

9 December 2008

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## **Chem-Bio News – Pandemic Influenza Edition #39**

**1. [JA] EDITORIAL: NEW-STRAIN INFLUENZA:** *"The government's basic stance on combating an outbreak of potentially disastrous influenza caused by a new strain of virus is about to undergo a major overhaul."*

**2. INFLUENZA VACCINE SUPPLY: BUILDING LONG-TERM SUSTAINABILITY:** *"As a result, vaccination strategies utilizing pre-pandemic vaccines, combined with vaccines matched to a pandemic Strain once available, offer for the first time a viable approach for mitigating an influenza pandemic."*

**3. ARMED FORCES INSTITUTE OF PATHOLOGY TO CONDUCT NANOVIRICIDES ANIMAL STUDIES AGAINST BIRD FLU:** *"We are very excited to study the effectiveness of nanoviricides against the most current strains of H5N1 in animal models," said lead AFIP scientist Dr. Mina Izadjoo."*

**4. ROLE OF VIRAL HEMAGGLUTININ GLYCOSYLATION IN ANTI-INFLUENZA ACTIVITIES OF RECOMBINANT SURFACTANT PROTEIN D:** *"Pandemic and avian strains appear to lack susceptibility to SP-D and this could be a contributory factor to their virulence."*

**5. CD8 T CELLS UTILIZE TRAIL TO CONTROL INFLUENZA VIRUS INFECTION:** *"Collectively, our results suggest that TRAIL is an important component of immunity to influenza infections and that TRAIL deficiency decreases CD8(+) T cell-mediated cytotoxicity, leading to more severe influenza infections."*

**6. AN IMPROVED EMBRYONATED CHICKEN EGG MODEL FOR THE EVALUATION OF ANTIVIRAL DRUGS AGAINST INFLUENZA A VIRUS:** *"Ribavirin treatment showed significant antiviral activity against IVA1 and IVA3 in this model, suggesting that the improved model would be useful for evaluating the anti-influenza virus activity of potential inhibitors."*

**7. A NEW AND RAPID GENOTYPIC ASSAY FOR THE DETECTION OF NEURAMINIDASE INHIBITOR RESISTANT INFLUENZA A VIRUSES OF SUBTYPE H1N1, H3N2, AND H5N1:** *"The detection limit of minor virus variants within the viral quasispecies amounts to 10%."*

# **CB Daily Report**

## ***Chem-Bio News***

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### **[JA] EDITORIAL: NEW-STRAIN INFLUENZA**

Asahi.com

December 3, 2008

"The government's basic stance on combating an outbreak of potentially disastrous influenza caused by a new strain of virus is about to undergo a major overhaul.

A panel representing the various ministries concerned completed drafting revisions to the government's existing action plan last week. The revised plan, which will be finalized early next year after input from the public, acknowledges that an overseas outbreak of a new-strain flu pandemic would inevitably reach Japan. Thus, the focus of the revisions is to prevent an outbreak from developing into a pandemic.

The current action plan is centered on trying to keep flu out of the nation and isolating infected people quickly. Facilities for such purposes have been set up, but the plan is still lacking in proactive measures to deal with a pandemic."

The full article can be found at: <http://www.asahi.com/english/Herald-asahi/TKY200812030063.html>

[Return to Top](#)

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### **INFLUENZA VACCINE SUPPLY: BUILDING LONG-TERM SUSTAINABILITY**

Biotech Week

December 10, 2008

"As a result, vaccination strategies utilizing pre-pandemic vaccines, combined with vaccines matched to a pandemic Strain once available, offer for the first time a viable approach for mitigating an influenza pandemic."

The full article can be found at: (N. Hehme, et. al., "Influenza vaccine supply: Building long-term sustainability". Vaccine, 2008;26(Suppl. 4):D23-D26).

[Return to Top](#)

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### **ARMED FORCES INSTITUTE OF PATHOLOGY TO CONDUCT NANOVIRICIDES ANIMAL STUDIES AGAINST BIRD FLU**

PR-inside.com

December 1, 2008

"NanoViricides, Inc., announced today that they have executed a Cooperative Research and

Development Agreement (CRADA) with the Armed Forces Institute of Pathology (AFIP). This joint R&D effort will enable AFIP scientists to test the effectiveness of several NanoViricides, Inc. anti-viral nanomedicines against deadly bird flu viruses (H5N1) at their facilities.

"We are very excited to study the effectiveness of nanoviricides against the most current strains of H5N1 in animal models," said lead AFIP scientist Dr. Mina Izadjoo.'

The full article can be found at: <http://www.pr-inside.com/armed-forces-institute-of-pathology-to-r943206.htm>

[Return to Top](#)

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## **ROLE OF VIRAL HEMAGGLUTININ GLYCOSYLATION IN ANTI-INFLUENZA ACTIVITIES OF RECOMBINANT SURFACTANT PROTEIN D**

Drug Week

December 12, 2008

"Surfactant protein D (SP-D) plays an important role in innate defense against influenza A viruses (IAVs) and other pathogens. We tested antiviral activities of recombinant human SP-D against a panel of IAV strains that vary in glycosylation sites on their hemagglutinin (HA)," scientists in the United States report.

"For these experiments a recombinant version of human SP-D of the Met11, Ala160 genotype was used after it was characterized biochemically and structurally. Oligosaccharides at amino acid 165 on the HA in the H3N2 subtype and 104 in the H1N1 subtype are absent in collectin-resistant strains developed in vitro and are important for mediating antiviral activity of SP-D; however, other glycans on the HA of these viral subtypes also are involved in inhibition by SP-D. H3N2 strains obtained shortly after introduction into the human population were largely resistant to SP-D, despite having the glycan at 165. H3N2 strains have become steadily more sensitive to SP-D over time in the human population, in association with addition of other glycans to the head region of the HA. In contrast, H1N1 strains were most sensitive in the 1970s 1980s and more recent strains have become less sensitive, despite retaining the glycan at 104. Two H5N1 strains were also resistant to inhibition by SP-D. By comparing sites of glycan attachment on sensitive vs. resistant strains, specific glycan sites on the head domain of the HA are implicated as important for inhibition by SP-D. Molecular modeling of the glycan attachment sites on HA and the carbohydrate recognition domain of SPD are consistent with these observations. Inhibition by SP-D correlates with presence of several glycan attachment sites on the HA."

"Pandemic and avian strains appear to lack susceptibility to SP-D and this could be a contributory factor to their virulence."

The full article can be found at: (K.L. Hartshorn, et. al., "Role of viral hemagglutinin glycosylation in anti-influenza activities of recombinant surfactant protein D". Respiratory Research, 2008; 9():65). Link not available.

[Return to Top](#)

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## **CD8 T CELLS UTILIZE TRAIL TO CONTROL INFLUENZA VIRUS INFECTION**

Immunotherapy Weekly

December 10, 2008

"Elimination of influenza virus-infected cells during primary influenza virus infections is thought to be mediated by CD8(+) T cells through perforin- and FasL-mediated mechanisms. However, recent studies suggest that CD8(+) T cells can also utilize TRAIL to kill virally infected cells."

"Therefore, we herein examined the importance of TRAIL to influenza-specific CD8(+) T cell immunity and to the control of influenza virus infections. Our results show that TRAIL deficiency increases influenza-associated morbidity and influenza virus titers, and that these changes in disease severity are coupled to decreased influenza-specific CD8(+) T cell cytotoxicity in TRAIL(-/-) mice, a decrease that occurs despite equivalent numbers of pulmonary influenza-specific CD8(+) T cells. Furthermore, TRAIL expression occurs selectively on influenza-specific CD8(+) T cells, and high TRAIL receptor (DR5) expression occurs selectively on influenza virus-infected pulmonary epithelial cells. Finally, we show that adoptive transfer of TRAIL(+ / +) but not TRAIL(- / -) CD8+ effector T cells alters the mortality associated with lethal dose influenza virus infections."

"Collectively, our results suggest that TRAIL is an important component of immunity to influenza infections and that TRAIL deficiency decreases CD8(+) T cell-mediated cytotoxicity, leading to more severe influenza infections."

The full article can be found at: (E.L.Brincks, et. al., "CD8 T cells utilize TRAIL to control influenza virus infection". *Journal of Immunology*, 2008; 181(7):4918-4925). Link not available.

[Return to Top](#)

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## **AN IMPROVED EMBRYONATED CHICKEN EGG MODEL FOR THE EVALUATION OF ANTIVIRAL DRUGS AGAINST INFLUENZA A VIRUS**

Drug Week

December 12, 2008

"In this study, an improved embryonated chicken egg model for evaluating antiviral activity against Influenza A virus was developed. In the model, the influenza A virus was injected into the allantoic cavity and ribavirin was injected into the albumen of the egg. The levels of influenza A virus in the allantoic fluid was titrated by the hemagglutination test after incubation for 72 h at 35.5 degrees C and 12 h at 4 degrees C. Ribavirin treatment at a dose of 25 mg/kg to 100 mg/kg decreased significantly the hemagglutination titers both of Influenza virus A/FM1, H1N1 (IVA1) ( $p < 0.01$ ) and influenza virus A/Wuhan/359/95, H3N2 (IVA3) ( $p < 0.01$ ). In a time-dependent drug addition assay, significant efficacy of ribavirin

against both IVA1 and IVA3 was observed when the drug was administered before and shortly after viral inoculation ( $p < 0.01$  or  $p < 0.05$ )."

"Ribavirin treatment showed significant antiviral activity against IVA1 and IVA3 in this model, suggesting that the improved model would be useful for evaluating the anti-influenza virus activity of potential inhibitors."

The full article can be found at: (J.X. Wang, et. al., "An improved embryonated chicken egg model for the evaluation of antiviral drugs against influenza A virus". Journal of Virological Methods, 2008; 153(2):218-22). Link not available.

[Return to Top](#)

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## **A NEW AND RAPID GENOTYPIC ASSAY FOR THE DETECTION OF NEURAMINIDASE INHIBITOR RESISTANT INFLUENZA A VIRUSES OF SUBTYPE H1N1, H3N2, AND H5N1**

Anti-Infectives Week

December 8, 2008

"Several amino acid substitutions, each as a consequence of one single nucleotide mutation, are known to confer resistance to NAI. An increase of NAI-resistant viruses appears to be likely as a result of a wider application of NAI for treatment and prophylaxis of seasonal influenza infections. Monitoring the occurrence and spread of resistant viruses is an important task. Therefore, RT-PCR assays were developed with subsequent pyrosequencing analysis (PSQ-PCR). These assays allow a rapid, high-throughput and cost-effective screening of subtype A/H1N1, A/H3N2, and A/H5N1 viruses. Various specimens such as respiratory swabs, allantoic fluid, or cell-propagated viruses can be used and results are available within hours. Several A/H1N1, A/H3N2, and A/H5N1 viruses isolated from human and avian specimens were tested to evaluate the method. Positive controls encoding resistance-associated mutations were created using site-directed mutagenesis. The results obtained with these controls showed that the assay can discriminate clearly the wild-type virus from a mutant virus."

"The detection limit of minor virus variants within the viral quasispecies amounts to 10%."

The full article can be found at: (S. Duwe, et. al., "A new and rapid genotypic assay for the detection of neuraminidase inhibitor resistant influenza A viruses of subtype H1N1, H3N2, and H5N1". Journal of Virological Methods, 2008; 153(2): 134-41). Link not available.

[Return to Top](#)

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