

19 February 2009

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

### **1. DISRUPTION OF THE EPITHELIAL BARRIER BY BOTULINUM HAEMAGGLUTININ (HA) PROTEINS - DIFFERENCES IN CELL TROPISM AND THE MECHANISM OF ACTION BETWEEN HA PROTEINS OF TYPES A OR B, AND HA PROTEINS OF TYPE C:**

*"These findings may indicate that type A and B HA proteins contribute to the development of food-borne botulism, at least in humans, by facilitating the intestinal transepithelial delivery of BoNTs, and that the relative inability of type C HA proteins to disrupt the paracellular barrier of the human intestinal epithelium is one of the reasons for the relative absence of food-borne human botulism caused by type C BoNT."*

### **2. EFFECT OF DRYING PROCESSES AND CURING TIME OF CHITOSAN-LYSINE SEMI-IPN BEADS ON CHLORPHENIRAMINE MALEATE DELIVERY:**

*"The rate of drug release from freeze-dried beads is much faster than that from the oven-dried and air-dried beads."*

### **3. WILLIAM T. CLOSE, WHO HELPED CONTROL EBOLA EPIDEMIC IN CONGO, DIES AT 84:**

*"Dr William T Close, an American surgeon who in 1976 played an important role in controlling the 1st epidemic of the deadly Ebola hemorrhagic fever in central Africa and preventing it from spreading, died on [15 Jan 2009] at his home in Big Piney, Wyoming. He was 84. The cause was a heart attack, said his daughter Glenn, the actress."*

### **4. SCANS FOR BUGS JUST FOR SHOW:**

*"Using temperature scanners in airports to try to block entry of sick travellers during a disease outbreak is unlikely to work, a report by French public health officials suggests."*

### **5. DISTINCT SENSORY PATHWAYS IN VIBRIO CHOLERAEL TOR AND CLASSICAL BIOTYPES MODULATE CYCLIC DIMERIC GMP LEVELS TO CONTROL BIOFILM**

**FORMATION:** *"Thus, different pandemic strains of V. cholerae modulate c-di-GMP levels and control biofilm formation in response to distinct sensory pathways."*

### **6. DENGUE VIRUS TYPE 2 INFECTIONS OF AEADES AEGYPTI ARE MODULATED BY THE MOSQUITO'S RNA INTERFERENCE PATHWAY:**

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double-stranded RNA (dsRNA), which occurs in the cytoplasm as a result of positive-sense RNA virus infection, leading to production of small interfering RNAs (siRNAs)."

**7. NEW SOFTWARE SPEEDS ENZYME DESIGN:** "The program -- a set of computer rules known as the algorithm "K\*" (pronounced K Star)-- is able to sort through all the possible shapes and changes of a key enzyme that produces a natural antibiotic called gramicidin S, said Bruce Donald, Duke's William and Sue Gross Professor of Computer Science and Biochemistry."

## CB Daily Report

### Chem-Bio News

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#### **DISRUPTION OF THE EPITHELIAL BARRIER BY BOTULINUM HAEMAGGLUTININ (HA) PROTEINS - DIFFERENCES IN CELL TROPISM AND THE MECHANISM OF ACTION BETWEEN HA PROTEINS OF TYPES A OR B, AND HA PROTEINS OF TYPE C**

TB & Outbreaks Week

February 17, 2009

"Orally ingested botulinum neurotoxin (BoNT) causes food-borne botulism, but BoNT must pass through the gut lining and enter the bloodstream. We have previously found that type B haemagglutinin (HA) proteins in the toxin complex play an important role in the intestinal absorption of BoNT by disrupting the paracellular barrier of the intestinal epithelium, and therefore facilitating the transepithelial delivery of BoNT."

"Here, we show that type A HA proteins in the toxin complex have a similar disruptive activity and a greater potency than type B HA proteins in the human intestinal epithelial cell lines Caco-2 and T84 and in the canine kidney epithelial cell line MDCK I. In contrast, type C HA proteins in the toxin complex (up to 300 nM) have no detectable effect on the paracellular barrier in these human cell lines, but do show a barrier-disrupting activity and potent cytotoxicity in MDCK I."

"These findings may indicate that type A and B HA proteins contribute to the development of food-borne botulism, at least in humans, by facilitating the intestinal transepithelial delivery of BoNTs, and that the relative inability of type C HA proteins to disrupt the paracellular barrier of the human intestinal epithelium is one of the reasons for the relative absence of food-borne human botulism caused by type C BoNT."

The full article can be found at: (Y. Jin, et. al., "Disruption of the epithelial barrier by botulinum haemagglutinin (HA) proteins - differences in cell tropism and the mechanism of action between HA proteins of types A or B, and HA proteins of type C". Microbiology, 2009; 155(Pt 1): 35-45). Link not available.

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## **EFFECT OF DRYING PROCESSES AND CURING TIME OF CHITOSAN-LYSINE SEMI-IPN BEADS ON CHLORPHENIRAMINE MALEATE DELIVERY**

Drug Law Weekly  
February 17, 2009

"Beads of semi-interpenetrating polymer network (semi-IPN) have been synthesized from chitosan and lysine with varying amounts of glutaraldehyde solution used as a cross-linker. The cross-linked beads are dried by different drying processes such as air-drying, oven-drying and freeze-drying," investigators in India report (see also Life Sciences).

"These semi-IPNs are characterized under a scanning electron microscope (SEM). Swelling studies of these beads are carried out in different pH (2.0 and 7.4) solutions. The effect of concentration of cross-linking agent and curing period on the swelling as well as on the drug release is analysed. The results indicate that the size of matrix depend on the curing time of beads, concentration of glutaraldehyde and technique of drying. The freeze-dried beads exhibit a relatively higher percentage of swelling in the range of 66-89% as compared to oven-dried beads (53-74%) and air-dried beads (39-61%). The drug loaded beads which are cured for different time intervals followed by drying are tested for in-vitro release of chlorpheniramine maleate (CPM) drug."

"The rate of drug release from freeze-dried beads is much faster than that from the oven-dried and air-dried beads."

The full article can be found at: (K. Kumari, et. al., "Effect of drying processes and curing time of chitosan-lysine semi-IPN beads on chlorpheniramine maleate delivery". Journal of Microencapsulation, 2009;26(1):54-62).

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## **WILLIAM T. CLOSE, WHO HELPED CONTROL EBOLA EPIDEMIC IN CONGO, DIES AT 84**

NY Times  
February 10, 2009

"Dr William T Close, an American surgeon who in 1976 played an important role in controlling the 1st epidemic of the deadly Ebola hemorrhagic fever in central Africa and preventing it from spreading, died on [15 Jan 2009] at his home in Big Piney, Wyoming. He was 84. The cause was a heart attack, said his daughter Glenn, the actress.

Dr Close was both personal physician to president Mobutu Sese Seko of Zaire, now known as Congo, and chief doctor of the army at the time of the epidemic, which caused widespread panic in the country, 3 doctors involved in helping to control it recalled in interviews. His connections, organizational ability, and medical expertise were essential in halting it, they said."

The full article can be found at: [http://www.nytimes.com/2009/02/08/health/08close.html?\\_r=1](http://www.nytimes.com/2009/02/08/health/08close.html?_r=1)

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## **SCANS FOR BUGS JUST FOR SHOW**

The Ottawa Sun

February 16, 2009

"Using temperature scanners in airports to try to block entry of sick travellers during a disease outbreak is unlikely to work, a report by French public health officials suggests.

Their analysis is based on a review of studies on temperature screening efforts such as those instituted during the 2003 SARS outbreak where 44 people died in Canada. The authors say the programs might be of limited use early in a flu pandemic, when governments might be tempted to order screening of incoming travellers to try to delay introduction of the illness within their borders.

The authors, from France's Health Watch Institute, said the available scientific data suggests there is little benefit to airport temperature screening when the incidence of disease is low, as it was with SARS -- and as it would be expected to be in the very early days of a pandemic."

The full article can be found at: <http://www.ottawasun.com/News/National/2009/02/16/pf-8405361.html>

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## **DISTINCT SENSORY PATHWAYS IN VIBRIO CHOLERAE EL TOR AND CLASSICAL BIOTYPES MODULATE CYCLIC DIMERIC GMP LEVELS TO CONTROL BIOFILM FORMATION**

Biotech Week

February 11, 2009

"Quorum sensing (QS), or cell-cell communication in bacteria, is achieved through the production and subsequent response to the accumulation of extracellular signal molecules called autoinducers (AIs). To identify AI-regulated target genes in *Vibrio cholerae*(EI) Tor (*V. cholerae*(EI)), the strain responsible for the current cholera pandemic, luciferase expression was assayed in an AI(-) strain carrying a random lux transcriptional reporter library in the presence and absence of exogenously added AIs."

"Twenty-three genes were identified and shown to require the QS transcription factor, HapR, for their regulation. Several of the QS-dependent target genes, annotated as encoding hypothetical proteins, in fact encode HD-GYP proteins, phosphodiesterases that degrade the intracellular second messenger cyclic dimeric GMP (c-di-GMP), which is important for

controlling biofilm formation. Indeed, overexpression of a representative QS-activated HD-GYP protein in *V. cholerae*(EI) reduced the intracellular concentration of c-di-GMP, which in turn decreased exopolysaccharide production and biofilm formation. The *V. cholerae* classical biotype (*V. cholerae*(CI)), which caused previous cholera pandemics and is HapR(-), controls c-di-GMP levels and biofilm formation by the VieA signaling pathway. We show that the VieA pathway is dispensable for biofilm formation in *V. cholerae*(EI) but that restoring HapR in *V. cholerae*(CI) reestablishes QS-dependent repression of exopolysaccharide production."

"Thus, different pandemic strains of *V. cholerae* modulate c-di-GMP levels and control biofilm formation in response to distinct sensory pathways."

The full article can be found at: (B.K. Hammer, et. al., "Distinct Sensory Pathways in *Vibrio cholerae* EI Tor and Classical Biotypes Modulate Cyclic Dimeric GMP Levels To Control Biofilm Formation". *Journal of Bacteriology*, 2009;191(1):169-177). Link not available.

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## **DENGUE VIRUS TYPE 2 INFECTIONS OF AEADES AEGYPTI ARE MODULATED BY THE MOSQUITO'S RNA INTERFERENCE PATHWAY**

By Irma Sánchez-Vargas, Jaclyn C. Scott, B. Katherine Poole-Smith, Alexander W. E. Franz, Valérie Barbosa-Solomieu, Jeffrey Wilusz, Ken E. Olson, Carol D. Blair

PLoS Pathogens

February 16, 2009

"A number of studies have shown that both innate and adaptive immune defense mechanisms greatly influence the course of human dengue virus (DENV) infections, but little is known about the innate immune response of the mosquito vector *Aedes aegypti* to arbovirus infection. We present evidence here that a major component of the mosquito innate immune response, RNA interference (RNAi), is an important modulator of mosquito infections. The RNAi response is triggered by double-stranded RNA (dsRNA), which occurs in the cytoplasm as a result of positive-sense RNA virus infection, leading to production of small interfering RNAs (siRNAs). These siRNAs are instrumental in degradation of viral mRNA with sequence homology to the dsRNA trigger and thereby inhibition of virus replication. We show that although dengue virus type 2 (DENV2) infection of *Ae. aegypti* cultured cells and oral infection of adult mosquitoes generated dsRNA and production of DENV2-specific siRNAs, virus replication and release of infectious virus persisted, suggesting viral circumvention of RNAi. We also show that DENV2 does not completely evade RNAi, since impairing the pathway by silencing expression of *dcr2*, *r2d2*, or *ago2*, genes encoding important sensor and effector proteins in the RNAi pathway, increased virus replication in the vector and decreased the extrinsic incubation period required for virus transmission. Our findings indicate a major role for RNAi as a determinant of DENV transmission by *Ae. aegypti*."

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000299;jsessionid=B2DA797F204604C4E4B3B3E62C4CCA6E>

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## NEW SOFTWARE SPEEDS ENZYME DESIGN

News-Medical.net

February 17, 2009

"A Duke University-led team has brought powerful software to the never-ending arms race between antibiotics and germs.

Working together, computer scientists and biochemists have developed and laboratory-tested a computer program that can show experimentalists how to change the machinery that bacteria use to make natural antibiotics.

The program -- a set of computer rules known as the algorithm "K\*" (pronounced K Star)-- is able to sort through all the possible shapes and changes of a key enzyme that produces a natural antibiotic called gramicidin S, said Bruce Donald, Duke's William and Sue Gross Professor of Computer Science and Biochemistry. The new technique might pave the way toward more automated redesign of old drugs to foil drug-resistance in germs.

"It really excites us that we can redesign enzymes on a computer, make them in the laboratory and have them work as planned," said Donald, who leads the extended research effort and is corresponding author of a new report to be published online the week of Feb 16 in the research journal Proceedings of the National Academy of Sciences ( PNAS )."

"The algorithm includes a "dead-end elimination" feature that can run through all possible chemical interactions and flexible molecular architectures to weed out scenarios that cannot work. Calculating just one redesign might take up to a week in the 230-processor computer cluster housed in Donald's lab, he said.

After all the calculations were completed, biochemist Cheng-Yu Chen, another of Donald's graduate students, confirmed the algorithm's predicted designs in Donald's biochemical wet lab, using bacteria to synthesize some "quite big and tricky proteins," Donald said. "It was not at all trivial to do that, and testing the functions of each protein was even trickier."

The full article can be found at: <http://www.news-medical.net/?id=45925>

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**Steve Tesko:** [Steve.Tesko@anser.org](mailto:Steve.Tesko@anser.org)

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