

19 March 2009

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## **Chem-Bio News - S&T Edition**

**1. EFFECTS OF XANTHOTOXIN TREATMENT ON TRICHOTHECENE PRODUCTION IN FUSARIUM SPOROTRICHIOIDES:** *"These results indicate that while xanthotoxin inhibits specific P450 oxygenase activity, it also has an effect on gene expression."*

**2. RESEARCHERS DEVELOP NOVEL ANTIBIOTICS THAT DON'T TRIGGER RESISTANCE:** *"The compounds work against two notorious microbes. Vibrio cholerae, which causes cholera; and E. coli O157:H7, the food contaminant."*

**3. MRSA STUDY SUGGESTS STRATEGY SHIFT NEEDED TO DEVELOP EFFECTIVE THERAPEUTICS:** *"Instead of the current focus on neutralizing MRSA by targeting products of mobile genetic elements—DNA molecules that bacteria acquire randomly by interacting with other bacteria—scientists should switch to looking at the permanent DNA backbone (core genome) of USA300 to understand how increased production of certain proteins such as toxins affects its virulence in humans."*

**4. ACUTE TOXICITY OF ORGANOPHOSPHORUS COMPOUNDS IN GUINEA PIGS IS SEX- AND AGE-DEPENDENT AND CANNOT BE SOLELY ACCOUNTED FOR BY ACETYLCHOLINESTERASE INHIBITION:** *"They also support the contention that mechanisms other than AChE inhibition contribute to the lethality of nerve agents."*

**5. LEGISLATION TO CURB MISUSE OF ANTIBIOTICS INTRODUCED IN HOUSE:** *"Congresswoman Slaughter (pictured) is a microbiologist with a Masters in Public Health. She noted medical experts have said the misuse of antibiotics in industrial farming is directly linked to the growing number of antibiotic-resistant infections in people."*

**6. REQUIREMENTS FOR CELL ROUNDING AND SURFACE PROTEIN DOWN-REGULATION BY EBOLA VIRUS GLYCOPROTEIN:** *"Overall, these results support a model in which the mucin domain of Ebola GP acts at the cell surface to induce protein down modulation and cytopathic effects."*

# **CB Daily Report**

### EFFECTS OF XANTHOTOXIN TREATMENT ON TRICHOTHECENE PRODUCTION IN FUSARIUM SPOROTRICHIOIDES

Drug Week

March 13, 2009

"There are 4 P450 oxygenases involved in the biosynthesis of T-2 toxin in *Fusarium sporotrichioides*. Exactly how these enzymes react to antimicrobial plant defense compounds is unknown."

"Xanthotoxin (8-methoxypsoralen) is a phototoxic furanocoumarin that acts as a P450 oxygenase inhibitor. The current study shows that the addition of concentrations of 1.0 mmol/L or less of xanthotoxin to liquid cultures of *F. sporotrichioides* NRRL3299 call effectively block T-2 toxin production and cause an increase in accumulation of trichodiene, the hydrocarbon precursor of trichothecenes. The addition of xanthotoxin to liquid cultures of its trichodiene-accumulating *F. sporotrichioides* TH4(-) mutant caused a 3- to 10-fold increase in trichodiene accumulation, suggesting that xanthotoxin not only blocks trichothecene oxygenation reactions, but may in some way also promote the synthesis of trichodiene. Feeding studies showed that 2 of the 4 P450 oxygenases, TRI4 and TRI1, were more sensitive to xanthotoxin, while oxygenases TRI11 and TRI13 were unaffected. Quantitative reverse-transcriptase PCR indicated that several of the genes in the toxin biosynthetic pathway were upregulated by xanthotoxin, with Tri4 showing the highest increase in expression."

"These results indicate that while xanthotoxin inhibits specific P450 oxygenase activity, it also has an effect on gene expression."

The full article can be found at: (N.J. Alexander, et. al., "Effects of xanthotoxin treatment on trichothecene production in *Fusarium sporotrichioides*". *Canadian Journal of Microbiology*, 2008; 54(12): 1023-1031). Link not available.

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### RESEARCHERS DEVELOP NOVEL ANTIBIOTICS THAT DON'T TRIGGER RESISTANCE

Infection Control Today Magazine

March 13, 2009

"In a study described in *Nature Chemical Biology*, researchers from Albert Einstein College of Medicine of Yeshiva University are developing a new generation of antibiotic compounds that do not provoke bacterial resistance. The compounds work against two notorious microbes: *Vibrio cholerae*, which causes cholera; and *E. coli* O157:H7, the food contaminant that each year in the U.S. causes approximately 110,000 illnesses and 50 deaths."

"Rather than killing *Vibrio cholerae* and *E. coli* O157:H7, the researchers aimed to disrupt their ability to communicate via quorum sensing. Their target: A bacterial enzyme, MTAN,

that is directly involved in synthesizing the autoinducers crucial to quorum sensing. Their plan: Design a substrate to which MTAN would bind much more tightly than to its natural substrate — so tightly, in fact, that the substrate analog permanently "locks up" MTAN and inhibits it from fueling quorum sensing."

"The study, "Transition State Analogs of 5' — Methylthioadenosine Nucleosidase Disrupt Quorum Sensing" by Vern L. Schramm et al., appears in the March 8, 2009 online edition of Nature Chemical Biology."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/novel-antibiotics-resistance.html>

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## **MRSA STUDY SUGGESTS STRATEGY SHIFT NEEDED TO DEVELOP EFFECTIVE THERAPEUTICS**

Infection Control Today Magazine  
March 17, 2009

"USA300—the major epidemic strain of methicillin-resistant Staphylococcus aureus (MRSA) causing severe infections in the United States during the past decade—inherits its destructiveness directly from a forefather strain of the bacterium called USA500 rather than randomly acquiring harmful genes from other MRSA strains. This finding comes from a new study led by scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health.

The study authors suggest that a radical shift may be needed in how scientists should design MRSA therapeutics. Instead of the current focus on neutralizing MRSA by targeting products of mobile genetic elements—DNA molecules that bacteria acquire randomly by interacting with other bacteria—scientists should switch to looking at the permanent DNA backbone (core genome) of USA300 to understand how increased production of certain proteins such as toxins affects its virulence in humans."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/effective-mrsa-therapeutics.html>

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## **ACUTE TOXICITY OF ORGANOPHOSPHORUS COMPOUNDS IN GUINEA PIGS IS SEX- AND AGE-DEPENDENT AND CANNOT BE SOLELY ACCOUNTED FOR BY ACETYLCHOLINESTERASE INHIBITION**

Drug Week  
March 27, 2009

"This study was designed to test the hypothesis that the acute toxicity of the nerve agents S-

[2-(diisopropylamino)ethyl]-O-ethyl methylphosphonothioate (VX), O-pinacolyl methylphosphonofluoridate (soman), and O-isopropyl methylphosphonofluoridate (sarin) in guinea pigs is age- and sex-dependent and cannot be fully accounted for by the irreversible inhibition of acetylcholinesterase (AChE). The subcutaneous doses of nerve agents needed to decrease 24-h survival of guinea pigs by 50% (LD50 values) were estimated by probit analysis."

"In all animal groups, the rank order of LD50 values was sarin > soman > VX. The LD50 value of soman was not influenced by sex or age of the animals. In contrast, the LD50 values of VX and sarin were lower in adult male than in age- matched female or younger guinea pigs. A colorimetric assay was used to determine the concentrations of nerve agents that inhibit in vitro 50% of AChE activity (IC50 values) in guinea pig brain extracts, plasma, red blood cells, and whole blood. A positive correlation between LD50 values and IC50 values for AChE inhibition would support the hypothesis that AChE inhibition is a major determinant of the acute toxicity of the nerve agents. However, such a positive correlation was found only between LD50 values and IC50 values for AChE inhibition in brain extracts from neonatal and prepubertal guinea pigs. These results demonstrate for the first time that the lethal potencies of some nerve agents in guinea pigs are age- and sex-dependent."

"They also support the contention that mechanisms other than AChE inhibition contribute to the lethality of nerve agents."

The full article can be found at: (W.P. Fawcett, et. al., "Acute Toxicity of Organophosphorus Compounds in Guinea Pigs Is Sex- and Age-Dependent and Cannot Be Solely Accounted for by Acetylcholinesterase Inhibition". Journal of Pharmacology and Experimental Therapeutics, 2009; 328(2):516-524). Link not available.

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## **LEGISLATION TO CURB MISUSE OF ANTIBIOTICS INTRODUCED IN HOUSE**

By Andy Eubank  
Hoosier Ag Today  
March 17, 2009

"Tuesday Shelley Hearne of the Pew Commission applauded legislation introduced by New York 28th District Congresswoman Louise Slaughter. Hearne described the Preservation of Antibiotics for Medical Treatment Act of 2009, saying, "This PAMTA bill phases out the use of medically important human antibiotics in food animals, unless the animals are sick with disease."

"Instead they are going to food animals in amounts too low to actually fight disease, but instead are to fatten the animals faster and compensate for the intensely crowded and unsanitary conditions that are found on many industrial farms. This bill is designed to help stop this dangerous practice."

Congresswoman Slaughter (pictured) is a microbiologist with a Masters in Public Health. She noted medical experts have said the misuse of antibiotics in industrial farming is directly

linked to the growing number of antibiotic-resistant infections in people.”

The full article can be found at: [http://www.hoosieragtoday.com/wire/news/02311\\_pamtapew\\_180941.php](http://www.hoosieragtoday.com/wire/news/02311_pamtapew_180941.php)

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## **REQUIREMENTS FOR CELL ROUNDING AND SURFACE PROTEIN DOWN-REGULATION BY EBOLA VIRUS GLYCOPROTEIN**

Medical Letter on the CDC & FDA

March 29, 2009

“Cellular pathogenesis can be modeled in vitro by expression of the Ebola viral glycoprotein (GP) in cells, which causes dramatic morphological changes, including cell rounding and surface protein down-regulation. These effects are known to be dependent on the presence of a highly glycosylated region of the glycoprotein, the mucin domain. Here we show that the mucin domain from the highly pathogenic Zaire subtype of Ebola virus is sufficient to cause characteristic cytopathology when expressed in the context of a foreign glycoprotein. Similarly to full length Ebola GP, expression of the mucin domain causes rounding, detachment from the extracellular matrix, and the down-regulation of cell surface levels of  $\alpha_5\beta_1$  integrin and major histocompatibility complex class I. These effects were not seen when the mucin domain was expressed in the context of a glycosylated phosphatidylinositol-anchored isoform of the foreign glycoprotein. In contrast to earlier analysis of full length Ebola glycoproteins, chimeras carrying the mucin domains from the Zaire and Reston strains appear to cause similar levels of down-modulation and cell detachment. Cytopathology associated with Ebola glycoprotein expression does not occur when GP expression is restricted to the endoplasmic reticulum. In contrast to a previously published report, our results demonstrate that GP-induced surface protein downregulation is not mediated through a dynamin-dependent pathway.”

“Overall, these results support a model in which the mucin domain of Ebola GP acts at the cell surface to induce protein down modulation and cytopathic effects.”

The full article can be found at: (J.R. Francica, et. al., “Requirements for cell rounding and surface protein down-regulation by Ebola virus glycoprotein”. *Virology*, 2009; 383(2):237-247). Link not available.

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