

5 August 2008

This supplement has been prepared to present scientific and technical news items that may be of more interest to technical personnel at RDT&E activities and the labs, or the medics rather than the broader readership of the basic CB Daily. Due to the nature of the material, the articles, if available online, are usually only available through subscription services thus making specific links generally unavailable. Thus, usually only the bibliographic citation is available for use by an activity's technical library.

Chem-Bio News – Pandemic Influenza Supplement #22

1. OSELTAMIVIR (TAMIFLU) INCREASES DOPAMINE LEVELS IN THE RAT MEDIAL PREFRONTAL CORTEX [mPFC]:

"These findings suggest that oseltamivir increased dopamine release in the mPFC; further, they suggest that the increase in dopamine during oseltamivir treatment may have caused abnormal behaviors in young patients."

2. LEXINGTON INSURANCE COMPANY INTRODUCES PANDEMIC RX:

"Endorsement to Lexington's Commercial Property Insurance Covers Financial Risks Faced by Healthcare Providers in the Event of a Pandemic Flu."

3. A SIMPLE SCREENING ASSAY FOR RECEPTOR SWITCHING OF AVIAN INFLUENZA VIRUSES:

"We have developed a simple screening assay capable of detecting avian influenza viruses that have switched their receptor-binding preference."

4. ANTI-INFLUENZA VIRUS ACTIVITY OF CHAENOMELES SINENSIS:

*"High molecular weight polyphenols in the fruits of *C. sinensis* neutralizes influenza virus by inhibiting hemagglutination activity and by suppressing NS2 protein synthesis."*

5. DIFFERENTIAL RESPONSE OF RESPIRATORY DENDRITIC CELL [RDC] SUBSETS

TO INFLUENZA VIRUS INFECTION: *"Our results indicate that RDC are targets of influenza virus infection and that distinct RDC subsets differ in their susceptibilities and responses to infection."*

6. INFLUENZA A VIRUS NEURAMINIDASE LIMITS VIRAL SUPERINFECTION:

"Our data indicate that NA alone among viral proteins limits influenza A virus superinfection."

7. HSP90 INHIBITORS REDUCE INFLUENZA VIRUS REPLICATION IN CELL

CULTURE: *"Hsp90 inhibitors may represent a new class of antiviral compounds against influenza viruses."*

CB Daily Report

Chem-Bio News

OSELTAMIVIR (TAMIFLU) INCREASES DOPAMINE LEVELS IN THE RAT MEDIAL PREFRONTAL CORTEX

Hospital Business Week

August 10, 2008

"However, neuropsychiatric behaviors including jumping and falling from balconies by young patients being treated by oseltamivir have been reported from Japan; this has led to warnings against its prescribing by many authorities. The pharmacological mechanism of the neuropsychiatric effects of oseltamivir remains unclear. Many studies reported that changes in neurotransmission and abnormal behaviors are closely related. We investigated the changes in dopamine and serotonin metabolism after systemic administration of oseltamivir in the medial prefrontal cortex (mPFC) of rats by using microdialysis. After systemic administration of oseltamivir (25mg/kg or 100mg/kg; intraperitoneally (i.p.)), extracellular dopamine in the mPFC was significantly increased as compared to the control values; 3,4-dihydroxyphenylacetic acid and homovanillic acid, the metabolites of dopamine, had also increased significantly. Serotonin was unchanged after the administration of oseltamivir. These findings suggest that oseltamivir increased dopamine release in the mPFC; further, they suggest that the increase in dopamine during oseltamivir treatment may have caused abnormal behaviors in young patients."

The full article can be found at: Neuroscience Letters (T. Yoshino, et. al., "Oseltamivir (Tamiflu) increases dopamine levels in the rat medial prefrontal cortex". Neuroscience Letters, 2008; 438(1): 67-9). Link not available.

ANALYST NOTE: Subscribers may wish to refer to the CB Daily – Pandemic Influenza Supplement #19 on 15 July 2008 for an opposing article.

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LEXINGTON INSURANCE COMPANY INTRODUCES PANDEMIC RX

Yahoo Finance

July 31, 2008

"Lexington Insurance Company, a unit of AIG Commercial Insurance, today announced Pandemic Rx, an endorsement to Lexington's commercial property policy for acute care medical facilities to cover business income loss and extra expenses incurred during a declared pandemic influenza public health emergency (as defined in the policy)."

"Pandemic Rx protects insureds against loss of income and extra expenses incurred as a result of a pandemic flu public health emergency and associated crisis management costs. The endorsement will pay, subject to the limits purchased, for up to six months of income loss during a pandemic flu event, resulting from increased expenses required to render care or reduced reimbursement due to a shift in case mix. Coverage also applies to certain extra expenses incurred due to a pandemic flu event, including procurement of vaccines, antibiotics, anti-viral medications or other similar medication; consumable resources such as hand hygiene supplies, surgical and procedure masks, gowns, gloves, food, water; and central lines kits and durable resources such as ventilators, respiratory care equipment, beds, and intravenous pumps. Pandemic Rx also provides up to \$100,000 for crisis response/public relations costs or to retain a service provider with expertise in applying for reimbursement of eligible expenses from state and federal agencies."

The full article can be found at: <http://biz.yahoo.com/bw/080731/20080731005903.html?v=1>

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A SIMPLE SCREENING ASSAY FOR RECEPTOR SWITCHING OF AVIAN INFLUENZA VIRUSES

Hospital Business Week
August 10, 2008

"Adaptation of the receptor-binding preference from alpha 2,3- to alpha 2,6-linked sialic acid is an essential step for an avian influenza virus to transmit efficiently in human population and become a pandemic virus. The currently available assays for receptor-binding preference are complex and not widely available."

"A simple high-throughput screening assay will facilitate early detection of a potential pandemic virus, which is crucial for the prevention and control of the possible pandemic. We wanted to develop a simple assay to differentiate influenza viruses with alpha 2,3- or alpha 2,6-linked receptor-binding preference. The assay employs a specific sialidase (from *Salmonella thyphimurium*) that can eliminate alpha 2,3-linked sialic acid from red blood cells. A reduction of hemagglutination titer indicates alpha 2,3-linked receptor preference in this assay. Using a panel of H5N1 avian influenza isolates and HUM human influenza isolates, as well as mutated H5 reverse genetics virus, the assay could accurately differentiate the viruses according to their receptor-binding preference. Furthermore, the assay was sufficiently sensitive to detect a minor variant with alpha 2,6-linkage-specificity in a background of alpha 2,3-linkage-specific virus."

"We have developed a simple screening assay capable of detecting avian influenza viruses that have switched their receptor-binding preference."

The full article can be found at: *Journal of Clinical Virology* (O. Suptawiwat, et. al., "A simple screening assay for receptor switching of avian influenza viruses". *Journal of Clinical Virology*, 2008; 42(2): 186-189). Link not available.

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ANTI-INFLUENZA VIRUS ACTIVITY OF CHAENOMELES SINENSIS

Drug Week
August 8, 2008

"This investigation evaluated anti-influenza virus activity of 50% ethanol extract of the fruit of *Chaenomeles sinensis* K(OEHNE), which is widely used as a traditional Chinese medicine to treat throat diseases. Type A and B influenza viruses were treated with the extract at various concentrations for 1h at room temperature; then the plaque titers of the treated

viruses were determined."

"The neutralizing component in the extract was partially purified using HP20 column chromatography. Treatment with the extract at concentrations greater than 5mg/ml reduced the plaque titers of the both viruses to less than 10% of those of untreated viruses. The treatment inhibited viral hemagglutination activity, too. When the 50mg/ml extract was added to the culture medium after inoculation of the virus, viral NS2 protein synthesis was selectively inhibited and progeny virus was not detected in the infected cell medium. Partial purification showed that the neutralizing component consisted of high molecular weight polyphenols."

"High molecular weight polyphenols in the fruits of *C. sinensis* neutralizes influenza virus by inhibiting hemagglutination activity and by suppressing NS2 protein synthesis."

The full article can be found at: Journal of Ethnopharmacology (R. Sawai, et. al., "Anti-influenza virus activity of *Chaenomeles sinensis*". Journal of Ethnopharmacology, 2008; 118 (1):108-12). Link not available.

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DIFFERENTIAL RESPONSE OF RESPIRATORY DENDRITIC CELL [RDC] SUBSETS TO INFLUENZA VIRUS INFECTION

Biotech Week
August 6, 2008

"In this report, we examined the susceptibilities of isolated murine RDC to influenza virus infection in vitro and the effect of the multiplicity of infection (MOI) on costimulatory ligand upregulation and inflammatory cytokine/chemokine production after infection."

"We found that the efficiency of influenza virus infection of RDC increased with increasing MOIs. Furthermore, distinct subpopulations of RDC differed in their susceptibilities to influenza virus infection and in the magnitude/tempo of costimulatory ligand expression. Additional characterization of the CD11c-positive (CD11c(+)) RDC revealed that the identifiable subsets of RDC differed in susceptibility to infection, with CD11c(+) CD103(+) DC exhibiting the greatest susceptibility, CD11c(+) CD11b(hi) DC exhibiting intermediate susceptibility, and CD11c(+) B220(+) plasmacytoid DC (pDC) exhibiting the least susceptibility to infection. A companion analysis of the in vivo susceptibilities of these RDC subsets to influenza virus revealed a corresponding infection pattern. The three RDC subsets displayed different patterns of cytokine/chemokine production in response to influenza virus infection in vitro: pDC were the predominant producers of most cytokines examined, while CD103(+) DC and CD11b(hi) DC produced elevated levels of the murine chemokine CXCL1 (KC), interleukin 12p40, and RANTES in response to influenza virus infection."

"Our results indicate that RDC are targets of influenza virus infection and that distinct RDC subsets differ in their susceptibilities and responses to infection."

The full article can be found at: Journal of Virology (T.J. Braciale, et. al., "Differential response of respiratory dendritic cell subsets to influenza virus infection". Journal of Virology, 2008; 82(10):4908-4919). Link not available.

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INFLUENZA A VIRUS NEURAMINIDASE LIMITS VIRAL SUPERINFECTION

Health & Medicine Week

August 4, 2008

"Here, we show that cellular expression of influenza A virus neuraminidase (NA), but not hemagglutinin (HA) or the M2 proton pump, inhibits entry of HA-pseudotyped retroviruses. Cells infected with H1N1 or H3N2 influenza A virus were similarly refractory to HA-mediated infection and to superinfection with a second influenza A virus. Both HA-mediated entry and viral superinfection were rescued by the neuraminidase inhibitors oseltamivir carboxylate and zanamivir. These inhibitors also prevented the removal of alpha-2,3- and alpha-2,6-linked sialic acid observed in cells expressing NA or infected with influenza A viruses."

"Our data indicate that NA alone among viral proteins limits influenza A virus superinfection."

The full article can be found at: Journal of Virology (I.C. Huang, et. al., "Influenza A virus neuraminidase limits viral superinfection". Journal of Virology, 2008; 82(10):4834-4843). Link not available.

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HSP90 INHIBITORS REDUCE INFLUENZA VIRUS REPLICATION IN CELL CULTURE

Health Risk Factor Week

August 5, 2008

"The viral RNA polymerase complex of influenza A virus consists of three subunits PB1, PB2 and PA. Recently, the cellular chaperone Hsp90 was shown to play a role in nuclear import and assembly of the trimeric polymerase complex by binding to PB1 and PB2."

"Here we show that Hsp90 inhibitors, geldanamycin or its derivative 17-AAG, delay the growth of influenza virus in cell culture resulting in a 1-2 log reduction in viral titer early in infection. We suggest that this is caused by the reduced half-life of PB1 and PB2 and inhibition of nuclear import of PB1 and PA which lead to reduction in viral RNP assembly."

"Hsp90 inhibitors may represent a new class of antiviral compounds against influenza viruses."

The full article can be found at: Virology (G. Chase, et. al., "Hsp90 inhibitors reduce influenza virus replication in cell culture". Virology, 2008; 377(2):431-9). Link not available.

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