

10 March 2009

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.

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Chem-Bio News– Pandemic Influenza Edition #51

1. SUSTAINING FOCUS ON THE NATION'S PLANNING AND PREPAREDNESS

EFFORTS: *"However, national priorities are shifting as a pandemic has yet to occur, and other national issues have become more immediate and pressing."*

2. MELBOURNE RESEARCHERS SAY THEY ARE CLOSER TO DEVELOPING A HUMAN

VACCINE FOR AVIAN INFLUENZA, COMMONLY KNOWN AS BIRD FLU: *"A Melbourne University research team has found boosting T-cell immunity would help rid people's bodies of the virus by finding and destroying infected cells."*

3. EVOLUTION OF DRUG RESISTANCE IN MULTIPLE DISTINCT LINEAGES OF H5N1

AVIAN INFLUENZA: *"Together, our phylogenetic methods, molecular evolutionary analyses, and geographic visualization provide a framework for analysis of globally distributed genomic data that can be used to monitor the evolution of drug resistance."*

4. STUDY: FLUID BUILDUP IN LUNGS IS PART OF THE DAMAGE DONE BY THE FLU:

"But new research suggests that the influenza virus can tip the balance toward too much fluid in the lungs, interfering with the supply of oxygen to the rest of the body."

5. INHIBITION OF INFLUENZA A VIRUS REPLICATION BY SHORT DOUBLE-

STRANDED OLIGODEOXYNUCLEOTIDES [dsODNs]: *"Thus, dsODNs may be developed as an additional class of nucleic acids for the inhibition of influenza virus replication."*

6. MICE LACKING THE ISG15 E1 ENZYME UBE1L DEMONSTRATE INCREASED

SUSCEPTIBILITY TO BOTH MOUSE-ADAPTED AND NON-MOUSE-ADAPTED INFLUENZA B VIRUS INFECTION: *"Thus, the conjugation of ISG15 to target proteins within stromal cells is critical to its activity against influenza virus."*

CB Daily Report

Chem-Bio News

SUSTAINING FOCUS ON THE NATION'S PLANNING AND PREPAREDNESS EFFORTS

United States Government Accountability Office

February 2009 (but released March 6, 2009)

"What GAO Found

Leadership roles and responsibilities need to be clarified and tested, and coordination mechanisms could be better utilized. Shared leadership roles and responsibilities between the Departments of Health and Human Services (HHS) and Homeland Security (DHS) and other entities are evolving, and will require further testing and exercising before they are well understood. Although there are mechanisms in place to facilitate coordination between federal, state, and local governments and the private sector to prepare for an influenza pandemic, these could be more fully utilized.

Efforts are underway to improve the surveillance and detection of pandemic-related threats, but targeting assistance to countries at the greatest risk has been based on incomplete information. Steps have been taken to improve international disease surveillance and detection efforts. However, information gaps limit the capacity for comprehensive comparisons of risk levels by country.

Pandemic planning and exercising has occurred, but planning gaps remain. The United States and other countries, as well as states and localities, have developed influenza pandemic plans. Yet, additional planning needs still exist. For example, the national strategy and implementation plan omitted some key elements, and HHS found many major gaps in states' pandemic plans.

Further actions are needed to address the capacity to respond to and recover from an influenza pandemic. An outbreak will require additional capacity in many areas, including the procurement of additional patient treatment space and the acquisition and distribution of medical and other critical supplies, such as antivirals and vaccines for an influenza pandemic.

Federal agencies have provided considerable guidance and pandemic-related information, but could augment their efforts. Federal agencies, such as HHS and DHS, have shared information in a number of ways, such as through Web sites and guidance, but state and local governments and private sector representatives would welcome additional information on vaccine distribution and other topics.

Performance monitoring and accountability for pandemic preparedness needs strengthening. Although certain performance measures have been established in the National Pandemic Implementation Plan to prepare for an influenza pandemic, these measures are not always linked to results. Further, the plan does not contain information on the financial resources needed to implement it.

GAO has made 23 recommendations in its reports—13 of these have been implemented and 10 remain outstanding. Continued leadership focus on pandemic preparedness remains vital, as the threat has not diminished."

The full article can be found at: <http://www.gao.gov/new.items/d09334.pdf>

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MELBOURNE RESEARCHERS SAY THEY ARE CLOSER TO DEVELOPING A HUMAN VACCINE FOR AVIAN INFLUENZA, COMMONLY KNOWN AS BIRD FLU

ABC Melbourne

March 3, 2009

"A Melbourne University research team has found boosting T-cell immunity would help rid people's bodies of the virus by finding and destroying infected cells.

In a report published today, the researchers say scientists should concentrate on modifying vaccines to boost T-cell levels in order to effectively fight flu strains.

Associate Professor Stephen Turner says a compound known to increase immunity could be added to existing flu vaccines in Australia."

The full article can be found at: <http://www.abc.net.au/news/stories/2009/03/03/2505881.htm?site=melbourne>

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EVOLUTION OF DRUG RESISTANCE IN MULTIPLE DISTINCT LINEAGES OF H5N1 AVIAN INFLUENZA

Drug Week

March 13, 2009

"However, it is known that multiple lineages of H5N1 are already resistant to another class of drugs, adamantane derivatives, and a few lineages are resistant to oseltamivir. What is less well understood is the evolutionary history of the mutations that confer drug resistance in the H5N1 population. In order to address this gap, we conducted phylogenetic analyses of 676 genomic sequences of H5N1 and used the resulting hypotheses as a basis for asking 3 molecular evolutionary questions: (1) Have drug-resistant genotypes arisen in distinct lineages of H5N1 through point mutation or through reassortment? (2) Is there evidence for positive selection on the codons that lead to drug resistance? (3) Is there evidence for covariation between positions in the genome that confer resistance to drugs and other positions, unrelated to drug resistance, that may be under selection for other phenotypes? We also examine how drug-resistant lineages proliferate across the landscape by projecting or phylogenetic analysis onto a virtual globe. Our results for H5N1 show that in most cases drug resistance has arisen by independent point mutations rather than reassortment or covariation. Furthermore, we found that some codons that mediate resistance to adamantane derivatives are under positive selection, but did not find positive selection on codons that mediate resistance to oseltamivir."

"Together, our phylogenetic methods, molecular evolutionary analyses, and geographic visualization provide a framework for analysis of globally distributed genomic data that can be used to monitor the evolution of drug resistance."

The full article can be found at: (A.W. Hill, et. al., "Evolution of drug resistance in multiple distinct lineages of H5N1 avian influenza". *Infection, Genetics and Evolution*, 2009;9(2): 169-78). Link not available.

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STUDY: FLUID BUILDUP IN LUNGS IS PART OF THE DAMAGE DONE BY THE FLU

Ohio State University Press Release

Undated

"In a fight against respiratory infections, the body typically produces a little fluid to help the lungs generate a productive cough. But new research suggests that the influenza virus can tip the balance toward too much fluid in the lungs, interfering with the supply of oxygen to the rest of the body.

An immune response ultimately is needed to eliminate the virus, but this research suggests that it's not the presence of the virus alone that does all the harm to a sick person. Instead, the fluid buildup deep inside the lungs might help kill a person infected with the flu, according to the research, which was conducted in mice.

"My take is that when people die of these illnesses, they're dying because they can't breathe," said Ian Davis, assistant professor of veterinary biosciences at Ohio State University and senior author of the study. "If the lungs aren't working well, then it doesn't matter whether a week from now you can make an immune response and clear the virus if you can't survive that long because you just can't get oxygen."

"The research is published in a recent issue of the *American Journal of Respiratory and Critical Care Medicine*."

"The scientists used an unusual method to observe the fluid clearance. After being infected, the mice were anesthetized and put on ventilators. The researchers then placed fluid containing protein into one lung of each mouse and tested the fluid 30 minutes later. The amount of protein left in the remaining fluid allowed the investigators to determine whether the infected lung was clearing fluid adequately.

Davis said the study showed that when the flu virus infects cells in the lung, those cells release small molecules, or nucleotides, that are part of the energy-producing and replication machinery of the cell. Those nucleotides then bind to receptors of other cells in a series of events that ultimately shut down the transport of sodium from airways to the blood. All of these interactions take place in the epithelium, the lining of the airways in the lungs."

The full article can be found at: <http://researchnews.osu.edu/archive/lungfluid.htm>

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INHIBITION OF INFLUENZA A VIRUS REPLICATION BY SHORT DOUBLE-STRANDED OLIGODEOXYNUCLEOTIDES [dsODNs]

Virus Weekly

March 10, 2009

Influenza A virus causes prevalent respiratory tract infections in humans. Small interfering RNA (siRNA) and antisense oligonucleotides (asODNs) have been used previously for silencing the RNA genome of influenza virus."

"Here, we explored the use of partially double-stranded oligodeoxynucleotides (dsODNs) to suppress the production of influenza A virus in cell cultures and animal models. We were able to inhibit influenza A virus replication in cultured human lung cells as well as in the lungs of infected C57BL/6 mice by treatment with dsODN 3-h post-infection. In about 20% of the cases (15/77) the titer was reduced by 10- to 100-fold and in 10% up to 1,000-fold. The antiviral effects of dsODNs were dose-dependent, sequence-dependent and comparable to those of its antisense and siRNA analogues."

"Thus, dsODNs may be developed as an additional class of nucleic acids for the inhibition of influenza virus replication."

The full article can be found at: (T. Kwok, et. al., "Inhibition of influenza A virus replication by short double-stranded oligodeoxynucleotides". Archives of Virology, 2009; 154(1): 109-114). Link not available.

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MICE LACKING THE ISG15 E1 ENZYME UBE1L DEMONSTRATE INCREASED SUSCEPTIBILITY TO BOTH MOUSE-ADAPTED AND NON-MOUSE-ADAPTED INFLUENZA B VIRUS INFECTION

Drug Week

March 6, 2009

"ISG15 functions as a critical antiviral molecule against influenza virus, with infection inducing both the conjugation of ISG15 to target proteins and production of free ISG15. Here, we report that mice lacking the ISG15 E1 enzyme UBE1L fail to form ISG15 conjugates."

"Both UBE1L(-/-) and ISG15(-/-) mice display increased susceptibility to influenza B virus infection, including non-mouse-adapted strains. Finally, we demonstrate that ISG15 controls influenza B virus infection through its action within radioresistant stromal cells and not bone marrow-derived cells."

"Thus, the conjugation of ISG15 to target proteins within stromal cells is critical to its activity against influenza virus."

The full article can be found at: (C. Lai, et. al., "Mice Lacking the ISG15 E1 Enzyme UbE1L Demonstrate Increased Susceptibility to both Mouse-Adapted and Non-Mouse-Adapted Influenza B Virus Infection". Journal of Virology, 2009;83(2):1147-1151). Link not available.

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