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Chem-Bio News - S&T Edition

1. FACILE HYDROLYSIS-BASED CHEMICAL DESTRUCTION OF THE WARFARE AGENTS VX, GB, AND HD BY ALUMINA-SUPPORTED FLUORIDE REAGENTS: *"All variations of the alumina-supported fluoride reagents Studied caused in immediate hydrolysis of the highly toxic GB ($t(1/2) < 10$ min) to form the corresponding nontoxic phosphonic acid IMPA."*

2. RIFT VALLEY FEVER VIRUS NSS PROTEIN PROMOTES POST-TRANSCRIPTIONAL DOWNREGULATION OF PROTEIN KINASE PKR AND INHIBITS EIF2A PHOSPHORYLATION: *"Thus, the two distinct functions of the NSs, i.e., the suppression of host transcription, including that of type I interferon mRNAs, and the downregulation of PKR, work together to prevent host innate antiviral functions, allowing efficient replication and survival of RVFV in infected mammalian hosts."*

3. PERSISTENCE OF BOTULINUM TOXIN IN PATIENTS' SERUM: ALASKA, 1959–2007: *"The findings from Alaska and Florida support administration of antitoxin up to 12 days after toxin ingestion but do not indicate when circulating toxin should no longer be present."*

4. ARTIFICIAL PLASMID ENGINEERED TO SIMULATE MULTIPLE BIOLOGICAL THREAT AGENTS: *"The novel simulant described here could reduce the need for infectious agents in the development of detection and diagnostic methods and should also be useful as a non-virulent positive control in nucleic-acid-based tests against biological threat agents."*

5. DEVELOPMENT OF A GENERIC PCR DETECTION OF 3-ACETYLDEOXYNIVALENOL-, 15-ACETYLDEOXYNIVALENOL- AND NIVALENOL-CHEMOTYPES OF FUSARIUM GRAMINEARUM CLADE: *"This is a rapid, reliable and cost-effective method for the identification of type B trichothecene mycotoxin chemotypes in Fusarium species and food safety controls."*

6. PARTICLE SIZE DESIGN OF PLGA MICROSPHERES FOR POTENTIAL PULMONARY DRUG DELIVERY USING RESPONSE SURFACE METHODOLOGY: *"It was also proved that response surface methodology could efficiently be applied for size characterization and optimization of PLGA microparticles for pulmonary drug delivery."*

7. DEVELOPMENT OF ANTIRICIN SINGLE DOMAIN ANTIBODIES TOWARD

DETECTION AND THERAPEUTIC REAGENTS: *"These results indicate that antiricin sdAb have great potential for both diagnostic and therapeutic applications."*

8. GEL CORE LIPOSOMES: AN ADVANCED CARRIER FOR IMPROVED VACCINE

DELIVERY: *"The gel core liposomal formulation provides good entrapment efficiency, enhanced in vitro stability, prolonged antigen release and effective immunoadjuvant property, justifying its potential for improved vaccine delivery."*

CB Daily Report

Chem-Bio News

FACILE HYDROLYSIS-BASED CHEMICAL DESTRUCTION OF THE WARFARE AGENTS VX, GB, AND HD BY ALUMINA-SUPPORTED FLUORIDE REAGENTS

Journal of Technology & Science
February 22, 2009

"A facile solvent-free hydrolysis (chemical destruction) of the warfare agents VX (O-ethyl S-2-(diisopropylamino)ethyl methylphosphonothioate), GB (O-isopropyl methylphosphonofluoridate or sarin), and HD (2,2'-dichloroethyl Sulfide or Sulfur mustard) upon reaction with various solid-supported fluoride reagents is described. These solid reagents include different alumina-based powders such as KF/Al₂O₃."

"AgF/KF/Al₂O₃, and KF/Al₂O₃ enriched by so-called coordinatively unsaturated fluoride ions (termed by us as ECUF-KF/Al₂O₃). When adsorbed on these sorbents, the nerve agent VX quickly hydrolyzed (t(1/2) range between 0.1-6.3 h) to the corresponding nontoxic phosphonic acid EMPA as a major product (> 90%) and to the relatively toxic desethyl-VX (< 10%). The latter byproduct was further hydrolyzed to the nontoxic MPA product (t(1/2) range between 2.2-161 h). The reaction rates and the product distribution were found to be strongly dependent on the nature of the fluoride ions in the KF/Al₂O₃ matrix and on its water content. All variations of the alumina-supported fluoride reagents studied caused in immediate hydrolysis of the highly toxic GB (t(1/2) < 10 min) to form the corresponding nontoxic phosphonic acid IMPA. A preliminary study of the detoxification of HD on these catalyst supports showed the formation of the nontoxic 1,4-thioxane as a major product together with minor amounts of TDG and vinylic compounds within a few days."

The full article can be found at: (E. Gershonov, et. al., "Facile Hydrolysis-Based Chemical Destruction of the Warfare Agents VX, GB, and HD by Alumina-Supported Fluoride Reagents". Journal of Organic Chemistry, 2009; 74(1): 329-338). Link not available.

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RIFT VALLEY FEVER VIRUS NSS PROTEIN PROMOTES POST-TRANSCRIPTIONAL DOWNREGULATION OF PROTEIN KINASE PKR AND INHIBITS EIF2A PHOSPHORYLATION

By Tetsuro Ikegami, Krishna Narayanan, Sungyong Won, Wataru Kamitani, C. J. Peters, Shinji Makino
PLoS Pathogens
10 February 2009

“Rift Valley fever virus (RVFV) (genus Phlebovirus, family Bunyaviridae) is a negative-stranded RNA virus with a tripartite genome. RVFV is transmitted by mosquitoes and causes fever and severe hemorrhagic illness among humans, and fever and high rates of abortions in livestock. A nonstructural RVFV NSs protein inhibits the transcription of host mRNAs, including interferon- β mRNA, and is a major virulence factor. The present study explored a novel function of the RVFV NSs protein by testing the replication of RVFV lacking the NSs gene in the presence of actinomycin D (ActD) or α -amanitin, both of which served as a surrogate of the host mRNA synthesis suppression function of the NSs. In the presence of the host-transcriptional inhibitors, the replication of RVFV lacking the NSs protein, but not that carrying NSs, induced double-stranded RNA-dependent protein kinase (PKR)-mediated eukaryotic initiation factor (eIF)2 α phosphorylation, leading to the suppression of host and viral protein translation. RVFV NSs promoted post-transcriptional downregulation of PKR early in the course of the infection and suppressed the phosphorylated eIF2 α accumulation. These data suggested that a combination of RVFV replication and NSs-induced host transcriptional suppression induces PKR-mediated eIF2 α phosphorylation, while the NSs facilitates efficient viral translation by downregulating PKR and inhibiting PKR-mediated eIF2 α phosphorylation. Thus, the two distinct functions of the NSs, i.e., the suppression of host transcription, including that of type I interferon mRNAs, and the downregulation of PKR, work together to prevent host innate antiviral functions, allowing efficient replication and survival of RVFV in infected mammalian hosts.”

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000287;jsessionid=FD807A12BE8F5FA0C125ECB4B948C680>

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PERSISTENCE OF BOTULINUM TOXIN IN PATIENTS' SERUM: ALASKA, 1959–2007

By Ryan P. Fagan, Joseph B. McLaughlin, and John P. Mittleman
The Journal of Infectious Diseases
November 15, 2008

“Persistence of circulating toxin in patients with foodborne botulism is not well characterized. Recommendations for administration of botulinum antitoxin are ambiguous for patients with late-presenting disease, such as a Florida woman with toxin-positive serum 12 days after toxin ingestion. We reviewed Alaska records of foodborne outbreaks of botulism that occurred during 1959–2007 to examine the period after ingestion during which toxin was detected. Of 64 cases with toxin-positive serum, toxin was detected up to 11 days after ingestion. The findings from Alaska and Florida support administration of antitoxin up to 12

days after toxin ingestion but do not indicate when circulating toxin should no longer be present."

The full article can be found at: <http://www.journals.uchicago.edu/doi/abs/10.1086/597310>

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ARTIFICIAL PLASMID ENGINEERED TO SIMULATE MULTIPLE BIOLOGICAL THREAT AGENTS

Medical Letter on the CDC & FDA
February 15, 2009

"The objective of this study was to develop a non-virulent simulant to replace several virulent organisms during the development of detection and identification methods for biological threat agents. We identified and selected specific genes to detect *Yersinia pestis*, *Francisella tularensis*, *Burkholderia mallei*, *Burkholderia pseudomallei*, *Rickettsia* sp., *Coxiella burnetii*, *Brucella* sp., enterohemorrhagic *Escherichia coli* O157:H7, *Bacillus anthracis*, and variola (smallpox) virus."

"We then designed and engineered a non-infectious simulant that included the nucleic-acid signature of each microorganism in a single chimerical molecule. Here, we reported an approach that by direct (de novo) chemical synthesis permitted the production of a single chimerical construct 2,040bp long that included the nucleic-acid signature of the bacterial and viral biological threat agents listed above without requiring access to these agents. Sequences corresponding to each one of the biological agents in the synthetic simulant were amplified by PCR, resulting in amplicons of the expected length, of similar intensity, and without any detectable unspecific products."

"The novel simulant described here could reduce the need for infectious agents in the development of detection and diagnostic methods and should also be useful as a non-virulent positive control in nucleic-acid-based tests against biological threat agents."

The full article can be found at: (M. Carrera, et. al., "Artificial plasmid engineered to simulate multiple biological threat agents". *Applied Microbiology and Biotechnology*, 2009; 81 (6): 1129-1139). Link not available.

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DEVELOPMENT OF A GENERIC PCR DETECTION OF 3-ACETYLDEOXYNIVALENOL-, 15-ACETYLDEOXYNIVALENOL- AND NIVALENOL-CHEMOTYPES OF FUSARIUM GRAMINEARUM CLADE

Life Science Weekly
February 17, 2009

"*Fusarium graminearum* clade pathogens cause *Fusarium* head blight (FHB) or scab of

wheat and other small cereal grains, producing different kinds of trichothecene mycotoxins that are detrimental to human and domestic animals. Type B trichothecene mycotoxins such as deoxynivalenol, 3-acetyldeoxynivalenol (3-AcDON), 15-acetyldeoxynivalenol (15-AcDON) and nivalenol (NIV) are the principal Fusarium mycotoxins reported in China, as well as in other countries."

"A genomic polymerase chain reaction (PCR) to predict chemotypes was developed based on the structural gene sequences of Tri13 genes involved in trichothecene mycotoxin biosynthesis pathways. A single pair of primers derived from the Tri13 genes detected a 583 bp fragment from 15-AcDON-chemotypes, a 644 bp fragment from 3-AcDON-chemotypes and an 859 bp fragment from NIV-producing strains. Fusarium strains from China, Nepal, USA and Europe were identified by this method, revealing their mycotoxin chemotypes identical to that obtained by chemical analyses of HPLC or GC/MS and other PCR assays. The mycotoxin chemotype-specific fragments were amplified from a highly variable region located in Tri13 genes with three deletions for 15-AcDON-chemotypes, two deletions for 3-AcDON-chemotypes and no deletion for NIV-producers. This PCR assay generated a single amplicon and thus should be more reliable than other PCR-based assays that showed the absence or presence of a PCR fragment since these assays may generate false-negative results. The results with strains from several different countries as well as from different hosts further indicated that this method should be globally applicable."

"This is a rapid, reliable and cost-effective method for the identification of type B trichothecene mycotoxin chemotypes in Fusarium species and food safety controls."

The full article can be found at: (J.H. Wang, et. al., "Development of a Generic PCR Detection of 3-Acetyldeoxynivalenol-, 15-Acetyldeoxynivalenol- and Nivalenol-Chemotypes of Fusarium graminearum Clade". International Journal of Molecular Sciences, 2008; 9 (12):2495-2504). Link not available.

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PARTICLE SIZE DESIGN OF PLGA MICROSPHERES FOR POTENTIAL PULMONARY DRUG DELIVERY USING RESPONSE SURFACE METHODOLOGY

Drug Week

February 20, 2009

Researchers at Isfahan University write: The large surface area, good vascularization, immense capacity for solute exchange and ultra-thinness of the alveolar epithelium are unique features of the lung facilitating systemic drug delivery via pulmonary administration. The efficacy and safety of many new and existing inhaled therapies may be enhanced through advanced controlled-release systems by using polymer particles."

"Poly (D,L-lactic-co-glycolic acid) (PLGA) is well known by its safety in biomedical preparations which has been approved for human use by the FDA. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized to be in the range of 1-5 microns. PLGA microspheres, therefore, were prepared by a developed oil-in-oil solvent evaporation method and characterized. A four-factor, three

levels Box-Behnken design was used for the optimization procedure with temperature, stirring speed, PLGA and surfactant concentration as independent variables. Particle size and polydispersity of microspheres were considered as dependent variables. PLGA microparticles were prepared successfully in desired size for pulmonary delivery by solvent evaporation method. It was found that the particle size of microspheres could be easily controlled."

"It was also proved that response surface methodology could efficiently be applied for size characterization and optimization of PLGA microparticles for pulmonary drug delivery."

The full article can be found at: (J. Emami, et. al., "Particle size design of PLGA microspheres for potential pulmonary drug delivery using response surface methodology". Journal of Microencapsulation, 2009;26(1):1-8). Link not available.

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DEVELOPMENT OF ANTIRICIN SINGLE DOMAIN ANTIBODIES TOWARD DETECTION AND THERAPEUTIC REAGENTS

Chemical & Chemistry

February 13, 2009

"Single domain antibodies (sdAb) that bind ricin with high affinity and specificity were selected from a phage display library derived from the mRNA of heavy chain antibodies obtained from lymphocytes of immunized llamas. The sdAb were found to recognize three distinct epitopes on ricin."

"Representative sdAb were demonstrated to function as both capture and tracer elements in fluid array immunoassays, a limit of detection of 1.6 ng/mL was obtained. One sdAb pair in particular was found to be highly specific for ricin. While polyclonal antibodies cross react strongly with RCA120, the sdAb pair had minimal cross reactivity. In addition, the binders were found to be thermal stable, regaining their ricin binding activity following heating to 85 T for an hour. Cycles of thermally induced unfolding of the sdAb and their subsequent refolding upon cooling was monitored by circular dichroism. As several of the sdAb were observed to bind to ricin's A chain, cell free translation assays were performed to monitor the ability of the sdAbs to inhibit ricin's biological activity. One of the sdAb (C8) was particularly effective and blocked ricin's biological activity with an effectiveness equal to that of a mouse antiricin antibody."

"These results indicate that antiricin sdAb have great potential for both diagnostic and therapeutic applications."

The full article can be found at: (G.P. Anderson, et. al., "Development of Antiricin Single Domain Antibodies Toward Detection and Therapeutic Reagents". Analytical Chemistry, 2008;80(24):9604-9611). Link not available.

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GEL CORE LIPOSOMES: AN ADVANCED CARRIER FOR IMPROVED VACCINE DELIVERY

Drug Week

February 20, 2009

"The use of liposomes as a delivery system for antigen is well recognized but they are unstable and release of antigen from them cannot be controlled over a prolonged period of time. To overcome the limitation of liposomes, this study has developed gel core liposomes in which a core of polymer was incorporated inside the liposomal vesicles, which serve the function of skeleton and provide mechanical strength to vesicles. In the present investigation BSA-loaded gel core liposomes were prepared by reverse phase evaporation method and characterized for vesicles size, shape, entrapment efficiency, in vitro release and stability studies. The in vivo studies to evaluate antigen presenting potential of the gel-core liposomes was performed in Balb/c mice by measuring the immune response elicited by intramuscular administration of BSA-loaded gel core liposomes and compared with intramuscularly administered BSA-loaded conventional liposomes, alum adsorbed BSA and plain antigen. Results indicate that intramuscular immunization with gel core liposomes induces efficient systemic antibody responses against BSA as compared to other formulations."

"The gel core liposomal formulation provides good entrapment efficiency, enhanced in vitro stability, prolonged antigen release and effective immunoadjuvant property, justifying its potential for improved vaccine delivery."

The full article can be found at: (S. Tiwari, et. al., "Gel core liposomes: An advanced carrier for improved vaccine delivery". Journal of Microencapsulation, 2009;26(1):75-82). Link not available.

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