

18 June 2009

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## **Chem-Bio News – S&T Edition**

**1. INVENTORY UNCOVERS 9,200 MORE PATHOGENS:** *“An inventory of potentially deadly pathogens at Fort Detrick's infectious disease laboratory found more than 9,000 vials that had not been accounted for, Army officials said yesterday, raising concerns that officials wouldn't know whether dangerous toxins were missing.”*

**2. DRUGS AGAINST NOROVIRUSES ONE STEP CLOSER:** *“The virus that causes winter vomiting disease invades cells by attaching to particular sugar molecules on the surface of the cells.”*

**3. MOLECULAR EVOLUTIONARY CONSEQUENCES OF NICHE RESTRICTION IN FRANCISELLA TULARENSIS, A FACULTATIVE INTRACELLULAR PATHOGEN:** *“Our observations suggest that despite an average nucleotide identity of >97%, *F. tularensis* and *F. novicida* have evolved as two distinct population lineages, the former characterized by clonal structure with weak purifying selection, the latter by more frequent recombination and strong purifying selection. *F. tularensis* and *F. novicida* could be considered the same bacterial species, given their high similarity, but based on the evolutionary analyses described in this work we propose retaining separate species names.”*

**4. BACTERIA ARE FIRST SENSED BY CELLS LINING BLOOD VESSELS, NOT IMMUNE CELLS:** *“Paul Kubes and colleagues, at the University of Calgary, Canada, have provided evidence in mice to refute the paradigm that the initial phase of the immune response to infection with Gram-negative bacteria (the recruitment of immune cells known as neutrophils to the site of infection) is triggered following immune sentinel-cell recognition of the bacterial molecule LPS via the protein TLR4.”*

**5. CDC REJECTS REPORT OF MUTANT H1N1 STRAIN IN BRAZIL:** *“The Centers for Disease Control and Prevention (CDC) and other experts have rejected a report that a new strain of the novel H1N1 influenza virus has been identified in a Brazilian patient.”*

**6. ALUMINIUM SULFATE AND SODIUM ALUMINATE BUFFER SOLUTIONS FOR THE DESTRUCTION OF PHOSPHORUS BASED CHEMICAL WARFARE AGENTS:** *“In the case of VX, no phosphorus containing hydrolysis products including the very toxic S-[2-(diisopropyl-amino)-ethyl] methylphosphonothiolate (EA-2192) are detected in the*

hydrolysate."

## **7. THE MARBURG VIRUS 3' NONCODING REGION STRUCTURALLY AND**

**FUNCTIONALLY DIFFERS FROM THAT OF EBOLA VIRUS:** *"Our data suggest that differences in the structure of the genomic replication promoters might account for the different transcription strategies of Marburg and Ebola viruses."*

## **8. ACTIVITY-BASED PROTEIN PROFILING REVEALS BROAD REACTIVITY OF THE**

**NERVE AGENT SARIN:** *"It is also shown that the newly developed probe 3 might find its way into the development of alternative, less laborious purification protocols for human butyrylcholinesterase, a potent bioscavenger currently under clinical investigation as a prophylactic/therapeutic for nerve agent intoxications."*

# CB Daily Report

## Chem-Bio News

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### **INVENTORY UNCOVERS 9,200 MORE PATHOGENS**

By Nelson Hernandez

The Washington Post

June 18, 2009

"An inventory of potentially deadly pathogens at Fort Detrick's infectious disease laboratory found more than 9,000 vials that had not been accounted for, Army officials said yesterday, raising concerns that officials wouldn't know whether dangerous toxins were missing.

After four months of searching about 335 freezers and refrigerators at the U.S. Army Medical Research Institute of Infectious Diseases in Frederick, investigators found 9,220 samples that hadn't been included in a database of about 66,000 items listed as of February, said Col. Mark Kortepeter, the institute's deputy commander.

The vials contained some dangerous pathogens, among them the Ebola virus, anthrax bacteria and botulinum toxin, and less lethal agents such as Venezuelan equine encephalitis virus and the bacterium that causes tularemia. Most of them, forgotten inside freezer drawers, hadn't been used in years or even decades. Officials said some serum samples from hemorrhagic fever patients dated to the Korean War.

Kortepeter likened the inventory to cleaning out the attic and said he knew of no plans for an investigation into how the vials had been left out of the database. "The vast majority of these samples were working stock that were accumulated over decades," he said, left there by scientists who had retired or left the institute.

The full article can be found at: <http://www.washingtonpost.com/wp-dyn/content/story/2009/06/17/ST2009061703604.html>

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## **DRUGS AGAINST NOROVIRUSES ONE STEP CLOSER**

Infection Control Today Magazine

June 10, 2009

"The virus that causes winter vomiting disease invades cells by attaching to particular sugar molecules on the surface of the cells. This is the conclusion of a thesis presented at the Sahlgrenska Academy at the University of Gothenburg in Sweden. This result may be an important step in the development of a drug against the regular hospital-based epidemics caused by the virus."

"Our results suggest that the sugar chains that have sialic acid are important for infection by the virus, but this must be confirmed. If it is true, it would be possible to develop a drug that blocks the access of the virus to the sugar molecule. One thing that we must investigate first, however, is whether there are other target molecules that the virus can use to enter the cell. These may be the starting point for even more effective drugs," says Rydell."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/noroviruses-drugs-winter-vomiting-disease.html>

**ANALYST NOTE:** Norovirus, also known as "Norwalk virus" or "Norwalk-like virus" is an extremely infectious and debilitating gastrointestinal disease that normally makes the news in a cruise ship context. While tainted food is usually the primary mode of transmission, contaminated surfaces especially those in the vicinity of the sick also pose significant hazards.

Although not considered a CBW agent and despite its holiday association, its military implications should not be overlooked. Early in the war, in 2002, there were a number of outbreaks at Allied bases in Afghanistan. These outbreaks not only affected troops but also, due to its high communicability, medical personnel as well. The outbreak at Bagram Airfield among British forces, for example, resulted in approximately five deaths and the aeromedical evacuation back to the UK of other service members. Thus, the disease can assume significance from a force health protection standpoint.

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## **MOLECULAR EVOLUTIONARY CONSEQUENCES OF NICHE RESTRICTION IN FRANCISELLA TULARENSIS, A FACULTATIVE INTRACELLULAR PATHOGEN**

By Pär Larsson, Daniel Elfsmark, Kerstin Svensson, Per Wikström, Mats Forsman, Thomas Brettin, Paul Keim, Anders Johansson

PLoS Pathogens

June 12, 2009

"Abstract

*Francisella tularensis* is a potent mammalian pathogen well adapted to intracellular habitats, whereas *F. novicida* and *F. philomiragia* are less virulent in mammals and appear to have less specialized lifecycles. We explored adaptations within the genus that may be linked to increased host association, as follows. First, we determined the genome sequence of *F. tularensis* subsp. *mediasiatica*, the only subspecies that had not been previously sequenced. This genome, and those of 12 other *F. tularensis* isolates, were then compared to the genomes of *F. novicida* (three isolates) and *F. philomiragia* (one isolate). Signs of homologous recombination were found in ~19.2% of *F. novicida* and *F. philomiragia* genes, but none among *F. tularensis* genomes. In addition, random insertions of insertion sequence elements appear to have provided raw materials for secondary adaptive mutations in *F. tularensis*, e.g. for duplication of the *Francisella* Pathogenicity Island and multiplication of a putative glycosyl transferase gene. Further, the five major genetic branches of *F. tularensis* seem to have converged along independent routes towards a common gene set via independent losses of gene functions. Our observations suggest that despite an average nucleotide identity of >97%, *F. tularensis* and *F. novicida* have evolved as two distinct population lineages, the former characterized by clonal structure with weak purifying selection, the latter by more frequent recombination and strong purifying selection. *F. tularensis* and *F. novicida* could be considered the same bacterial species, given their high similarity, but based on the evolutionary analyses described in this work we propose retaining separate species names.

## Author Summary

The intracellular bacterium *Francisella tularensis* causes the disease tularemia in various mammals, including humans, and is highly infectious (so infectious that highly virulent forms of the pathogen were developed as biological aerosol weapons during the Cold War). Little is known about where *F. tularensis* resides in nature and how it evolved but, intriguingly, closely related *Francisella* bacteria are less dangerous. Therefore, we have explored the evolutionary events that shaped *F. tularensis* by analyzing 17 *Francisella* genome sequences. Its evolution appears to have involved many losses of metabolic functions and random mutations, with little exchange of genetic material among *F. tularensis* strains. Furthermore, increased host association appears to have irreversibly separated *F. tularensis* populations from other populations of *Francisella* bacteria. This study provides new information on the processes whereby relatively harmless *Francisella* bacteria evolved into aggressive invaders of mammalian cells. Our findings support previous proposals that identification of distinct population lineages provides meaningful species boundaries among bacteria.

The full article can be found at: <http://www.plospathogens.org/article/info%3Adoi%2F10.1371%2Fjournal.ppat.1000472;jsessionid=555A1B69DFF0746D5AF356AF4B57FDDB>

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## **BACTERIA ARE FIRST SENSED BY CELLS LINING BLOOD VESSELS, NOT IMMUNE CELLS**

Medical News Today  
June 17, 2009

"Paul Kubes and colleagues, at the University of Calgary, Canada, have provided evidence in mice to refute the paradigm that the initial phase of the immune response to infection with Gram-negative bacteria (the recruitment of immune cells known as neutrophils to the site of infection) is triggered following immune sentinel-cell recognition of the bacterial molecule LPS via the protein TLR4. Rather, the researchers found that LPS recognition by TLR4 on the cells that line blood vessels (endothelial cells) is the crucial event that initiates neutrophil recruitment and bacterial clearance in mice."

The full article can be found at: <http://www.medicalnewstoday.com/articles/154152.php>

The original article can be found at: <https://www.the-jci.org/article.php?id=36411>

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## **CDC REJECTS REPORT OF MUTANT H1N1 STRAIN IN BRAZIL**

By Robert Roos

CIDRAP News (Center for Infectious Disease Research & Policy – University of Minnesota)

June 17, 2009

"The Centers for Disease Control and Prevention (CDC) and other experts have rejected a report that a new strain of the novel H1N1 influenza virus has been identified in a Brazilian patient.

Scientists at Adolfo Lutz Bacteriological Institute in Sao Paulo said they found the new strain in a local patient who has recovered, according to a Medical News Today (MNT) report, which was based on information from the institute and Agence France-Presse.

The story said the scientists found "a number of discrete alterations in nucleotide and amino acid sequences" in the isolate's hemagglutinin (HA) gene. They also analyzed the matrix-protein (MP) gene and found no changes.

But CDC spokesman Joe Quimby in Atlanta discounted the report that the isolate is a new strain. "Our scientists have no knowledge of a new strain of novel A H1N1 influenza," he said.

"It's the same strain, it's not a new strain," Quimby added.

The Brazilian researchers labeled the isolate A/Sao/PAOLO/1454/H1N1. They deposited the nucleotide sequences for the HA and MP genes in GenBank under accession numbers GQ247724 and GQ250156, the MNT report said.

Vincent Racaniello, PhD, a Columbia University virologist who writes Virology Blog, also dismissed the claim of a new strain.

"Comparison of the amino acid sequence of the HA protein of A/Sao Paulo/1454/H1N1 with those of other isolates of the current pandemic strain reveals no alterations in the HA protein which would allow the virus to infect new hosts," Racaniello wrote in his blog. "The

HA protein of this virus and many other 2009 H1N1 isolates are identical. The few amino acid differences with other 2009 H1N1 isolates are in areas that would not be expected to influence antigenicity or host range."

The MNT report said the virus came from a 26-year-old Sao Paulo man who fell ill shortly after returning from a trip to Mexico. He was hospitalized on Apr 24 and later recovered."

The full article can be found at: <http://www.cidrap.umn.edu/cidrap/content/influenza/swineflu/news/jun1709flustrain.html>

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## **ALUMINIUM SULFATE AND SODIUM ALUMINATE BUFFER SOLUTIONS FOR THE DESTRUCTION OF PHOSPHORUS BASED CHEMICAL WARFARE AGENTS**

News of Science

June 21, 2009

"Nerve agents VX and GB (sarin) are sequestered and removed by aluminium sulfate and sodium aluminate mixtures adjusted to pH 4 in solution. The products of hydrolysis are removed with the alum floc below NMR detection limits over time depending and the amount of aluminium molar excess relative to agent."

"Half-lives for GB decomposition are 3.1 h and 1.1 h, respectively, for a 120 and a 1200 molar excess. For VX, the half-lives are 8.5 d and 2.9 d for a 240 and a 5000 molar aluminium excess. In the case of GB, fluorine is sequestered as the hexafluoroaluminate ion."

"In the case of VX, no phosphorus containing hydrolysis products including the very toxic S-[2-(diisopropyl-amino)-ethyl] methylphosphonothiolate (EA-2192) are detected in the hydrolysate."

The full article can be found at: (D.J. Williams, et. al., "Aluminium sulfate and sodium aluminate buffer solutions for the destruction of phosphorus based chemical warfare agents". New Journal of Chemistry, 2009; 33(5): 1006-1009). Link not available.

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## **THE MARBURG VIRUS 3' NONCODING REGION STRUCTURALLY AND FUNCTIONALLY DIFFERS FROM THAT OF EBOLA VIRUS**

Blood Weekly

June 18, 2009

"We have previously shown that the first transcription start signal (TSS) of Zaire Ebola virus ( ZEBOV) is involved in formation of an RNA secondary structure regulating VP30-dependent transcription activation. Interestingly, transcription of Marburg virus ( MARV) minigenomes occurs independently of VP30."

"In this study, we analyzed the structure of the MARV 3' noncoding region and its influence on VP30 necessity. Secondary structure formation of the TSS of the first gene was experimentally determined and showed substantial differences from the structure formed by the ZEBOV TSS. Chimeric MARV minigenomes mimicking the ZEBOV-specific RNA secondary structure were neither transcribed nor replicated. Mapping of the MARV genomic replication promoter revealed that the region homologous to the sequence involved in formation of the regulatory ZEBOV RNA structure is part of the MARV promoter. The MARV promoter is contained within the first 70 nucleotides of the genome and consists of two elements separated by a spacer region, comprising the TSS of the first gene. Mutations within the spacer abolished transcription activity and led to increased replication, indicating competitive transcription and replication initiation. The second promoter element is located within the nontranslated region of the first gene and consists of a stretch of three UN5 hexamers. Recombinant full-length MARV clones, in which the three conserved U residues were substituted, could not be rescued, underlining the importance of the UN5 hexamers for replication activity."

"Our data suggest that differences in the structure of the genomic replication promoters might account for the different transcription strategies of Marburg and Ebola viruses."

The full article can be found at: (S. Enterlein, et. al., "The Marburg Virus 3' Noncoding Region Structurally and Functionally Differs from That of Ebola Virus". *Journal of Virology*, 2009;83(9):4508-4519). [Link not available.](#)

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## **ACTIVITY-BASED PROTEIN PROFILING REVEALS BROAD REACTIVITY OF THE NERVE AGENT SARIN**

Life Science Weekly  
June 23, 2009

"Elucidation of noncholinesterase protein targets of organophosphates, and nerve agents in particular, may reveal additional mechanisms for their high toxicity as well as clues for novel therapeutic approaches toward intoxications with these agents."

"Within this framework, we here describe the synthesis of the activity-based probe 3, which contains a phosphonofluoridate moiety, a P-Me moiety, and a biotinylated O-alkyl group, and its use in activity-based protein profiling with two relevant biological samples, that is, rhesus monkey liver and cultured human A549 lung cells. In this way, we have unearthed eight serine hydrolases (fatty acid synthase, acylpeptide hydrolase, dipeptidyl peptidase 9, prolol oligopeptidase, carboxylesterase, long-chain acyl coenzyme A thioesterase, PAF acetylhydrolase 1b, and esterase D/S-formyl glutathione hydrolase) as targets that are modified by the nerve agent sarin."

"It is also shown that the newly developed probe 3 might find its way into the development of alternative, less laborious purification protocols for human butyrylcholinesterase, a potent bioscavenger currently under clinical investigation as a prophylactic/therapeutic for nerve

agent intoxications."

The full article can be found at: (A.W. Tuin, et. al., "Activity-Based Protein Profiling Reveals Broad Reactivity of the Nerve Agent Sarin". *Chemical Research in Toxicology*, 2009; 22 (4):683-689). Link not available.

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