report

AN ALTERNATIVE APPROACH TO COMBINATION VACCINES: INTRADERMAL ADMINISTRATION OF ISOLATED COMPONENTS FOR CONTROL OF ANTHRAX, BOTULISM, PLAGUE AND STAPHYLOCOCCAL TOXIC SHOCK

By Garry L Morefield, Ralph F Tammariello, Bret K Purcell, Patricia L Worsham, Jennifer Chapman, Leonard A Smith, Jason B Alarcon , John A Mikszta and Robert G Ulrich
Journal of Immune Based Therapies and Vaccines
September 3, 2008

“As a possible alternative to combination vaccines, we used specially designed microneedles to inject rhesus macaques with four separate recombinant protein vaccines for anthrax, botulism, plague and staphylococcal toxic shock next to each other just below the surface of the skin, thus avoiding potentially incompatible vaccine mixtures.

Results

The intradermally-administered vaccines retained potent antibody responses and were well-tolerated by rhesus macaques. Based on tracking of the adjuvant, the vaccines were transported from the dermis to draining lymph nodes by antigen-presenting cells. Vaccinated primates were completely protected from an otherwise lethal aerosol challenge by *Bacillus anthracis* spores, botulinum neurotoxin A, or staphylococcal enterotoxin B.

Conclusions

Our results demonstrated that the physical separation of vaccines both in the syringe and at the site of administration did not adversely affect the biological activity of each component. The vaccination method we describe may be scalable to include a greater number of antigens, while avoiding the physical and chemical incompatibilities encountered by combining multiple vaccines together in one product.”

The full article can be found at: <http://www.jibtherapies.com/content/pdf/1476-8518-6-5.pdf>

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MY CORONA! NOVEL SPECTROSCOPIC TECHNIQUE COULD REVOLUTIONIZE CHEMICAL ANALYSIS

By Michael Berger
Nanowerk.com
September 3, 2008

“LIBS [laser-induced breakdown spectroscopy] has been shown to be capable of analyzing extremely small samples with high sensitivity – nanoliter volumes with levels of detection in water of part per million. LIBS works by focusing short laser pulses onto the surface of a sample to create a hot plasma with temperatures of 10,000 - 20,000 °C. The plasma emits radiation that allows the observation of the characteristic atomic emission lines of the elements. On the downside, LIBS is complicated by the need for multiple laser pulses to

generate a sufficiently hot plasma and the need for focusing and switching a powerful laser, requiring relatively large and expensive instruments.

New research coming out of Drexel University has now shown that light emitted from a new form of cold plasma in liquid – field emission generated, highly non-equilibrium and high energy density – permits Optical Emission Spectroscopy (OES) analysis of the elemental composition of solutions within nanoseconds from femtoliter volumes.”

“In comparison to LIBS, the researchers found that the observed spectra are 1) of better quality 2) have significantly smaller analytical volumes and 3) are accomplished using drastically simpler, smaller and less expensive equipment and materials. Furthermore, OES can be performed remotely, using nanorods and nanotubes dispersed in fluid.”

The full article can be found at: <http://www.nanowerk.com/spotlight/spotid=7063.php>

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APPLICATION OF A MICROCOIL PROBE HEAD IN NMR ANALYSIS OF CHEMICALS RELATED TO THE CHEMICAL WEAPONS CONVENTION

Pharma Law Weekly
September 9, 2008

"Methylphosphonic acid, the common secondary degradation product of satin [sic – sarin], soman, and VX, was detected at level 50 ng (0.52 nmol) from a 30- μ L water sample using proton-observed experiments. Direct phosphorus observation of methylphosphonic acid with P-31{H-1} NMR experiment was feasible at the 400-ng (4.17 nmol) level. Application of the microcoil probe head in the spiked sample analysis was studied with a test water sample containing 2-10 μ g/mL of three organophosphorus compounds. High-quality H-1 NMR, P-31{H-1} NMR, 2D H-1-P-31 fast-HMQC, and 2D TOCSY spectra were obtained in 3 h from the concentrated 1.7-mm NMR sample prepared from 1 mL of the water solution."

"Furthermore, a 2D H-1-C-13 fast-HMQC spectrum with sufficient quality was possible to measure in 5 h. The microcoil probe head demonstrated a considerable sensitivity improvement and reduction of measurement times for the NMR spectroscopy in identification of chemicals related to the Chemical Weapons Convention."

The full article can be found at: (H. Koskela, et. al., "Application of a microcoil probe head in NMR analysis of chemicals related to the Chemical Weapons Convention". Analytical Chemistry, 2008; 80(14):5556-5564). Link not available.

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DUAL-PROBE REAL-TIME PCR ASSAY FOR DETECTION OF VARIOLA OR OTHER ORTHOPOXVIRUSES WITH DRIED REAGENTS

By Mohamed A, Sharron SS, Park K, John H, Monica O, Peter JB, Sofi IM

August 22, 2008

"A real-time, multiplexed polymerase chain reaction (PCR) assay based on dried PCR reagents was developed. Only variola virus could be specifically detected by a FAM (6-carboxyfluorescein)-labeled probe while camelpox, cowpox, monkeypox and vaccinia viruses could be detected by a TET (6-carboxytetramethylrhodamine)-labeled probe in a single PCR reaction. Approximately 25 copies of cloned variola virus DNA and 50 copies of genomic orthopoxviruses DNA could be detected with high reproducibility. The assay exhibited a dynamic range of seven orders of magnitude with a correlation coefficient value greater than 0.97. The sensitivity and specificity of the assay, as determined from 100 samples that contained nucleic acids from a multitude of bacterial and viral species were 96% and 98%, respectively. The limit of detection, sensitivity and specificity of the assay were comparable to standard real-time PCR assays with wet reagents. Employing a multiplexed format in this assay allows simultaneous discrimination of the variola virus from other closely related orthopoxviruses. Furthermore, the implementation of dried reagents in real-time PCR assays is an important step towards simplifying such assays and allowing their use in areas where cold storage is not easily accessible."

The full article can be found at: http://www.ncbi.nlm.nih.gov/pubmed/18725245?ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum

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MODELING THE INCUBATION PERIOD OF INHALATIONAL ANTHRAX

Health & Medicine Week

September 8, 2008

"This article modifies a theoretical model originally developed by Brookmeyer and others for the inhalational anthrax incubation period distribution in humans by using a more accurate distribution to represent the in vivo bacterial growth phase and by extending the model to represent the time from exposure to death, thereby allowing the model to be fit to nonhuman primate time-to-death data. The resulting incubation period distribution and the dose dependence of the median incubation period are in good agreement with human data from the 1979 accidental atmospheric anthrax release in Sverdlovsk, Russia, and limited nonhuman primate data. The median incubation period for the Sverdlovsk victims is 9.05 (95% confidence interval=8.0-10.3) days, shorter than previous estimates, and it is predicted to drop to less than 2.5 days at doses above 10⁶ spores."

"The incubation period distribution is important because the left tail determines the time at which clinical diagnosis or syndromic surveillance systems might first detect an anthrax outbreak based on early symptomatic cases, the entire distribution determines the efficacy of medical intervention-which is determined by the speed of the prophylaxis campaign relative to the incubation period-and the right tail of the distribution influences the recommended duration for antibiotic treatment."

The full article can be found at: (D.A. Wilkening, et. al., "Modeling the incubation period of

inhalational anthrax". Medical Decision Making, 2008;28(4):593-605). Link not available.

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AN IMMUNOCHROMATOGRAPHIC ASSAY TO DETECT REDUCED LEVEL OF LAMININ-5 GAMMA2 IN SULFUR MUSTARD-EXPOSED NORMAL HUMAN EPIDERMAL KERATINOCYTES

Medical Letter on the CDC & FDA
September 14, 2008

Researchers at the Walter Reed Army Institute of Research, Division of Experimental Therapeutics report:

"The injuries resulting from SM-exposure [sulfur mustard] are mainly characterized by epithelial damage of the tissues through which it is absorbed, i.e. skin, eye and the respiratory tract. Proteins in the skin mostly affected by SM-exposure are laminin-5 and integrin alpha6beta4. Laminin-5 constitutes the anchoring filaments and binds the transmembrane protein integrin alpha6beta4. Recent studies have shown that SM alkylation causes a significant reduction of laminin-5, disruption of alpha6beta4 integrin and decreases the expression of integrin alpha6 and beta4 subunits, therefore, leads to destabilization of dermal-epidermal attachments and potentiates vesication. This study established a unique immunochromatographic detection method (strip assay) to detect the degradation of laminin-5 in SM-exposed NHEK (normal human epidermal keratinocytes) extract."

"This method may serve as a rapid SM-exposure diagnostic/screening procedure that could be applied directly to skin extracts of individuals who have supposedly been exposed to SM."

The full article can be found at: (X. Jin, et. al., "An immunochromatographic assay to detect reduced level of laminin-5 gamma2 in sulfur mustard-exposed normal human epidermal keratinocytes". Journal of Applied Toxicology, 2008;28(6):759-64). Link not available.

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TOWARD SINGLE MOLECULE DETECTION OF STAPHYLOCOCCAL ENTEROTOXIN B [SEB]: MOBILE SANDWICH IMMUNOASSAY ON GLIDING MICROTUBULES

Blood Weekly
September 11, 2008

"An immunoassay based on gliding microtubules (MTs) is described for the detection of staphylococcal enterotoxin B. Detection is performed in a sandwich immunoassay format. Gliding microtubules carry the antigen-specific "capture" antibody, and bound analyte is detected using a fluorescent viral scaffold as the tracer."

"A detailed modification scheme for the MTs postpolymerization is described along with corresponding quantification by fluorescence spectroscopy. The resultant antibody-MTs

maintain their morphology and gliding capabilities. We report a limit of detection down to 0.5 ng/mL during active transport in a 30 min assay time and down to 1 ng/mL on static surfaces."

"This study demonstrates the kinesin/MT-mediated capture, transport, and detection of the biowarfare agent SEB in a microfluidic format."

The full article can be found at: (C.M. Soto, et. al., "Toward single molecule detection of staphylococcal enterotoxin B: Mobile sandwich immunoassay on gliding microtabules". Analytical Chemistry, 2008; 80(14):5433-5440). Link not available.

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CLONING AND DEVELOPMENT OF SYNTHETIC INTERNAL AMPLIFICATION CONTROL [IAC] FOR BACILLUS ANTHRACIS REAL-TIME POLYMERASE CHAIN REACTION ASSAYS

Medical Device Law Weekly
September 14, 2008

"An internal amplification control (IAC) was developed for Bacillus anthracis rpoB gene detection using TaqMan assay. Synthetic IAC oligonucleotides were subcloned using vector pDG1730 for ectopic integration into host Bacillus subtilis strain 1A772 genome."

"Differentially labeled target and IAC probes were used in real-time polymerase chain reaction (PCR) assays. There was no nonspecific cross-detection in single-well reactions. Limit of detection for both target and IAC DNA was 5 fg corresponding to a single gene copy."

"The IAC, in conjunction with target system, should decrease the rate of false-positive and false-negative results in real-time PCR assays."

The full article can be found at: (Y. Sonhi, et. al., "Cloning and development of synthetic internal amplification control for Bacillus anthracis real-time polymerase chain reaction assays". Diagnostic Microbiology and Infectious Disease, 2008; 61(4):471-5). Link not available.

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KILLING BACTERIA ISN'T ENOUGH TO RESTORE IMMUNE FUNCTION AFTER INFECTION

Infection Control Magazine
September 10, 2008

"A bacterial molecule that initially signals to animals that they have been invaded must be wiped out by a special enzyme before an infected animal can regain full health, researchers

at UT Southwestern Medical Center have found.

Using a genetically engineered mouse model, the team found that simply eradicating the infection-causing bug isn't enough to restore an animal's immune function. Lipopolysaccharide, or LPS, the dominant bacterial "signal" molecule that heralds the invasion, must also be inactivated. The findings are to appear online Sept. 11 in *Cell Host & Microbe*."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/immune-function-after-infection.html>

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SYNTHESIS OF BIOINORGANIC ANTIMICROBIAL PEPTIDE NANOPARTICLES WITH POTENTIAL THERAPEUTIC PROPERTIES

By D. Matthew Eby, Karen E. Farrington, and Glenn R. Johnson

Biomacromolecules

June 17, 2008

"Amphiphilicity and cationicity are properties shared between antimicrobial peptides and proteins that catalyze biomineralization reactions. Merging these two functionalities, we demonstrate a reaction where a cationic antimicrobial peptide catalyzes self-biomineralization within inorganic matrices. The resultant antimicrobial peptide nanoparticles retain biocidal activity, protect the peptide from proteolytic degradation, and facilitate a continuous release of the antibiotic over time. Taken together, these properties demonstrate the therapeutic potential of self-synthesizing biomaterials that retain the biocidal properties of antimicrobial peptides.

The full article can be found at: <http://pubs.acs.org/cgi-bin/sample.cgi/bomaf6/2008/9/i09/pdf/bm800512e.pdf?sessid=6177>

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SCIENTISTS FORM ALLIANCE TO DEVELOP NANOTOXICOLOGY PROTOCOLS

Nanotechwire.com

September 11, 2008

"A team of materials scientists and toxicologists announced the formation of a new international research alliance to establish protocols for reproducible toxicological testing of nanomaterials in both cultured cells and animals. The International Alliance for NanoEHS Harmonization (IANH) was unveiled today at Nanotox 2008, one of the world's largest biennial nanotoxicological research meetings.

"When this team of scientists from Europe, the U.S., and Japan are able to get the same results for interactions of nanomaterials with biological organisms, then science and society

can have higher confidence in the safety of these materials," said Kenneth Dawson, of University College Dublin and current chair of the IANH team."

The full article can be found at: <http://nanotechwire.com/news.asp?nid=6602>

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LOW COST GRAPHITE ALTERNATIVE TO FABRICATING NANOTECHNOLOGY BIOSENSORS

Nanowerk Spotlight
September 8, 2008

"Now, for the first time, scientists have tested nanometal decorated graphene (actually graphite nanoplatelets, a thickness of 10 nm would contain approximately 30 graphene sheets, considering an interlayer spacing of 0.335 nm) in biosensor application. As it turned out, this novel biosensor is among the best reported to date in both sensing performance and production cost.

Researchers have already demonstrated that metal decorated graphene can be an inexpensive alternative to carbon nanotubes and carbon black as support for fuel cell applications (Dissertation: Metal Decoration of Exfoliated Graphite Nanoplatelets (xGnP) For Fuel Cell Application)."

"The researcher published their findings in the September 3, 2008 edition of ACS Nano ("Nanometal-Decorated Exfoliated Graphite Nanoplatelet Based Glucose Biosensors with High Sensitivity and Fast Response").

In previous work ("Simple Fabrication of a Highly Sensitive Glucose Biosensor Using Enzymes Immobilized in Exfoliated Graphite Nanoplatelets Nafion Membrane"), Lee and collaborators have demonstrated that graphene, prepared in one of the coauthors' (Dr. Drzal) lab at the Michigan State University, can be an inexpensive alternative (~\$10/kg) to carbon nanotubes for use in biosensor application.

Lee explains that the decoration of xGnP with metal nanoparticles further improved their catalytic effects; meanwhile, xGnPs provide high surface area and facilitate uniform distribution of metal nanoparticles, which improved the metal nanoparticle catalyst activity/performance.

The article can be found at: <http://www.nanowerk.com/spotlight/spotid=7144.php>

The original article can be found at: <http://dx.doi.org/doi:10.1021/nn800244k>

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INTRINSIC CURVATURE ASSOCIATED WITH THE COORDINATELY REGULATED ANTHRAX TOXIN GENE PROMOTERS

Biotech Week

September 10, 2008

"The current model for virulence gene regulation in *Bacillus anthracis* involves several trans-acting factors, the most important of which appears to be the anthrax toxin activator encoded by the *atxA* gene. *AtxA* is a positive regulator of the toxin genes *pagA*, *cya* and *lef*, and of a number of other plasmid- and chromosome-encoded genes."

"The *AtxA* protein (56 kDa) possesses a predicted winged-helix DNA-binding domain and phosphotransferase system-regulated domains, but the mechanism for positive regulation of *AtxA* target genes is not known. Sequence similarities in the promoter regions of *AtxA*-regulated genes are not apparent, and recombinant *AtxA* binds DNA with a high affinity in a non-specific manner. We hypothesized that the toxin genes possess common structural features or cis-acting elements that are required for positive regulation. We employed deletion analyses to determine the minimal sequences required for *atxA*-mediated toxin gene expression. In silico modelling and in vitro experiments using double-stranded DNA corresponding to the toxin gene promoter regions indicated significant curvature associated with these regions."

"These findings suggest that the structural topology of the DNA plays an important role in the control of anthrax toxin gene expression."

The full article can be found at: (M. Hadjifrangiskou, et. al., "Intrinsic curvature associated with the coordinately regulated anthrax toxin gene promoters". *Microbiology*, 2008; 154(Pt 8):2501-12). Link not available.

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INHIBITING THE SPREAD OF SUPERBUGS

By Richard Kelly

Chemical Science

September 11, 2008

"UK chemists have found a small molecule with the potential to overcome one of the most serious problems facing the healthcare profession today - the spread of the deadly infection MRSA."

"The diversity-oriented synthesis used by Spring involved making a library of 200+ structurally-diverse compounds and screening them for the required antibacterial activity against two epidemic strains of MRSA. The successful compounds were narrowed down to those with key frameworks and functional groups and were then subjected to further screening. The most potent of these was a substituted dihydropyrimidine named emmacin."

The full article can be found at: http://www.rsc.org/Publishing/ChemScience/Volume/2008/11/Inhibiting_superbugs.asp

The original article can be found at: <http://www.rsc.org/Publishing/Journals/CC/article.asp?doi=b812901k>

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