

30 March 2010

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 #105

1. AN M2E-BASED MULTIPLE ANTIGENIC PEPTIDE VACCINE PROTECTS MICE FROM LETHAL CHALLENGE WITH DIVERGENT H5N1 INFLUENZA VIRUSES:

"These results suggest that M2e-MAP presenting M2e of H5N1 virus has a great potential to be developed into an effective subunit vaccine for the prevention of infection by a broad spectrum of HPAI H5N1 viruses."

2. SAFETY, IMMUNOGENICITY, AND EFFICACY OF A COLD-ADAPTED A/ANN ARBOR/6/60 (H2N2) VACCINE IN MICE AND FERRETS:

"The AA ca vaccine is safe, immunogenic, and efficacious against homologous and heterologous challenge in mice and ferrets, supporting the evaluation of this vaccine in clinical trials."

3. GAS-PERMEABLE ETHYLENE BAGS FOR THE SMALL SCALE CULTIVATION OF HIGHLY PATHOGENIC AVIAN INFLUENZA H5N1 AND OTHER VIRUSES IN EMBRYONATED CHICKEN EGGS:

"For many small-scale applications, ethylene breather bags can be used to encase ECE inoculated with various viruses."

4. VIRAL AGENTS RESPONSIBLE FOR FEBRILE RESPIRATORY ILLNESSES AMONG MILITARY RECRUITS TRAINING IN TROPICAL SINGAPORE:

"The laboratory findings identified influenza A virus as the primary causative viral agent for FRI in the Singapore military, in strong contrast to findings from temperate countries and countries where recruits are often vaccinated for influenza. Our results suggest that influenza vaccination should be considered as a requirement to reduce the incidence of influenza infections."

5. HUMAN HOST FACTORS REQUIRED FOR INFLUENZA VIRUS REPLICATION:

"Notably, growth of swine-origin H1N1 influenza virus is also dependent on the identified host factors, and we show that small molecule inhibitors of several factors, including vATPase and CAMK2B, antagonize influenza virus replication."

6. PROPHYLACTIC ADMINISTRATION OF BACTERIALLY DERIVED IMMUNOMODULATORS IMPROVES THE OUTCOME OF INFLUENZA VIRUS INFECTION IN A MURINE MODEL:

"Collectively, these results suggest that, despite different immunomodulatory mechanisms, CT, LT(R192G), and CpG induce an initial inflammatory process and enhance the immune response to primary influenza virus challenge while preventing potentially damaging chemokine expression."

7. AN EFFICIENT METHOD FOR N-ACETYL-D-NEURAMINIC ACID PRODUCTION USING COUPLED BACTERIAL CELLS WITH A SAFE TEMPERATURE-INDUCED SYSTEM:

"Our Neu5Ac biosynthetic process is favorable compared with natural product extraction, chemical synthesis, or even many other biocatalysis processes."

8. CHEST X-RAYS CAN HELP PREDICT WHICH H1N1 PATIENTS ARE AT GREATEST RISK:

"Abnormal findings in the periphery of both lungs and in multiple zones of the lungs were associated with poor clinical outcomes," Aviram said."

9. 1918 AND 2009 PANDEMIC INFLUENZA VIRUSES LACK A SUGAR TOPPING:

"Although they emerged more than 90 years apart, the influenza viruses responsible for the pandemics of 1918 and 2009 share a structural detail that makes both susceptible to neutralization by the same antibodies."

10. CHINA DROUGHT MAY PROMPT TAMIFLU PRODUCER TO REPLACE MAJOR INGREDIENT:

"Southwest China produces 85 percent of the world's Star Anise, an ingredient of Tamiflu, and the region's production may be "substantially reduced" as a result of the drought, said Li Changxin of zyctd.com, China's biggest traditional medicine trading website."

CB Daily Report

Chem-Bio News

AN M2E-BASED MULTIPLE ANTIGENIC PEPTIDE VACCINE PROTECTS MICE FROM LETHAL CHALLENGE WITH DIVERGENT H5N1 INFLUENZA VIRUSES

Health Risk Factor Week
March 23, 2010

"In the present study, we designed a tetra-branched multiple antigenic peptide (MAP)-based vaccine, designated M2e-MAP, which contains the sequence overlapping the highly conserved extracellular domain of matrix protein 2 (M2e) of a HPAI H5N1 virus, and investigated its immune responses and cross-protection against different clades of H5N1 viruses. Our results showed that M2e-MAP vaccine induced strong M2e-specific IgG antibody responses following 3-dose immunization of mice with M2e-MAP in the presence of Freund's or aluminium (alum) adjuvant. M2e-MAP vaccination limited viral replication and attenuated histopathological damage in the challenged mouse lungs. The M2e-MAP-based vaccine protected immunized mice against both clade1: VN/1194 and clade2.3.4: SZ/406H H5N1 virus challenge, being able to counteract weight lost and elevate survival rate following lethal challenge of H5N1 viruses."

"These results suggest that M2e-MAP presenting M2e of H5N1 virus has a great potential to be developed into an effective subunit vaccine for the prevention of infection by a broad spectrum of HPAI H5N1 viruses."

The full article can be found at: (G. Zhao, et. al., "An M2e-based multiple antigenic peptide vaccine protects mice from lethal challenge with divergent H5N1 influenza viruses". Virology Journal, 2010;7():9). Link not available.

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SAFETY, IMMUNOGENICITY, AND EFFICACY OF A COLD-ADAPTED A/ANN ARBOR/6/60 (H2N2) VACCINE IN MICE AND FERRETS

Health Risk Factor Week
March 23, 2010

"We studied the attenuation, immunogenicity and efficacy of the cold-adapted A/Ann Arbor/6/60 (AA ca) (H2N2) virus in mice and ferrets to evaluate its use in the event of an H2 influenza pandemic. The AA ca virus was restricted in replication in the respiratory tract of mice and ferrets."

"In mice, 2 doses of vaccine elicited a >4-fold rise in hemagglutination-inhibition (HAI) titer and resulted in complete inhibition of viral replication following lethal homologous wild-type virus challenge. In ferrets, a single dose of the vaccine elicited a >4-fold rise in HAI titer and conferred complete protection against homologous wild-type virus challenge in the upper respiratory tract. In both mice and ferrets, the AA ca virus provided significant protection from challenge with heterologous H2 virus challenge in the respiratory tract."

"The AA ca vaccine is safe, immunogenic, and efficacious against homologous and heterologous challenge in mice and ferrets, supporting the evaluation of this vaccine in clinical trials."

The full article can be found at: (G.L. Chen, et. al., "Safety, immunogenicity, and efficacy of a cold-adapted A/Ann Arbor/6/60 (H2N2) vaccine in mice and ferrets". Virology, 2010;398(1):109-14). Link not available.

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GAS-PERMEABLE ETHYLENE BAGS FOR THE SMALL SCALE CULTIVATION OF HIGHLY PATHOGENIC AVIAN INFLUENZA H5N1 AND OTHER VIRUSES IN EMBRYONATED CHICKEN EGGS

World Disease Weekly
March 23, 2010

"Embryonated chicken eggs (ECE) are sometimes used for the primary isolation or passage of influenza viruses, other viruses, and certain bacteria. For small-scale experiments with pathogens that must be studied in biosafety level three (BSL3) facilities, inoculated ECE are sometimes manipulated and maintained in small egg incubators within a biosafety cabinet (BSC)."

"To simplify the clean up and decontamination of an egg incubator in case of egg breakage, we explored whether ethylene breather bags could be used to encase ECE inoculated with pathogens. This concept was tested by determining embryo survival and examining virus yields in bagged ECE. Virus yields acceptable for many applications were attained when influenza-, alpha-, flavi-, canine distemper-, and mousepox viruses were propagated in ECE sealed within ethylene breather bags."

"For many small-scale applications, ethylene breather bags can be used to encase ECE inoculated with various viruses."

The full article can be found at: (S.B. Hamilton, et. al., "Gas-permeable ethylene bags for the small scale cultivation of highly pathogenic avian influenza H5N1 and other viruses in embryonated chicken eggs". Virology Journal, 2010;7():23). Link not available.

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VIRAL AGENTS RESPONSIBLE FOR FEBRILE RESPIRATORY ILLNESSES AMONG MILITARY RECRUITS TRAINING IN TROPICAL SINGAPORE

Preventive Medicine Week
March 28, 2010

"Military personnel are highly susceptible to febrile respiratory illnesses (FRI), likely due to crowding, stress and other risk factors present in the military environment. Our objective was to investigate the viral etiological agents responsible for FRI among military recruits training in a tropical climate in Singapore."

"From March 2006 through April 2007, a total of 1354 oropharyngeal (throat) swabs were collected from military recruits who reported sick with an oral temperature of ≥ 38 degrees C and a cough and/or sore throat. Real-time polymerase chain reaction (PCR) was used to assay for the presence of influenza A and B viruses and adenoviruses (H-AdV), and conventional PCR used for the remaining respiratory viruses in all specimens. Influenza A virus was the dominant infection with a laboratory-confirmed incidence of 24% (326/1354) and a predominance of the H3N2 subtype. The temporal pattern for influenza A virus infections coincided with the nation-wide pattern in the civilian community. Detection rates of 12% (159/1354) and 2.7% (5/1354) were obtained for influenza B virus and other respiratory viruses, respectively. The laboratory findings identified influenza A virus as the primary causative viral agent for FRI in the Singapore military, in strong contrast to findings from temperate countries and countries where recruits are often vaccinated for influenza. Our results suggest that influenza vaccination should be considered as a requirement to reduce the incidence of influenza infections."

The full article can be found at: (S.G. Seah, et. al., "Viral agents responsible for febrile respiratory illnesses among military recruits training in tropical Singapore". Journal of Clinical Virology, 2010;47(3):289-92). Link not available.

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HUMAN HOST FACTORS REQUIRED FOR INFLUENZA VIRUS REPLICATION

Pharma Investments, Ventures & Law Weekly
March 28, 2010

"Influenza A virus is an RNA virus that encodes up to 11 proteins and this small coding capacity demands that the virus use the host cellular machinery for many aspects of its life cycle(1). Knowledge of these host cell requirements not only informs us of the molecular pathways exploited by the virus but also provides further targets that could be pursued for antiviral drug development."

"Here we use an integrative systems approach, based on genome-wide RNA interference screening, to identify 295 cellular cofactors required for early-stage influenza virus replication. Within this group, those involved in kinase-regulated signalling, ubiquitination and phosphatase activity are the most highly enriched, and 181 factors assemble into a highly significant host-pathogen interaction network. Moreover, 219 of the 295 factors were confirmed to be required for efficient wild-type influenza virus growth, and further analysis of a subset of genes showed 23 factors necessary for viral entry, including members of the vacuolar ATPase (vATPase) and COPI-protein families, fibroblast growth factor receptor (FGFR) proteins, and glycogen synthase kinase 3 (GSK3)-beta. Furthermore, 10 proteins were confirmed to be involved in post-entry steps of influenza virus replication. These include nuclear import components, proteases, and the calcium/calmodulin-dependent protein kinase (CaM kinase) II beta (CAMK2B)."

"Notably, growth of swine-origin H1N1 influenza virus is also dependent on the identified host factors, and we show that small molecule inhibitors of several factors, including vATPase and CAMK2B, antagonize influenza virus replication."

The full article can be found at: (R. Konig, et. al., "Human host factors required for influenza virus replication". Nature, 2010;463(7282):813-817). Link not available.

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PROPHYLACTIC ADMINISTRATION OF BACTERIALLY DERIVED IMMUNOMODULATORS IMPROVES THE OUTCOME OF INFLUENZA VIRUS INFECTION IN A MURINE MODEL

Preventive Medicine Week
March 28, 2010

"Prophylactic or therapeutic immunomodulation is an antigen-independent strategy that induces nonspecific immune system activation, thereby enhancing host defense to disease. In this study, we investigated the effect of prophylactic immunomodulation on the outcome of influenza virus infection using three bacterially derived immune-enhancing agents known for promoting distinct immunological profiles."

"BALB/c mice were treated nasally with either cholera toxin (CT), a mutant form of the CT-related Escherichia coli heat-labile enterotoxin designated LT(R192G), or CpG oligodeoxynucleotide. Mice were subsequently challenged with a lethal dose of influenza A/PR/8/34 virus 24 h after the last immunomodulation treatment and either monitored for survival or sacrificed postchallenge for viral and immunological analysis. Treatment with the three immunomodulators prevented or delayed mortality and weight loss, but only CT and LT(R192G) significantly reduced initial lung viral loads as measured by plaque assay. Analysis performed 4 days postinfection indicated that prophylactic treatments with CT, LT(R192G), or CpG resulted in significantly increased numbers of CD4 T cells, B cells, and dendritic cells and altered costimulatory marker expression in the airways of infected mice, coinciding with reduced expression of pulmonary chemokines and the appearance of inducible bronchus-associated lymphoid tissue-like structures in the lungs. Collectively, these results suggest that, despite different immunomodulatory mechanisms, CT, LT(R192G), and CpG induce an initial inflammatory process and enhance the immune response to primary influenza virus challenge while preventing potentially damaging chemokine expression."

The full article can be found at: (E.B. Norton, et. al., "Prophylactic administration of bacterially derived immunomodulators improves the outcome of influenza virus infection in a murine model". Journal of

Virology, 2010;84(6):2983-95). Link not available.

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AN EFFICIENT METHOD FOR N-ACETYL-D-NEURAMINIC ACID PRODUCTION USING COUPLED BACTERIAL CELLS WITH A SAFE TEMPERATURE-INDUCED SYSTEM

Health Risk Factor Week

March 23, 2010

"N-Acetyl-d-neuraminic acid (Neu5Ac) is a precursor for producing many pharmaceutical drugs such as zanamivir which have been used in clinical trials to treat and prevent the infection with influenza virus, such as the avian influenza virus H5N1 and the current 2009 H1N1. Two recombinant Escherichia coli strains capable of expressing N-acetyl-d-glucosamine 2-epimerase and N-acetyl-d-neuraminic acid aldolase were constructed based on a highly efficient temperature-responsive expression system which is safe compared to chemical-induced systems and coupled in Neu5Ac production."

"Carbon sources were optimized for Neu5Ac production, and the concentration effects of carbon sources on the production were investigated. With 2,200 mM pyruvate as carbon source and substrate, 61.9 mM (19.1 g l(-1)) Neu5Ac was produced from 200 mM N-acetyl-d-glucosamine (GlcNAc) in 36 h by the coupled cells."

"Our Neu5Ac biosynthetic process is favorable compared with natural product extraction, chemical synthesis, or even many other biocatalysis processes."

The full article can be found at: (Y.N. Zhang, et. al., "An efficient method for N-acetyl-d-neuraminic acid production using coupled bacterial cells with a safe temperature-induced system". Applied Microbiology and Biotechnology, 2010;86(2):481-489). Link not available.

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CHEST X-RAYS CAN HELP PREDICT WHICH H1N1 PATIENTS ARE AT GREATEST RISK

Infection Control Today Magazine

March 23, 2010

"In the study, Aviram's research team analyzed the chest X-rays of 97 consecutive patients with flu-like symptoms and laboratory-confirmed diagnosis of H1N1, admitted to the emergency department of Tel Aviv Sourasky Medical Center between May and September 2009. The researchers then correlated the X-ray findings with adverse patient outcomes.

"To our knowledge, this is the largest series describing the presentation of chest X-ray findings in patients diagnosed with H1N1 influenza," Aviram said.

The chest X-rays revealed abnormal findings for 39 of the patients, five (12.8 percent) of whom experienced adverse outcomes, including death or the need for mechanical ventilation. For the other 58 patients, chest X-ray findings were normal, although two (3.4 percent) of the patients experienced adverse outcomes. The mean age of patients in the study, which included 53 men and 44 women, was 40.4 years.

"Abnormal findings in the periphery of both lungs and in multiple zones of the lungs were associated with poor clinical outcomes," Aviram said."

The full article can be found at: <http://www.infectioncontroltoday.com/hotnews/chest-xrays-predict-h1n1-patients-at-risk.html>

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1918 AND 2009 PANDEMIC INFLUENZA VIRUSES LACK A SUGAR TOPPING

Infection Control Today Magazine

March 25, 2010

"Although they emerged more than 90 years apart, the influenza viruses responsible for the pandemics of 1918 and 2009 share a structural detail that makes both susceptible to neutralization by the same antibodies.

Scientists led by Gary J. Nabel, MD, PhD, of the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, describe the molecular basis for this shared vulnerability and suggest how it might be exploited to design vaccines matched to future pandemic influenza virus strains. The research appears online in the journal *Science Translational Medicine*.

"This study defines an unexpected similarity between two pandemic-causing strains of influenza," says NIAID Director Anthony S. Fauci, MD. "It gives us a new understanding of how pandemic viruses evolve into seasonal strains, and, importantly, provides direction for developing vaccines to slow or prevent that transformation."

In one set of experiments, the NIAID scientists and their colleagues including Terrence M. Tumpey, PhD, of the Centers for Disease Control and Prevention (CDC), injected mice with a vaccine made from inactivated 1918 influenza virus. Then they exposed the mice to high levels of 2009 H1N1 virus. All of the vaccinated mice survived. The reverse was also true: Mice vaccinated with inactivated 2009 H1N1 virus and then exposed to 1918 virus were protected from death. The researchers concluded that vaccination with either pandemic virus caused the mice to produce antibodies capable of neutralizing the other virus."

The full article can be found at: <http://www.infectioncontrolday.com/hotnews/pandemic-flu-viruses-lack-sugar-coating.html>

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CHINA DROUGHT MAY PROMPT TAMIFLU PRODUCER TO REPLACE MAJOR INGREDIENT

Xinhua.net

March 27, 2010

"Southwest China produces 85 percent of the world's Star Anise, an ingredient of Tamiflu, and the region's production may be "substantially reduced" as a result of the drought, said Li Changxin of zyctd.com, China's biggest traditional medicine trading website.

Two thirds of the Star Anise used by Tamiflu's biggest producer, F.Hoffmann-La Roche Ltd., comes from China, said Lu Shunzhong from the Forestry Research Institute of south China's Guangxi Zhuang Autonomous Region.

But Roche spokesman Cao Yong told Xinhua he is "not aware of any possible effect on Tamiflu's production posed by the drought."

Star Anise is the best source of shikimic acid, an indispensable part of Tamiflu, which is used against the A/H1N1 flu, said Li Yi, secretary general of Guangxi's Flavors and Fragrances Industry Association.

While it is true a major event like the drought could have a ripple effect, Star Anise can be substituted, and so Tamiflu's production will not be greatly affected, Cao said."

The full article can be found at: http://news.xinhuanet.com/english2010/china/2010-03/26/c_13226274.htm

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