

9 April 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. STRUCTURE OF THE EBOLA VP35 INTERFERON INHIBITORY DOMAIN: *"Our results suggest a structure-based model for dsRNA-mediated innate immune antagonism by Ebola VP35 and other similarly constructed viral antagonists."*

2. GOLDMAN SCHOOL PORTAL TAKES THE WORRY OUT OF 'EXPERIMENTS OF CONCERN': *"Scientists call them "experiments of concern" — research projects designed to advance human knowledge or cure disease, but with potentially lethal applications should the results fall into in the wrong hands."*

3. PULMONARY DEPOSITION OF AEROSOLIZED BACILLUS ATROPHAEUS IN A SWINE MODEL DUE TO EXPOSURE FROM A SIMULATED ANTHRAX LETTER INCIDENT: *"Aerosolized spores were detected in the room in seconds and peak concentrations occurred by three minutes."*

4. DIFFERENT PATHOLOGIES BUT EQUAL LEVELS OF RESPONSIVENESS TO THE RECOMBINANT F1 AND V ANTIGEN VACCINE AND CIPROFLOXACIN IN A MURINE MODEL OF PLAGUE CAUSED BY SMALL- AND LARGE-PARTICLE AEROSOLS: *"Although there were major differences in pathogenesis, the recombinant F1 and V antigen vaccine and ciprofloxacin protected against plague infections caused by small-and large-particle aerosols."*

5. REAL-TIME PCR ASSAY FOR DETECTION OF A NEW SIMULANT FOR POXVIRUS BIOTHREAT AGENTS: *"We suggest that our PCR assay allows Cydia pomonella granulovirus to be used as a simulant for poxviruses. This assay may also be useful for environmental or crop treatment studies."*

6. BEHAVIORAL EVALUATION OF RATS FOLLOWING LOW-LEVEL INHALATION EXPOSURE TO SARIN: *"These results demonstrate that in rats, inhalation exposure to sarin at levels below those causing overt signs of clinical toxicity can produce cognitive and performance deficits."*

CB Daily Report

STRUCTURE OF THE EBOLA VP35 INTERFERON INHIBITORY DOMAIN

Medical Letter on the CDC & FDA

April 5, 2009

"The Ebola VP35 protein is multifunctional, acting as a component of the viral RNA polymerase complex, a viral assembly factor, and an inhibitor of host interferon (IFN) production."

"Mutation of select basic residues within the C-terminal half of VP35 abrogates its dsRNA-binding activity, impairs VP35-mediated IFN antagonism, and attenuates EBOV growth in vitro and in vivo. Because VP35 contributes to viral escape from host innate immunity and is required for EBOV virulence, understanding the structural basis for VP35 dsRNA binding, which correlates with suppression of IFN activity, is of high importance. Here, we report the structure of the C-terminal VP35 IFN inhibitory domain (IID) solved to a resolution of 1.4 angstrom and show that VP35 IID forms a unique fold. In the structure, we identify 2 basic residue clusters, one of which is important for dsRNA binding. The dsRNA binding cluster is centered on Arg-312, a highly conserved residue required for IFN inhibition. Mutation of residues within this cluster significantly changes the surface electrostatic potential and diminishes dsRNA binding activity. The high-resolution structure and the identification of the conserved dsRNA binding residue cluster provide opportunities for antiviral therapeutic design."

"Our results suggest a structure-based model for dsRNA-mediated innate immune antagonism by Ebola VP35 and other similarly constructed viral antagonists."

The full article can be found at: (D.W. Leung, et. al., "Structure of the Ebola VP35 interferon inhibitory domain". Proceedings of the National Academy of Sciences of the United States of America, 2009; 106(2):411-416). Link not available.

[Return to Top](#)

GOLDMAN SCHOOL PORTAL TAKES THE WORRY OUT OF 'EXPERIMENTS OF CONCERN'

By Barry Bergman

UCBerkeleyNews

April 2, 2009

"Scientists call them "experiments of concern" — research projects designed to advance human knowledge or cure disease, but with potentially lethal applications should the results fall into in the wrong hands. The burgeoning field of synthetic biology, which aims for nothing less than to chemically engineer new forms of microbial life (or replicate existing ones), poses special risks.

Yet just how concerned we need be about such experiments is an open question. Now Steve Maurer, director of the Information Technology and Homeland Security Project at the Goldman School of Public Policy, is about to launch an online advice portal he hopes will not only provide some answers, but will also represent a significant step toward mitigating the dangers — whatever they might be — of well-intentioned synthetic-biology research.

The Berkeley-based website, created under the technical supervision of Goldman IT manager Jason Christopher, aims to give researchers a terrorist's-eye view of the possible weaponry applications of their work before they begin an experiment, much less try to publish their findings. Maurer has lined up a stable of some two dozen volunteer reviewers — including security experts from academia, D.C. think tanks, and national laboratories — who will form rotating three-person panels to weigh in on the wisdom of moving ahead with a given project.

Although the advice won't be binding, Maurer hopes the existence of the portal — along with a new virulent-gene database, VIREP, he and Christopher are working to create — will give the synthetic-biology community a meaningful way to regulate its own behavior."

The full article can be found at: http://www.berkeley.edu/news/berkeleyan/2009/04/02_concern.shtml

[Return to Top](#)

PULMONARY DEPOSITION OF AEROSOLIZED BACILLUS ATROPHAEUS IN A SWINE MODEL DUE TO EXPOSURE FROM A SIMULATED ANTHRAX LETTER INCIDENT

Health & Medicine Week

April 6, 2009

"The specific aim of this study was to quantify the respirable aerosol hazard associated with opening an envelope/letter contaminated with a dry spore powder of the biological pathogen anthrax in a typical office environment."

"An envelope containing a letter contaminated with 1.0 g of dry *Bacillus atrophaeus* (BG) spores (pathogen simulant) was opened in the presence of an unrestrained swine model. Aerosolized spores were detected in the room in seconds and peak concentrations occurred by three minutes. The swine, located approximately 1.5 m from the source, was exposed to the aerosol for 28 min following the letter opening event and then moved to a clean room for 30 min. A necropsy was completed to determine the extent of in vivo spore deposition in the lungs. The median number of viable colony forming units (CFU) measured in the combined right and left lung was 21,200: the average mass of both lungs was 283 g. In excess of 100 CFU per gram of lung tissue was found at sites within the anterior, intermediate and posterior lobes. The results of this study confirmed that opening an envelope containing spores generated an aerosol spanning the respirable particle size range of 1-10 microm, and that normal respiration of swine led to spore deposition throughout the lungs. The observed deposition of spores in the lungs of the swine is within the LD(50) range of 2,500-55,000 estimated for humans for inhaled anthrax."

The full article can be found at: (E.J. Duncan, et. al., "Pulmonary deposition of aerosolized Bacillus atrophaeus in a Swine model due to exposure from a simulated anthrax letter incident". Inhalation Toxicology, 2009;21(2):141-52). Link not available.

[Return to Top](#)

DIFFERENT PATHOLOGIES BUT EQUAL LEVELS OF RESPONSIVENESS TO THE RECOMBINANT F1 AND V ANTIGEN VACCINE AND CIPROFLOXACIN IN A MURINE MODEL OF PLAGUE CAUSED BY SMALL- AND LARGE-PARTICLE AEROSOLS

Medical Letter on the CDC & FDA

April 5, 2009

"However, deliberate aerosol release of *Y. pestis* will generate both small and large inhalable particles. We report in this study that the pathogenesis patterns of plague infections caused by the deposition of 1- and 12-microm-particle aerosols of *Y. pestis* in the lower and upper respiratory tracts (URTs) of mice are different. The median lethal dose for 12-mum particles was 4.9-fold greater than that for 1-microm particles. The 12-microm-particle infection resulted in the degradation of the nasal mucosa and nasal-associated lymphoid tissue (NALT) plus cervical lymphadenopathy prior to bacteremic dissemination. Lung involvement was limited to secondary pneumonia. In contrast, the 1-microm-particle infection resulted in primary pneumonia; in 40% of mice, the involvement of NALT and cervical lymphadenopathy were observed, indicating entry via both URT lymphoid tissues and lungs. Despite bacterial deposition in the gastrointestinal tract, the involvement of Peyer's patches was not observed in either infection."

"Although there were major differences in pathogenesis, the recombinant F1 and V antigen vaccine and ciprofloxacin protected against plague infections caused by small- and large-particle aerosols."

The full article can be found at: (R.J. Thomas, et. al., "Different pathologies but equal levels of responsiveness to the recombinant F1 and V antigen vaccine and ciprofloxacin in a murine model of plague caused by small- and large-particle aerosols". Infection and Immunity, 2009; 77(4): 1315-23). Link not available.

[Return to Top](#)

REAL-TIME PCR ASSAY FOR DETECTION OF A NEW SIMULANT FOR POXVIRUS BIOTHREAT AGENTS

Life Science Weekly

April 7, 2009

"The bacteriophage MS2, a small RNA virus, is classically used as the reference simulant for bioterror viruses within the biodefense community. However, variola virus, considered a major threat, displays very different features (size, envelope, and double-stranded DNA genome). The size parameter is critical for aerosol sampling, detection, and protection/

filtration technologies. Therefore, a panel of relevant simulants should be used to cover the diversity of biothreat agents. Thus, we investigated a new virus model, the *Cydia pomonella* granulovirus (baculovirus), which is currently used as a biopesticide. It displays a size similar to that of poxviruses, is enveloped, and contains double-stranded DNA. To provide a molecular tool to detect and quantify this model virus, we developed an assay based on real-time PCR, with a limit of detection ranging from roughly 10 to a few tens of target copies per μ l according to the sample matrix. The specificity of the assay against a large panel of potential cross-reactive microorganisms was checked, and the suitability of the assay for environmental samples, especially aerosol studies, was determined."

"We suggest that our PCR assay allows *Cydia pomonella* granulovirus to be used as a simulant for poxviruses. This assay may also be useful for environmental or crop treatment studies."

The full article can be found at: (L. Garnier, et. al., "Real-Time PCR Assay for Detection of a New Simulant for Poxvirus Biothreat Agents". *Applied and Environmental Microbiology*, 2009; 75(6):1614-1620). Link not available.

[Return to Top](#)

BEHAVIORAL EVALUATION OF RATS FOLLOWING LOW-LEVEL INHALATION EXPOSURE TO SARIN

Drug Week

April 10, 2009

"We evaluated the effects, in rats, of single and multiple low-level inhalation exposures to sarin. Rats were trained on a variable-interval, 56 s (VI56) schedule of food reinforcement and then exposed to sarin vapor (1.7-4.0 mg/m³ x 60 min) or air control."

"The exposures did not produce clinical signs of toxicity other than miosis. Subsequently, performance on the VI56 and acquisition of a radial-arm maze spatial memory task was evaluated over approximately 11 weeks. Single exposures did not affect performance on the VI56 and had little effect on acquisition of the radial-arm maze task. Multiple exposures (4.0 mg/m³ x 60 min/day x 3) disrupted performance on the VI56 schedule during the initial post-exposure sessions. The disruption, however, resolved after several days. Multiple exposures also produced a deficit on the radial-arm maze task in that sarin-exposed rats tended to take it longer to complete the maze and to make more errors. The deficit, however, resolved during the first three weeks of acquisition. These results demonstrate that in rats, inhalation exposure to sarin at levels below those causing overt signs of clinical toxicity can produce cognitive and performance deficits."

The full article can be found at: (R.F. Genovese, et. al., "Behavioral evaluation of rats following low-level inhalation exposure to sarin". *Pharmacology, Biochemistry and Behavior*, 2009; 91(4):517-25). Link not available.

[Return to Top](#)

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