

25 June 2009

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Chem-Bio News – S&T Edition

1. THE DESTRUCTION OF SULPHUR MUSTARD BY IONIZING RADIATION: *Briefing slides from a Royal Military College of Canada presentation.*

2. BACILLUS ANTHRACIS HSSRS SIGNALLING TO HRTAB REGULATES HAEM RESISTANCE DURING INFECTION: *"Further, these data suggest that haem stress is experienced by bacterial pathogens during infection."*

3. CRYSTAL STRUCTURE OF THE VIBRIO CHOLERAEE FERRIC UPTAKE REGULATOR (FUR) REVEALS INSIGHTS INTO METAL CO-ORDINATION: *"An analysis of the metal binding properties shows that V. cholerae Fur can be activated by a range of divalent metals."*

4. QUANTITATIVE DETECTION OF STAPHYLOCOCCAL ENTEROTOXIN B BY RESONANT ACOUSTIC PROFILING: *"In addition to detection, we evaluated RAP's [Resonant Acoustic Profiling] ability to measure the toxin in unknown samples rapidly by measuring the initial binding rate of the interaction, thereby further shortening the assay time to 6 min."*

5. SIDEROPHORE-MEDIATED IRON ACQUISITION SYSTEMS IN BACILLUS CEREUS: IDENTIFICATION OF RECEPTORS FOR ANTHRAX VIRULENCE-ASSOCIATED PETROBACTIN: *"The biochemical characterization of these SBPs provides the first identification of the transporter candidates that most likely play a role in the B. cereus group pathogenicity."*

6. ASSESSMENT OF LOW LEVEL WHOLE-BODY SOMAN VAPOR EXPOSURE IN RATS: *"These results demonstrate that, in rats, single exposures to soman vapors at levels that produce substantial AChE and BChE inhibition, but below those producing convulsions and other severe clinical signs of toxicity, may not produce observable effects on the performance of a previously learned task or the acquisition of a new task."*

7. COMPOUND SHOWS PROMISE FOR TREATING POTENTIALLY LETHAL VIRAL – INFECTIONS: *"In the recent publication, the authors show that CSA-13 exhibits potent antiviral activity against the vaccinia virus by (1) direct antiviral effects against vaccinia; and (2) stimulating the expression of endogenous antimicrobial peptides with known antiviral activity against vaccinia."*

8. SCIENTISTS BLOCK EBOLA INFECTION IN CELL-CULTURE EXPERIMENTS: *"Researchers at the University of Texas Medical Branch at Galveston have discovered two biochemical pathways that the Ebola virus relies on to infect cells. Using substances that block the activation of those pathways, they've prevented Ebola infection in cell culture experiments – potentially providing a critical early step in developing the first successful therapy for the deadly virus."*

CB Daily Report

Chem-Bio News

THE DESTRUCTION OF SULPHUR MUSTARD BY IONIZING RADIATION:

By K.A.M. Creber, P.V. Samuleev and W.S. Andrews

Department of Chemistry and Chemical Engineering, Royal Military College of Canada
Date unk.

Briefing slides from a Royal Military College of Canada presentation.

The full article can be found at: <http://www.dstl.gov.uk/conferences/cwd/2009/pres/AndrewsW-01.pdf>
[Return to Top](#)

BACILLUS ANTHRACIS HSSRS SIGNALLING TO HRTAB REGULATES HAEM RESISTANCE DURING INFECTION

Medical Letter on the CDC & FDA
June 28, 2009

"*Bacillus anthracis* proliferates to high levels within vertebrate tissues during the pathogenesis of anthrax. This growth is facilitated by the acquisition of nutrient iron from host haem."

"However, haem acquisition can lead to the accumulation of toxic amounts of haem within *B. anthracis*. Here, we show that *B. anthracis* resists haem toxicity by sensing haem through the HssRS two-component system, which regulates expression of the haem-detoxifying transporter HrtAB. In addition, we demonstrate that *B. anthracis* exhibits elevated HssRS function compared with its evolutionary relative *Staphylococcus aureus*. Elevated haem sensing is likely required by *B. anthracis* due to the significant haem sensitivity exhibited by members of the genus *Bacilli*. We also demonstrate that *B. anthracis* depends on conserved residues within the previously uncharacterized sensing domain of the histidine kinase HssS for HssRS function. Finally, we show that the haem- and HssRS-regulated hrtAB promoter is activated in a murine model of anthrax. These results demonstrate the evolutionary conservation of haem sensing among multiple Gram-positive bacteria and begin to provide a mechanistic explanation for the haem resistance of *B. anthracis*."

"Further, these data suggest that haem stress is experienced by bacterial pathogens during infection."

The full article can be found at: (D.L. Stauff, et. al., "*Bacillus anthracis* HssRS signalling to HrtAB regulates haem resistance during infection". *Molecular Microbiology*, 2009;72(3):763-778). Link not available.

[Return to Top](#)

CRYSTAL STRUCTURE OF THE VIBRIO CHOLERAE FERRIC UPTAKE REGULATOR (FUR) REVEALS INSIGHTS INTO METAL CO-ORDINATION

Pharma Investments, Ventures & Law Weekly
June 28, 2009

"The ferric uptake regulator (Fur) is a metal-dependent DNA-binding protein that acts as both a repressor and an activator of numerous genes involved in maintaining iron homeostasis in bacteria. It has also been demonstrated in *Vibrio cholerae* that Fur plays an additional role in pathogenesis, opening up the potential of Fur as a drug target for cholera."

"Here we present the crystal structure of *V. cholerae* Fur that reveals a very different orientation of the DNA-binding domains compared with that observed in *Pseudomonas aeruginosa* Fur. Each monomer of the dimeric Fur protein contains two metal binding sites occupied by zinc in the crystal structure. In the *P. aeruginosa* study these were designated as the regulatory site (Zn1) and structural site (Zn2). This *V. cholerae* Fur study, together with studies on Fur homologues and paralogues, suggests that in fact the Zn2 site is the regulatory iron binding site and the Zn1 site plays an auxiliary role. There is no evidence of metal binding to the cysteines that are conserved in many Fur homologues, including *Escherichia coli* Fur."

"An analysis of the metal binding properties shows that *V. cholerae* Fur can be activated by a range of

divalent metals."

The full article can be found at: (M.A. Sheikh, et. al., "Crystal structure of the Vibrio cholerae ferric uptake regulator (Fur) reveals insights into metal co-ordination". Molecular Microbiology, 2009;72(5):1208-20). Link not available.

[Return to Top](#)

QUANTITATIVE DETECTION OF STAPHYLOCOCCAL ENTEROTOXIN B BY RESONANT ACOUSTIC PROFILING

Pharma Investments, Ventures & Law Weekly
June 28, 2009

"A rapid and sensitive detection of staphylococcal enterotoxin B (SEB) was developed using a novel acoustic sensing technique: Resonant Acoustic Profiling (RAP), which utilizes high-frequency piezoelectric quartz resonators for monitoring biomolecular interactions. An automated four-channel instrument consisting of acoustic sensors covalently conjugated with anti-SEB antibodies was used."

"As the samples flowed across control and active sensors simultaneously, binding was measured as a change in the resonant frequency. The lower limit Of detection (LWD) for the label free direct format was 25 ng/mL. Detection sensitivity was increased by adding mass sequentially to the captured SEB on the sensor in the form of sandwich antibodies and biotin-avidin-based gold nanoparticles. The LLOD for the mass enhanced formats were 5 and 0.5 ng/mL of SEB, respectively. The lowest sensitivity corresponds to 1.3 fM in a 75 μ L sample. The total assay time including the enhancement steps was less than 10 min. SEB was detected in both neat urine and PBS buffer-spiked samples, with linear correlations between resonant frequency signals and SEB concentrations (R-2 of 0.999 and 0.998, respectively). No significant cross-reactivity was observed with homologue toxins SEA, SED, and TSST, but some cross-reactivity was observed with the closely related toxin SEC, when we used a polyclonal antibody in the assay.,SEC, cross-reactivity was not observed when a SEB-specific monoclonal antibody was employed in the assay. Thus the specificity of the assay presented here was dependent on the quality of the antibodies used."

"In addition to detection, we evaluated RAP's ability to measure the toxin in unknown samples rapidly by measuring the initial binding rate of the interaction, thereby further shortening the assay time to 6 min."

The full article can be found at: (M. Natesan, et. al., "Quantitative Detection of Staphylococcal Enterotoxin B by Resonant Acoustic Profiling". Analytical Chemistry, 2009;81(10):3896-3902). Link not available.

[Return to Top](#)

SIDEROPHORE-MEDIATED IRON ACQUISITION SYSTEMS IN BACILLUS CEREUS: IDENTIFICATION OF RECEPTORS FOR ANTHRAX VIRULENCE-ASSOCIATED PETROBACTIN

Drug Week
June 26, 2009

"During growth under iron limitation, Bacillus cereus and Bacillus anthracis, two human pathogens from the Bacillus cereus group of Gram-positive bacteria, secrete two siderophores, bacillibactin (BB) and petrobactin (PB), for iron acquisition via membrane-associated substrate-binding proteins (SBPs) and other ABC transporter components. Since PB is associated with virulence traits in B. anthracis, the PB-mediated iron uptake system presents a potential target for antimicrobial therapies; its characterization in B. cereus."

"Separate transporters for BB, PB, and several xenosiderophores are suggested by Fe-55-siderophore uptake studies. The PB precursor, 3,4-dihydroxybenzoic acid (3,4-DHB), and the photoproduct of FePB (FePB nu) also mediate iron delivery into iron-deprived cells. Putative SBPs were recombinantly

expressed, and their ligand specificity and binding affinity were assessed using fluorescence spectroscopy. The noncovalent complexes of the SBPs with their respective siderophores were characterized using ESI-MS. The differences between solution phase behavior and gas phase measurements are indicative of noncovalent interactions between the siderophores and the binding sites of their respective SBPs. These studies combined with bioinformatics sequence comparison identify SBPs from five putative transporters specific for BB and enterobactin (FeuA), 3,4-DHB and PB (FatB), PB (FpuA), schizokinen (YfiY), and desferrioxamine and ferrichrome (YxeB). The two PB receptors show different substrate ranges: FatB has the highest affinity for ferric 3,4-DHB, iron-free PB, FePB, and FePB nu, whereas FpuA is specific to only apo- and ferric PB."

"The biochemical characterization of these SBPs provides the first identification of the transporter candidates that most likely play a role in the *B. cereus* group pathogenicity."

The full article can be found at: (A.M. Zawadzka, et. al., "Siderophore-Mediated Iron Acquisition Systems in *Bacillus cereus*: Identification of Receptors for Anthrax Virulence-Associated Petrobactin". *Biochemistry*, 2009;48(16):3645-3657). Link not available.

[Return to Top](#)

ASSESSMENT OF LOW LEVEL WHOLE-BODY SOMAN VAPOR EXPOSURE IN RATS

Health & Medicine Week

June 22, 2009

"We evaluated biochemical and behavioral effects of single, low-level exposures to the chemical warfare nerve agent soman (GD). Male Sprague-Dawley rats were trained on a variable-interval, 56-sec schedule of food reinforcement (VI56)."

"The schedule specifies that a single lever press, following an average interval of 56 s, produces food reinforcement (i.e., a single food pellet). After training, rats received a single 60 min exposure to soman vapor at concentrations of 1.0-7.0 mg/m³, or air control (n = 8 for each treatment condition). Blood was sampled before and after the exposure. Following exposures, performance on the VI56 was evaluated for approximately 11 weeks. Additionally, the acquisition and maintenance of a radial-arm maze (RAM) spatial memory task were evaluated in the same subjects during the same 11-week period. Soman exposures produced miosis in all subjects but were otherwise essentially asymptomatic. That is, no convulsions or major signs of toxicity were observed in any subjects, a result consistent with a low-level concentration. Soman exposures produced significant and concentration-dependent decreases in circulating acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activity. Soman exposures also produced concentration-dependent levels of regenerated soman in plasma and red blood cell fractions that served to verify the systemic exposure and estimate the total body burden. Soman exposure did not disrupt performance on the VI56 schedule as responding was maintained at pre-exposure levels throughout the 11-week period in all treatment groups. All subjects acquired, and maintained, performance on the RAM task and no significant differences were observed as a result of soman exposure. That is, soman-exposed rats learned the RAM task at the same general rate and to the same general level of accuracy as air-control rats. No delayed effects from exposures were observed. These results demonstrate that, in rats, single exposures to soman vapors at levels that produce substantial AChE and BChE inhibition, but below those producing convulsions and other severe clinical signs of toxicity, may not produce observable effects on the performance of a previously learned task or the acquisition of a new task."

The full article can be found at: (R.F. Genovese, et. al., "Assessment of low level whole-body soman vapor exposure in rats". *Neurotoxicology and Teratology*, 2009;31(2):110-118). Link not available.

[Return to Top](#)

COMPOUND SHOWS PROMISE FOR TREATING POTENTIALLY LETHAL VIRAL INFECTIONS

CentreDaily.com

June 22, 2009

“Ceragenix Pharmaceuticals, Inc. (“Ceragenix”) (OTCBB:CGXP), a medical device company focused on infectious disease and dermatology, today announced that researchers at National Jewish Health, led by Dr. Donald Y. Leung and Dr. Michael Howell, in collaboration with Dr. Paul B. Savage of Brigham Young University, have demonstrated in a series of in vitro experiments and preclinical animal testing that an investigational drug compound known as CSA-13 shows promise as a potential therapy to treat viral infections from the vaccinia virus. The research appears ahead of print in an advanced online publication of the Journal of Investigate Dermatology, the official journal of the Society for Investigative Dermatology. This work was funded by the National Institute of Allergy and Infectious Diseases Atopic Dermatitis Vaccinia Network.”

“CSA-13 is a member of the Company’s developmental Ceragenin™ class of compounds. Ceragenins are synthetic antimicrobial compounds designed to mimic the structure and function of endogenous antimicrobial peptides which form a key component of the body’s innate immune system. In the recent publication, the authors show that CSA-13 exhibits potent antiviral activity against the vaccinia virus by (1) direct antiviral effects against vaccinia; and (2) stimulating the expression of endogenous antimicrobial peptides with known antiviral activity against vaccinia . In addition, the research shows that a topical application of CSA-13 penetrates the skin and reduces subsequent satellite lesion formation.

According to Dr. Leung: “In our current study, we demonstrate that CSA-13 exhibits potent anti-viral activity by preferentially targeting and killing the vaccinia virus directly and by inducing antimicrobial peptides with known activity against the virus. Additionally, we demonstrate that topical administration of CSA-13 significantly reduces the development of satellite lesions. Taken together, our current study suggests that CSAs may be effective as an anti-viral agent against disseminated vaccinia virus infections. The development of these synthetic agents for treatment of disseminated viral skin infection represents an exciting advance.”

The full article can be found at: <http://www.centredaily.com/business/technology/v-print/story/1357842.html>

[Return to Top](#)

SCIENTISTS BLOCK EBOLA INFECTION IN CELL-CULTURE EXPERIMENTS

Infection Control Today Magazine

June 23, 2009

“Researchers at the University of Texas Medical Branch at Galveston have discovered two biochemical pathways that the Ebola virus relies on to infect cells. Using substances that block the activation of those pathways, they've prevented Ebola infection in cell culture experiments — potentially providing a critical early step in developing the first successful therapy for the deadly virus.”

“To make sense of the data, the researchers turned to a newly developed statistical algorithm designed especially to prioritize the results of siRNA screens. After subjecting that output to further computational analysis, they found that two networks of biochemical reactions seemed particularly important to Ebola's entry into cells: The PI3 kinase pathway and the CAMK2 pathway. Since drugs to block both pathways are available, the UTMB group decided to investigate whether they would interfere with Ebola infection of cells — first using virus pseudotypes, and then, in UTMB's maximum containment BSL4 "spacesuit" lab, with Ebola Zaire itself, the variety of the virus most associated with high mortality rates.

"With the real virus in the BSL4, we found that the PI3 kinase inhibitor dropped virus titers by 65 percent, and if we used drugs which block CAMK2 function, it was just killed — stopped dead," Davey said. "This is really, very, very interesting because this pathway has a lot of potential for future pharmaceutical exploitation."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/ebola-virus-infection->

blocked.html
[Return to Top](#)

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