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Chem-Bio News – S&T Supplement

1. WASHOUT KINETICS OF INHALED HYDROGEN CYANIDE IN BREATH: *"The time-course of cyanide in exhaled air was measured with an electrochemical detector in 10 volunteers during and after a 1 min x 10 ppm exposure to HCN."*

2. RAPID PROTECTION IN A MONKEYPOX MODEL BY A SINGLE INJECTION OF A REPLICATION-DEFICIENT VACCINIA VIRUS: *"With only 4 days between immunization and intravenous challenge, however, MVA still protected whereas Dryvax failed."*

3. LAYER-BY-LAYER ASSEMBLED DNA FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBE HYBRIDS FOR ARSENIC(III) DETECTION: *"The biosensor can be reused up to 16 times."*

4. ONE-STEP MULTICOMPONENT ENCAPSULATION BY COMPOUND-FLUIDIC ELECTROSPRAY: *"The as-prepared microcapsules have multiple compartments inside, in each of which different content can be addressably loaded."*

5. KINETICS OF THE IMMUNE RESPONSE ASSOCIATED WITH TULAREMIA: COMPARISON OF AN ENZYME-LINKED IMMUNOSORBENT ASSAY, A TUBE AGGLUTINATION TEST, AND A NOVEL WHOLE-BLOOD LYMPHOCYTE STIMULATION TEST: *"Comparison of the kinetics of the two assays and those of the traditional tube agglutination test shows that the cellular immune response can be detected earlier by the lymphocyte stimulation assay."*

6. 2-CHLOROCARBINOL (CC-2), A POTENTIAL DECONTAMINANT OF SULFUR MUSTARD (SM): *"A new eco-friendly process has been developed for the production of CC-2 involving aqueous phase conversion of HCC to CC-2."*

7. NANOTECHNOLOGY SOLUTION FOR RADIOACTIVE WASTE CLEANUP: *"The novelty of our project is that the adsorption of bivalent toxic radioactive cations by the nanofibers*

finally induces structure collapse and deformation of the nanofibers, which permanently locks in the toxic radioactive cations," Zhu explains."

8. IMMUNIZATION WITH A SINGLE DOSE OF A MICROENCAPSULATED BRUCELLA MELITENSIS MUTANT ENHANCES PROTECTION AGAINST WILD-TYPE CHALLENGE:

"Together, these results suggest that microencapsulation of live attenuated organisms offers the ability to increase the efficacy of vaccine candidates."

9. BIOSYNTHETIC INTERMEDIATE ANALYSIS AND FUNCTIONAL HOMOLOGY

REVEAL A SAXITOXIN GENE CLUSTER IN CYANOBACTERIA: *"The distribution of these genes also supports the idea of the involvement of this gene cluster in STX production in various cyanobacteria."*

10. CATALYTIC FEATURES OF THE BOTULINUM NEUROTOXIN A LIGHT CHAIN

REVEALED BY HIGH RESOLUTION STRUCTURE OF AN INHIBITORY PEPTIDE COMPLEX: *"This observation suggests that the enzyme active site is prearranged to stabilize the tetrahedral intermediate of the protease reaction."*

CB Daily Report

Chem-Bio News

WASHOUT KINETICS OF INHALED HYDROGEN CYANIDE IN BREATH

By Stamy K, Nord P, Johanson G.

Toxicology Letters

June 10, 2008

"Hydrogen cyanide (HCN) intoxication causes or contributes significantly to many of the fatalities among fire victims. To enable fast treatment of HCN poisoning, a more rapid diagnostic method than currently available is required. One possibility would be measurement in exhaled air. However, as HCN is highly water soluble, it may be absorbed during inhalation and reabsorbed during exhalation. If this, so-called, washin-washout effect is substantial it may interfere with the diagnosis, as a major part of breath HCN may originate from the respiratory tract, due to recent exposure, and not from systemic exposure. The aim of this study was to estimate the importance of the washin-washout effect of HCN. The time-course of cyanide in exhaled air was measured with an electrochemical detector in 10 volunteers during and after a 1 min x 10 ppm exposure to HCN. The experiment revealed an average half-life of 16s (range 10-24s) in breath. Extrapolating the results to higher exposures suggests that the contribution from washin-washout from the airways will be negligible even at fatal exposures. The results support the use of breath HCN as a potential indicator of systemic intoxication."

The full article can be found at: http://www.ncbi.nlm.nih.gov/sites/entrez?cmd=Retrieve&db=pubmed&dopt=AbstractPlus&list_uids=18490114&tool=MedlinePlus

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RAPID PROTECTION IN A MONKEYPOX MODEL BY A SINGLE INJECTION OF A REPLICATION-DEFICIENT VACCINIA VIRUS

By Patricia L. Earl, Jeffrey L. Americo, Linda S. Wyatt, Ondraya Espenshade, Jocelyn Bassler, Kathy Gong, Shuling Lin, Elizabeth Peters, Lowrey Rhodes, Jr, Yvette Edghill Spano, Peter M. Silvera, and Bernard Moss

Proceedings of the National Academy of Science

August 2008

"The success of the World Health Organization smallpox eradication program three decades ago resulted in termination of routine vaccination and consequent decline in population immunity. Despite concerns regarding the reintroduction of smallpox, there is little enthusiasm for large-scale redeployment of licensed live vaccinia virus vaccines because of medical contraindications and anticipated serious side effects. Therefore, highly attenuated strains such as modified vaccinia virus Ankara (MVA) are under evaluation in humans and animal models. Previous studies showed that priming and boosting with MVA provided protection for >2 years in a monkeypox virus challenge model. If variola virus were used as a biological weapon, however, the ability of a vaccine to quickly induce immunity would be essential. Here, we demonstrate more rapid immune responses after a single vaccination with MVA compared to the licensed Dryvax vaccine. To determine the kinetics of protection of the two vaccines, macaques were challenged intravenously with monkeypox virus at 4, 6, 10, and 30 days after immunization. At 6 or more days after vaccination with MVA or Dryvax, the monkeys were clinically protected (except for 1 of 16 animals vaccinated with MVA), although viral loads and number of skin lesions were generally higher in the MVA vaccinated group. With only 4 days between immunization and intravenous challenge, however, MVA still protected whereas Dryvax failed. Protection correlated with the more rapid immune response to MVA compared to Dryvax, which may be related to the higher dose of MVA that can be tolerated safely."

The full article can be found at: <http://www.pnas.org/content/105/31/10889.full>

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LAYER-BY-LAYER ASSEMBLED DNA FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBE HYBRIDS FOR ARSENIC(III) DETECTION

Science Letter

August 12, 2008

"Based on layer-by-layer assembled DNA functionalized single-walled carbon nanotube hybrids, a DNA biosensor for the detection of arsenic(III) in a nearly physiological pH environment was developed. The redox process between arsenic(III) and arsenic(0) on the biosensor was proved."

"The growth of those hybrids on glassy carbon electrode was monitored by detecting arsenic (III). The arsenic(III) current on the biosensor was similar over a broad pH range (3.0-8.0) and the limit of detection (S/N= 3) was 0.05 $\mu\text{g L}^{-1}$ at pH 7.0."

"The biosensor can be reused up to 16 times."

The full article can be found at: (Y.X. Liu, et. al., "Layer-by-layer assembled DNA functionalized single-walled carbon nanotube hybrids for arsenic(III) detection". *Electrochemistry Communications*, 2008; 10(6): 872-875). Link not available.

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ONE-STEP MULTICOMPONENT ENCAPSULATION BY COMPOUND-FLUIDIC ELECTROSPRAY

Science Letter

August 12, 2008

"Most of conventional microencapsulation strategies merely envelop one content into a shell every time."

"We report a compound-fluidic electrospray method could one-step enclose multiple components into a single microcapsule without contact. The as-prepared microcapsules have multiple compartments inside, in each of which different content can be addressably loaded."

"This approach gives flexibility for generating diverse microcapsules that could one-step integrate different active components in microscopic domain free of contact, which may find potential applications in multicomponent drug delivery, microreactors and others."

The full article can be found at: (H.Y. Chen, et. al., "One-step multicomponent encapsulation by compound-fluidic electrospray". *Journal of the American Chemical Society*, 2008; 130(25): 7800+). Link not available.

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KINETICS OF THE IMMUNE RESPONSE ASSOCIATED WITH TULAREMIA: COMPARISON OF AN ENZYME-LINKED IMMUNOSORBENT ASSAY, A TUBE AGGLUTINATION TEST, AND A NOVEL WHOLE-BLOOD LYMPHOCYTE STIMULATION TEST

By Henrik Eliasson, Per Olcén, Anders Sjöstedt, Margareta Jurstrand, Erik Bäck, and Sören Andersson

Clinical and Vaccine Immunology

August 2008

"We have developed and evaluated a novel and simplified whole-blood lymphocyte stimulation assay that focuses on the measurement of gamma interferon after 24 h of stimulation with whole-cell tularemia antigen and a tularemia enzyme-linked immunosorbent assay (ELISA) based on highly purified lipopolysaccharide antigen. Comparison of the kinetics of the two assays and those of the traditional tube agglutination test shows that the cellular immune response can be detected earlier by the lymphocyte stimulation assay. This

test already shows a high proportion of positive results during the first week after the onset of the disease, may be applicable in everyday laboratory practice, and has the potential of changing routine diagnostics for tularemia. The new ELISA has a high sensitivity and becomes positive to a high degree during the second week of disease."

The full article can be found at: <http://cvi.asm.org/cgi/content/abstract/15/8/1238>

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2-CHLOROCARBINOL (CC-2), A POTENTIAL DECONTAMINANT OF SULFUR MUSTARD (SM)

Science Letter

August 12, 2008

"2-Chlorocarbino1 (CC-2) is a potential decontaminant of sulfur mustard (SM), an well known warfare agent. A new eco-friendly process has been developed for the production of CC-2 involving aqueous phase conversion of HCC to CC-2."

"Eco-friendly solvents were used in this process and experiments were carried out in aqueous medium for the synthesis of CC-2. The effect of different parameters on conversion, yield and purity of the product were studied. An efficient solvent extraction was used for in situ separation of the product from the reaction mixture. The reactor used in this process performed both unit operations i.e., the chemical reaction and separation, and can be termed as hybrid reactor. Proper solvent was selected for the separation of the product from the reaction mixture. Three flow sheets that can be used for the production of CC-2 are described and their merits and demerits are highlighted. A comparison of the different flow sheets has been highlighted. A complete process solution has been suggested for efficient production of CC-2."

"The process is cost effective, more environmental friendly and less hazardous compared to earlier reported processes."

The full article can be found at: (B.C. Bag, et. al., "An eco-friendly and separation efficient process involving water phase reaction for production of CC-2". Chemical Engineering and Processing, 2008; 47(8):1339-1345). Link not available.

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NANOTECHNOLOGY SOLUTION FOR RADIOACTIVE WASTE CLEANUP

Nanowerk.com

August 13, 2008

"Radioactive material is toxic because it creates ions – by stripping away electrons from atoms – when it reacts with biological molecules. These ions can form free radicals, which damage proteins, membranes, and nucleic acids. Free radicals damage components of the

cells' membranes, proteins or genetic material by "oxidizing" them – the same chemical reaction that causes iron to rust. This is called "oxidative stress".

"Then again, it has also been found that nanoparticles of inorganic solids readily react with other species or are quickly converted to other crystal phases under moderate conditions, and thus are substantially less stable than the corresponding bulk material."

Based on this, Zhu and his colleagues from Queensland University of Technology and Dr. Xue Ping Gao from the Institute of New Energy Material Chemistry at Nankai University in Tianjin, PR China, focused their search for potential candidates for intelligent absorbents on nanoparticles of inorganic ion exchange materials with a layered structure."

"The novelty of our project is that the adsorption of bivalent toxic radioactive cations by the nanofibers finally induces structure collapse and deformation of the nanofibers, which permanently locks in the toxic radioactive cations," Zhu explains. "The permanent entrapment prevents the radioactive cations to be released from the adsorbents and assures that they can be safely disposed. Furthermore, the titanate nanofiber can selectively remove the radioactive ions in the presence of plentiful competitive ions."

The full article can be found at: <http://www.nanowerk.com/spotlight/spotid=6726.php>

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IMMUNIZATION WITH A SINGLE DOSE OF A MICROENCAPSULATED BRUCELLA MELITENSIS MUTANT ENHANCES PROTECTION AGAINST WILD-TYPE CHALLENGE

Vaccine Weekly
August 20, 2008

"The development of safe and efficacious immunization systems to prevent brucellosis is needed to overcome the disadvantages of the currently licensed vaccine strains that restrict their use in humans. Alginate microspheres coated with a protein of the parasite *Fasciola hepatica* (vitelline protein B [VpB]) and containing live *Brucella melitensis* attenuated mutant vjbR::Tn5 (BME11116) were evaluated for vaccine efficacy and immunogenicity in mice."

"A single immunization dose in BALB/c mice with the encapsulated vjbR mutant improved protection against wild-type *B. melitensis* 16M challenge compared to the nonencapsulated vaccine strain ($P < 0.05$). The encapsulated mutant was also shown to induce a sustained elevation of Immunoglobulin G levels. Cytokine secretion from spleen cells of mice vaccinated with the encapsulated vjbR::Tn5 revealed elevated secretion of gamma interferon and interleukin-12, but no interleukin-4, suggesting an induction of a T helper I response reflecting the enhanced immunity associated with microencapsulation."

"Together, these results suggest that microencapsulation of live attenuated organisms offers the ability to increase the efficacy of vaccine candidates."

The full article can be found at: (A.M. Arenasgamboa, et. al., "Immunization with a single dose of a microencapsulated *Brucella melitensis* mutant enhances protection against wild-

type challenge". *Infection and Immunity*, 2008;76(6):2448-2455). Link not available.

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BIOSYNTHETIC INTERMEDIATE ANALYSIS AND FUNCTIONAL HOMOLOGY REVEAL A SAXITOXIN GENE CLUSTER IN CYANOBACTERIA

Life Science Weekly
August 19, 2008

"Here we describe a candidate PSP toxin biosynthesis gene cluster (sxt) from *Cylindrospermopsis raciborskii* T3. The saxitoxin biosynthetic pathway is encoded by more than 35 kb, and comparative sequence analysis assigns 30 catalytic functions to 26 proteins. STX biosynthesis is initiated with arginine, S-adenosylmethionine, and acetate by a new type of polyketide synthase, which can putatively perform a methylation of acetate, and a Claisen condensation reaction between propionate and arginine. Further steps involve enzymes catalyzing three heterocyclizations and various tailoring reactions that result in the numerous isoforms of saxitoxin. In the absence of a gene transfer system in these microorganisms, we have revised the description of the known STX biosynthetic pathway, with *in silico* functional inferences based on sxt open reading frames combined with liquid chromatography-tandem mass spectrometry analysis of the biosynthetic intermediates. Our results indicate the evolutionary origin for the production of PSP toxins in an ancestral cyanobacterium with genetic contributions from diverse phylogenetic lineages of bacteria and provide a quantum addition to the catalytic collective available for future combinatorial biosyntheses."

"The distribution of these genes also supports the idea of the involvement of this gene cluster in STX production in various cyanobacteria."

The full article can be found at: (R. Kellmann, et. al., "Biosynthetic intermediate analysis and functional homology reveal a saxitoxin gene cluster in cyanobacteria". *Applied and Environmental Microbiology*, 2008;74(13):4044-4053). Link not available.

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CATALYTIC FEATURES OF THE BOTULINUM NEUROTOXIN A LIGHT CHAIN REVEALED BY HIGH RESOLUTION STRUCTURE OF AN INHIBITORY PEPTIDE COMPLEX

Bioterrorism Week
August 18, 2008

"The *Clostridium botulinum* neurotoxin serotype A light chain (BoNT/A-LC) is a Zn(II) dependent metalloprotease that blocks the release of acetylcholine at the neuromuscular junction by cleaving SNAP-25, one of the SNARE proteins required for exocytosis. Because of the potential for use of the toxin in bioterrorism and the increasingly widespread application of the toxin in the medical field, there is significant interest in the development of small-

molecule inhibitors of the metalloprotease."

"Efforts to design such inhibitors have not benefited from knowledge of how peptides bind to the active site since the enzyme-peptide structures available previously either were not occupied in the vicinity of the catalytic Zn(II) ion or did not represent the product of SNAP-25 substrate cleavage. Herein we report the 1.4 angstrom-resolution X-ray crystal structure of a complex between the BoNT/A-LC and the inhibitory peptide N-Ac-CRATKML, the first structure of the light chain with an inhibitory peptide bound at the catalytic Zn(II) ion. The peptide is bound with the Cys S gamma atom coordinating the metal ion. Surprisingly, the cysteine sulfur is oxidized to the sulfenic acid form. Given the unstable nature of this species in solution, is it likely that oxidation occurs on the enzyme. In addition to the peptide-bound structure, we report two structures of the unliganded light chain with and without the Zn(II) cofactor bound at 1.25 and 1.20 angstrom resolution, respectively. The two structures are nearly identical, confirming that the Zn(II) ion plays a purely catalytic role. Additionally, the structure of the Zn(II)-bound uncomplexed enzyme allows identification of the catalytic water molecule and a second water molecule that occupies the same position as the peptidic oxygen in the tetrahedral intermediate."

"This observation suggests that the enzyme active site is prearranged to stabilize the tetrahedral intermediate of the protease reaction."

The full article can be found at: (N.R. Silvaggi, et. al., "Catalytic features of the botulinum neurotoxin a light chain revealed by high resolution structure of an inhibitory peptide complex". *Biochemistry*, 2008; 47(21):5736-5745). Link not available.

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