

15 September 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 #78

1. SEVERE RESPIRATORY DISEASE CONCURRENT WITH THE CIRCULATION OF H1N1

INFLUENZA: *"During the early phase of this influenza pandemic, there was a sudden increase in the rate of severe pneumonia and a shift in the age distribution of patients with such illness, which was reminiscent of past pandemics and suggested relative protection for persons who were exposed to H1N1 strains during childhood before the 1957 pandemic."*

2. SEEGENE'S NEW SEEPLEX® FLUA ACE SUBTYPING TEST ACCURATELY DIFFERENTIATES

PANDEMIC NOVEL INFLUENZA A: *"The Seeplex FluA ACE subtyping test is based on the company's novel DPO™-based Multiplex RT-PCR technology, and is in accordance with the World Health Organization (WHO) guidelines for diagnosis of new virus strains."*

3. IDENTIFICATION AND CHARACTERISATION OF A NOVEL ANTI-VIRAL PEPTIDE AGAINST

AVIAN INFLUENZA VIRUS H9N2: *"Our findings show that we have successfully identified a novel antiviral peptide against avian influenza virus H9N2 which act by binding with the hemagglutination protein of the virus."*

4. SCIENTISTS WARN OVER SWINE FLU VIRUS POTENCY: *"Swine flu can infect cells deeper in the lungs than seasonal flu, making people who catch it more likely to develop serious complications, research suggests."*

5. ATIVS: ANALYTICAL TOOL FOR INFLUENZA VIRUS SURVEILLANCE:

"To meet this need, we have developed a web server, ATIVS (Analytical Tool for Influenza Virus Surveillance), for analyzing serological data of all influenza viruses and hemagglutinin sequence data of human influenza A/H3N2 viruses so as to generate antigenic maps for influenza surveillance and vaccine strain selection."

6. INCORPORATION OF INFLUENZA A VIRUS GENOME SEGMENTS DOES NOT ABSOLUTELY

REQUIRE WILD-TYPE SEQUENCES: *"To understand further the signalling requirements for genome packaging, this study performed linker-scanning mutagenesis in the latter region and found that nt 27-35 made an appreciable contribution to the efficient incorporation of the NS segment."*

7. A QUANTITATIVE STRATEGY TO DETECT CHANGES IN ACCESSIBILITY OF PROTEIN

REGIONS TO CHEMICAL MODIFICATION ON HETERODIMERIZATION: *"The Q-POP assay should be a generally applicable approach and may detect novel functional sites suitable for targeting by drugs.."*

8. LOCATION OF ANTIGENIC SITES RECOGNIZED BY MONOCLONAL ANTIBODIES IN THE

INFLUENZA A VIRUS NUCLEOPROTEIN MOLECULE: *"When mapped in a 3D X-ray model of NP, the four antigenically relevant amino acid positions were found to be located in separate physical sites of the NP molecule.."*

9. SWINE FLU VACCINE STUDY SAYS ONE SHOT MAY BE ENOUGH:

"A new study from an Australian vaccine manufacturer suggests that just one shot of vaccine may produce a robust enough response in the immune system to protect people from being infected by the 2009 pandemic A/H1N1 swine flu virus."

10. NEW FLU DRUG MAY RESIST MUTATIONS: RESEARCHERS:

"A new type of experimental flu drug that stops the virus from infecting cells appears to stop it from mutating into drug-resistant forms, researchers reported on Sunday."

CB Daily Report

Chem-Bio News

SEVERE RESPIRATORY DISEASE CONCURRENT WITH THE CIRCULATION OF H1N1 INFLUENZA

Medical Letter on the CDC & FDA

September 13, 2009

"In the spring of 2009, an outbreak of severe pneumonia was reported in conjunction with the concurrent isolation of a novel swine-origin influenza A (H1N1) virus (S-OIV), widely known as swine flu, in Mexico. Influenza A (H1N1) subtype viruses have rarely predominated since the 1957 pandemic."

"The analysis of epidemic pneumonia in the absence of routine diagnostic tests can provide information about risk factors for severe disease from this virus and prospects for its control. From March 24 to April 29, 2009, a total of 2155 cases of severe pneumonia, involving 821 hospitalizations and 100 deaths, were reported to the Mexican Ministry of Health. During this period, of the 8817 nasopharyngeal specimens that were submitted to the National Epidemiological Reference Laboratory, 2582 were positive for S-OIV. We compared the age distribution of patients who were reported to have severe pneumonia with that during recent influenza epidemics to document an age shift in rates of death and illness. During the study period, 87% of deaths and 71% of cases of severe pneumonia involved patients between the ages of 5 and 59 years, as compared with average rates of 17% and 32%, respectively, in that age group during the referent periods. Features of this epidemic were similar to those of past influenza pandemics in that circulation of the new influenza virus was associated with an off-season wave of disease affecting a younger population. During the early phase of this influenza pandemic, there was a sudden increase in the rate of severe pneumonia and a shift in the age distribution of patients with such illness, which was reminiscent of past pandemics and suggested relative protection for persons who were exposed to H1N1 strains during childhood before the 1957 pandemic."

The full article can be found at: (G. Chowell, et. al., "Severe Respiratory Disease Concurrent with the Circulation of H1N1 Influenza". New U.K. Journal of Medicine, 2009;361(7):674-679). Link not available.

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SEEGENE'S NEW SEEPLEX® FLUA ACE SUBTYPING TEST ACCURATELY DIFFERENTIATES PANDEMIC NOVEL INFLUENZA A

PR-Canada.net

September 01, 2009

"Seegene today released a new influenza A sub-type screening test, Seeplex® FluA ACE Subtyping, that enables simultaneous detection of pandemic novel influenza A (H1N1), seasonal human influenza A H1, seasonal human influenza A H3 and avian influenza A H5 in a single reaction. The Seeplex FluA ACE subtyping test is based on the company's novel DPO™-based Multiplex RT-PCR technology, and is in accordance with the World Health Organization (WHO) guidelines for diagnosis of new virus strains.

Currently screening kits available to national health organizations bracing for an expected influenza pandemic this autumn test separately for one viral strain, some using the immunochromatography method, commonly known as 'rapid test.' This testing methodology is not being adopted as a standard method due to its low accuracy.

Furthermore, the U.S. CDC provides a real-time PCR protocol with primers and probe sequence information, but this approach can confirm only pandemic novel H1N1 type by conducting four different

single-targeted PCR tests of each patient sample.

In contrast, Seegene's new FluA subtyping test enables simultaneous detection of 4 major influenza A subtypes, including current pandemic novel H1N1, at a price point that makes it a viable tool for thorough mass screenings of a population."

The full article can be found at: http://pr-canada.net/index.php?option=com_content&task=view&id=121700&Itemid=65

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IDENTIFICATION AND CHARACTERISATION OF A NOVEL ANTI-VIRAL PEPTIDE AGAINST AVIAN INFLUENZA VIRUS H9N2

Drug Week

September 4, 2009

"The virus has two immunologically important glycoproteins, hemagglutinin (HA), neuraminidase (NA), and one ion channel protein M2 which are the most important targets for drug discovery, on its surface. In order to identify a peptide-based virus inhibitor against any of these surface proteins, a disulfide constrained heptapeptide phage display library was biopanned against purified AIV sub-type H9N2 virus particles. After four rounds of panning, four different fusion phages were identified. Among the four, the phage displaying the peptide NDFRSKT possessed good anti-viral properties in vitro and in ovo. Further, this peptide inhibited the hemagglutination activity of the viruses but showed very little and no effect on neuraminidase and hemolytic activities respectively. The phage-antibody competition assay proved that the peptide competed with anti-influenza H9N2 antibodies for the binding sites. Based on yeast two-hybrid assay, we observed that the peptide inhibited the viral replication by interacting with the HA protein and this observation was further confirmed by coimmunoprecipitation. Our findings show that we have successfully identified a novel antiviral peptide against avian influenza virus H9N2 which act by binding with the hemagglutination protein of the virus."

The full article can be found at: (M. Rajik, et. al., "Identification and characterisation of a novel anti-viral peptide against avian influenza virus H9N2". *Virology Journal*, 2009;6():74). Link not available.

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SCIENTISTS WARN OVER SWINE FLU VIRUS POTENCY

By David Rose

TimesOnline.co.uk

September 10, 2009

"Swine flu can infect cells deeper in the lungs than seasonal flu, making people who catch it more likely to develop serious complications, research suggests.

The study published in the journal *Nature Biotechnology* provides the first laboratory corroboration of reports from front-line doctors.

Seasonal strains of flu attach themselves almost exclusively to cells found in the nose, throat and upper airway, producing some of influenza's signature symptoms: a runny nose, scratchy throat and a dry cough. But the research shows that swine flu — by sticking to a greater range of receptors — can also breach cells deep in the lungs."

The full article can be found at:

http://www.timesonline.co.uk/tol/news/uk/health/Swine_flu/article6828915.ece

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ATIVS: ANALYTICAL TOOL FOR INFLUENZA VIRUS SURVEILLANCE

Biotech Law Weekly
September 18, 2009

"The WHO Global Influenza Surveillance Network has routinely performed genetic and antigenic analyses of human influenza viruses to monitor influenza activity. Although these analyses provide supporting data for the selection of vaccine strains, it seems desirable to have user-friendly tools to visualize the antigenic evolution of influenza viruses for the purpose of surveillance."

"To meet this need, we have developed a web server, ATIVS (Analytical Tool for Influenza Virus Surveillance), for analyzing serological data of all influenza viruses and hemagglutinin sequence data of human influenza A/H3N2 viruses so as to generate antigenic maps for influenza surveillance and vaccine strain selection. Functionalities are described and examples are provided to illustrate its usefulness and performance."

"The ATIVS web server is available at [http://influenza.nhri.org.tw/ATIVS/..](http://influenza.nhri.org.tw/ATIVS/)"

The full article can be found at: (Y.C. Liao, et. al., "ATIVS: analytical tool for influenza virus surveillance". Nucleic Acids Research, 2009;37(Suppl. S):W643-W646). Link not available.
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INCORPORATION OF INFLUENZA A VIRUS GENOME SEGMENTS DOES NOT ABSOLUTELY REQUIRE WILD-TYPE SEQUENCES

Biotech Law Weekly
September 18, 2009

"The efficient incorporation of influenza virus genome segments into virions is mediated by cis-acting regions at both ends of the viral RNAs. It was shown previously that nt 16-26 at the 3' end of the non-structural (NS) viral RNA of influenza A virus are important for efficient virion incorporation and that nt 27-56 also contribute to this process."

"To understand further the signalling requirements for genome packaging, this study performed linker-scanning mutagenesis in the latter region and found that nt 27-35 made an appreciable contribution to the efficient incorporation of the NS segment. An NS vRNA library was then generated composed of an RNA population with randomized nucleotides at positions 16-35 such that the virus could select the sequences it required for virion incorporation. The sequences selected differed from the wild-type sequence and no conserved nucleotides were selected."

"The ability of non-wild-type sequences to function in this manner indicates that the incorporation of influenza A virus genome segments does not absolutely require specific sequences.."

The full article can be found at: (K. Fujii, et. al., "Incorporation of influenza A virus genome segments does not absolutely require wild-type sequences". Journal of General Virology, 2009;90(Part 7):1734-1740). Link not available.
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A QUANTITATIVE STRATEGY TO DETECT CHANGES IN ACCESSIBILITY OF PROTEIN REGIONS TO CHEMICAL MODIFICATION ON HETERODIMERIZATION

Biotech Law Weekly
September 18, 2009

"We describe a method for studying quantitative changes in accessibility of surface lysine residues of the PB1 subunit of the influenza RNA polymerase as a result of association with the PA subunit to form a PB1-PA heterodimer. Our method combines two established methods: (i) the chemical modification of surface lysine residues of native proteins by N-hydroxysuccinimidobiotin (NHS-biotin) and (ii) the stable

isotope labeling of amino acids in cell culture (SILAC) followed by tryptic digestion and mass spectrometry."

"By linking the chemical modification with the SILAC methodology for the first time, we obtain quantitative data on chemical modification allowing subtle changes in accessibility to be described. Five regions in the PB1 monomer showed altered reactivity to NHS-biotin when compared with the [PB1-PA] heterodimer. Mutational analysis of residues in two such regions-at K265 and K481 of PB1, which were about three-and twofold, respectively, less accessible to biotinylation in the PB1-PA heterodimer compared with the PB1 monomer, demonstrated that both K265 and K481 were crucial for polymerase function. This novel assay of quantitative profiling of biotinylation patterns (Q-POP assay) highlights likely conformational changes at important functional sites, as observed here for PB1, and may provide information on protein-protein interaction interfaces."

"The Q-POP assay should be a generally applicable approach and may detect novel functional sites suitable for targeting by drugs.."

The full article can be found at: (M. Dreger, et. al., "A quantitative strategy to detect changes in accessibility of protein regions to chemical modification on heterodimerization". Protein Science, 2009;18(7):1448-1458). Link not available.

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LOCATION OF ANTIGENIC SITES RECOGNIZED BY MONOCLONAL ANTIBODIES IN THE INFLUENZA A VIRUS NUCLEOPROTEIN MOLECULE

Biotech Law Weekly
September 18, 2009

"The locations of amino acid positions relevant to antigenic variation in the nucleoprotein (NP) of influenza virus are not conclusively known. We analysed the antigenic structure of influenza A virus NP by introducing site-specific mutations at amino acid positions presumed to be relevant for the differentiation of strain differences by anti-NP monoclonal antibodies."

"Mutant proteins were expressed in a prokaryotic; system and analysed by performing ELISA with monoclonal antibodies. Four amino acid residues were found to determine four different antibody-binding sites."

"When mapped in a 3D X-ray model of NP, the four antigenically relevant amino acid positions were found to be located in separate physical sites of the NP molecule.."

The full article can be found at: (N.L. Varich, et. al., "Location of antigenic sites recognized by monoclonal antibodies in the influenza A virus nucleoprotein molecule". Journal of General Virology, 2009;90(Part 7):1730-1733). Link not available.

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SWINE FLU VACCINE STUDY SAYS ONE SHOT MAY BE ENOUGH

Medical News Today
September 11, 2009

"A new study from an Australian vaccine manufacturer suggests that just one shot of vaccine may produce a robust enough response in the immune system to protect people from being infected by the 2009 pandemic A/H1N1 swine flu virus. The news is expected to be welcomed by health authorities because it means more people can be protected more quickly as vaccine becomes available.

The study is the work of researchers at CSL Ltd, a global vaccine and plasma protein company with headquarters in Australia. In order to make the data available as quickly as possible, a preliminary version of the study is published in today's issue of the New England Journal of Medicine, which also has

reports of other swine flu vaccine studies.

The researchers report the early results of an ongoing trial that is evaluating a two-dose vaccine in healthy adults between the ages of 18 and 64 at a single site in Australia.

The findings suggest that one dose was enough to produce an immunogenic response, with "mild to moderate" side effects."

The full article can be found at: <http://www.medicalnewstoday.com/articles/163633.php>

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NEW FLU DRUG MAY RESIST MUTATIONS: RESEARCHERS

By Maggie Fox

Reuters

September 13, 2009

"A new type of experimental flu drug that stops the virus from infecting cells appears to stop it from mutating into drug-resistant forms, researchers reported on Sunday.

Tests in mice and in lab dishes show that NexBio Inc.'s drug Fludase can stop the seasonal influenza virus from infecting cells and can fight strains of virus that have evolved resistance to Tamiflu, Roche AG's popular influenza drug, the company said.

"Extensive, prolonged nonclinical influenza studies have not shown the development of any meaningful resistance," the company said in a statement released at the Interscience Conference on Antimicrobial Agents and Chemotherapy in San Francisco.

Privately held NexBio Inc. said tests showed that Fludase, also known as DAS181, worked against the new H1N1 swine flu virus too."

The full article can be found at: <http://www.reuters.com/article/healthNews/idUSTRE58C1SP20090913>

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