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2nd International Conference on

Influenza

September 12-13, 2016 Berlin, Germany

Posters

Jana Pokorna et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

H1N1 2009 pandemic influenza virus: Kinetic, structural and thermodynamic analysis of the H275Y, I223V and S247N neuraminidase resistant mutants

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Influenza is an acute viral infection that can cause serious complications and death, especially among elderly individuals and patients at risk. Neuraminidase, which plays an essential role in virus replication, is the main influenza drug target. At present, two neuraminidase inhibitors (NAIs) are licensed worldwide for therapeutic and prophylactic uses (oseltamivir marketed as Tamiflu and zanamivir, Relenza) and two others have been authorized in various countries for the emergency treatment during pandemics. However, drug resistant viruses readily emerge because of the high mutation rate of their RNA dependent RNA polymerase. Indeed, resistance to oseltamivir, the most prescribed NAI was detected not only during treatment and prophylaxis but also in influenza virus variants in untreated individuals. Novel neuraminidase inhibitor resistance substitutions I223V and S247N alone or in combination with a major oseltamivir resistance mutation H275Y have been observed recently in the 2009 pandemic H1N1 viruses. We overexpressed the ectodomain of the wild type neuraminidase from the influenza virus A/California/07/2009 (H1N1) as well as recombinants containing H275Y, I223V and S247N single mutation and the H275Y, I223V and H275Y, S247N double mutants in Drosophila Schneider S2 cells and purified them by one-step purification using a streptavidin derivative. In order to quantify the level of resistance we enzymologically characterized these enzymes with the set of in-house designed and synthesized derivatives of oseltamivir. Thermodynamic analyses of oseltamivir binding to neuraminidase monomutants were performed by protein micro-calorimetry. Finally, we crystallized neuraminidase variants in complexes with oseltamivir to structurally explain the resistance mechanism.

Biography

Jana Pokorna has completed her PhD in Biochemistry from Charles University in Prague in 2013. She is working as a Postdoctoral Fellow at the Institute of Organic Chemistry and Biochemistry ASCR, v.v.i. Her research interests are activity, inhibition, drug and resistance development focusing on HIV protease and neuraminidase from the influenza virus. She has published 11 peer viewed papers and she is the author of 3 patents.

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Ya-tzu Chang et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Influenza epidemic of 2015-16 influenza season in Taiwan

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The 2015-2016 influenza season, was a tough period for Taiwan, having 1932 confirmed severe and complicated influenza cases including 328 estimated deaths. Most severe cases (about 77%) were infected with influenza A (H1N1) pdm09 virus. The majority of severe complicated influenza cases and deaths were adult aged 50-64 years. The incidences among all age groups were highest compared to the same period in the last 3 years, especially in the 50-64 age group. The main attacked age group changed from 65 years above to 50-64 years, similar demographic pattern seen in 2009 H1N1 pandemic. The government-funded influenza vaccination program in 2015-2016, following the international consensus, mainly targeted the elders aged more than 65 years, children aged six months through elementary school students and people aged above 50 years with chronic medical conditions. As a result, most people aged 50-64 years have not received influenza vaccines. In addition, the coverage rate of people with chronic diseases was only about 9%. Due to these reasons, in 2016/17 season, we plan to increase the purchase of influenza vaccines and vaccination points, as well as the awareness of the public, to improve the vaccination coverage rates and subsequently lower influenza incidence among people with chronic diseases.

Biography

Ya-tzu Chang is a Public Health Officer of the Department of Division of Preparedness and Emerging Infectious Disease in Taiwan Centers for Disease Control. She is responsible for policy making of influenza prevention and control and has handled experiences on 2009 H1N1 pandemic influenza and H7N9 influenza in Taiwan.

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Milan Kozisek et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Development and optimization of the assay for screening the compounds disrupting protein-protein interaction in influenza A polymerase

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Influenza virus causes severe respiratory infections in birds and mammals that are responsible for up to half a million deaths of human beings worldwide each year. Two targets of therapeutic interventions in influenza life cycle, viral neuraminidase and M2 channel are exploited in treatment. However, the recent emergence of new pandemic type along with increasing resistance against approved drugs has urged the need for a new drug target and design of its inhibitor. Recently, an interesting protein-protein interaction between two subunits of viral polymerase PA and PB1 has been identified as a new promising drug target. The fact that relatively few residues drive the binding and the binding interface is highly conserved presents an intriguing possibility to identify antiviral lead compounds effective against all subtypes of influenza A virus. In our laboratory, we have expressed and purified recombinant C-terminal part of the PA polymerase subunit with GST at its N-terminus from pandemic isolate A/California/07/2009 H1N1. The biotinylated peptide representing the N-terminal interacting part of PB1 subunit was synthesized by using a solid-phase synthesizer. The protein-protein interaction between PA and PB1 was then kinetically characterized using a surface Plasmon resonance (SPR). Finally, we developed and optimized an assay for screening the compounds disrupting the interaction between polymerase subunits, based on the AlphaScreen technology and validated the assay that has the potential to be used in drug discovery.

Biography

Milan Kozisek is a Senior Scientist at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague. He has completed his PhD in 2010. He is an author of 29 papers in peer-reviewed international journals and 4 patents.

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Hyeon Jang et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Comparison of microporous membranes in the concentration process for high- dose influenza vaccines

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It is generally known that as people get older, immune responses diminish. A series of studies support the decreased immune response to influenza vaccination in the elderly might cause severe respiratory complications associated with influenza infection. For this reason, Fluad (Seqirus) and Fluzone High Dose (Sanofi Pasteur), which were recently approved adjuvanted and high-dose (HD) influenza vaccines, respectively, are recommended for the elderly as they produce higher SCR and SPR than conventional influenza vaccines.

Especially, manufacturing of HD influenza vaccines need an additional concentration step in which micro-porous membranes are usually applied. High concentration of HA (hemagglutinin) and low levels of surfactant residues should be achieved in HD vaccines. To establish the concentration process, contents of HA and surfactant residues were compared among 3 membranes of different manufacturers(Sartorius, Merck, and PALL). We found that HA concentration increased proportionally to the concentration factor, and the sequential dilution step decreased levels of surfactant residues. Meanwhile, cellulose acetate (CA) and polyether sulfone (PES) are commonly used as micro-porous membrane materials but the characteristics of each material and the interaction between concentrates and membranes may have different influences on the concentration capability of membranes. In our study, PES showed equivalent capability to CA in concentrating HA, but 2-fold higher capability than CA in decreasing surfactant residues.In conclusion, selection of a more appropriate membrane for the additional concentration step may provide an opportunity for further improvement of the manufacturing process of high-dose influenza vaccines.

Biography

Hyeon Jang has completed his Master of Science degree in Medicine from Seoul National University. He has been working as an Associate II (Research Worker) for 2 years in GCC, a leading pharmaceutical company in ROK.

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Jin-Wook Jang et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Application of non-pathogenic PB2 gene of low pathogenic avian influenza virus to H5N1 highly pathogenic avian influenza to generate novel vaccine against HPAI in Korea

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Avian influenza (AI) vaccines for poultry are based on hemagglutinin (HA) proteins and protection is specific to the vaccine subtype. Since 2004, AI vaccine strains have been developed using reverse genetic systems. Recent pair-wise comparison with internal genes of A/chicken/Korea/01310/2011 (H9N2; 01310) and A/chicken/Korea/KBNP-0028/2000 (H9N2; 0028) revealed that recombinant PR8 viruses possessing the PB2 of 01310 or NS of 0028 decreased pathogenicity in mice, protected against PR8 challenge and increased replication efficiency in embryonated chicken eggs (ECEs). And the LPAI H5N1 recombinant virus containing PB2 of 01310 or NS of 0028 reduced pathogenicity in mice and had high replication efficiency in ECEs. In the present study, we generated PR8-derived H5N1 recombinant viruses which have HA and NA gene of H5N1 HPAI virus A/mandarin duck/Korea/K10-483/2010 (K10-483), PB2 of 01310 and NS of 0028. The reassorted H5N1 virus possessing PB2 of 01310 [rH5N1-PB2(01310)] showed significantly higher replication efficacy in ECEs than the control H5N1 recombinant virus that containing six internal genes of PR8 (rH5N1). In contrast, replication efficacy in MDCK cell of recombinant virus that is harboring PB2 of 01310 and NS of 0028 [rH5N1-PB2(01310)-NS(0028)] was significantly lower than that of rH5N1. All recombinant viruses did not cause body weight loss in mice, although only control rH5N1 virus replicated in the lungs of inoculated mice. Thus, the novel vaccine strains that containing PB2 and NS gene of LPAIV may be useful to develop safe and efficacious vaccines.

Biography

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Aliou Barry, J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Early outbreak detection through sentinel surveillance system in Senegal

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In Senegal, since 2012, a sentinel syndromic-based surveillance system was established with the main goal of rapidly identifying outbreaks and issuing alerts. We describe the steps involved in developing a sentinel surveillance system and the well-timed information it provides for improving public health decision-making. The Senegalese sentinel surveillance network is based on data for fever and diarrheal syndromes collected by sentinel general practitioners (SGP). The SGPs were expected to communicate at least once a day encrypted short messages (number of fever cases, rapid test confirmed Malaria, ILI and Dengue-like syndromes or Diarrheal disease) from mobile phone. Standard WHO case definitions are used to ensure comparability. Data are validated by the management team and analyzed daily at the IPD. This data transmission costs 750 FCFA, around US$1 per month per sentinel center. In 2015, the sentinel surveillance system included 17 health centers and identified four (4) outbreaks confirmed: Two with an increase in ILI indicators (Influenza *AH1N1, H3N2*), one with an increase in RDT-confirmed cases of malaria and one with an increase in diarrhea disease. Of the 181,955 visits to SGPs, 22% were related to fever syndromes. Of these 40,030 fever cases, 32% were related to influenza-like illness, 6% to dengue-like syndrome, 16% to malaria cases confirmed by a specific rapid diagnostic test and 4% to diarrhea. Senegal's sentinel syndromic surveillance system represents the country's first nationwide "real-time" surveillance system. It has proved the feasibility of improving disease surveillance capacity through innovative systems despite resource constraints.

Biography

Aliou Barry holds a Doctorate degree in Medicine. He has obtained a Diploma of specialized studies at the Cheikh Anta Diop University of Dakar, Senegal in 2012. He has received a Master II Scholarship in Tropical Medicine, Public Health and Research account of University agency of the Francophonie which he has completed in 2014. He has worked as a Public Health Doctor In-Charge of coordinating the influenza surveillance within the unity of infectious disease epidemiology at Institute Pastor of Dakar, Senegal. He is currently finalizing a university degree in Epidemiology at the University of Bordeaux, France.

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Hind Bouguerra et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Influenza severe cases and deaths in Tunisia: Season 2015-2016

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Introduction: Seasonal influenza continues to be a major public health problem worldwide. In fact, this acute viral infection is highly contagious and affects all ages. Although in most cases it is a minor illness, it may lead to severe complications and death especially in high risk populations.

Purpose: To describe influenza severe cases and deaths in the season of 2015-2016 and compare it to previous seasons, to determine what are the influenza viruses currently circulating and which types have particular virulence in this season and to suggest recommendations to improve influenza control.

Methods: This is a retrospective study based on data provided by the national influenza surveillance unit. It is a descriptive analysis of influenza surveillance data collected from the network of sentinel sites and national influenza center.

Results & Discussion: Influenza surveillance for 2015-2016 lasted from week 40/2015 to week 18/2016. During this season, 96240 cases of ILI (Influenza-like illness) were collected representing 6.9% of total patients seen at ILI sites. Among these cases, 190 were severe and hospitalized. Their age ranged from 6 months to 73 years with an average of 46.5 years. The hospitalization rate was 0.19% and comparable to the previous season (0.2%). However, the lethality of these severe cases was significantly higher in 2015-2016 Season. In fact, 38 deaths were reported representing 20% (vs. 3% in 2014-2015 Season). The majority of them were men (57%). The average age was 46.9 years with extremes varying from 6 months to 73 years. The most affected age group was the 50- 65 year group. Most of the cases who died had risk factors (62.9%) especially diabetes, HTA and obesity. All the cases were not vaccinated. The virological analysis showed that 57% of severe cases and 77% of influenza deaths were infected with type A (H1N1) pmd09 virus. The rest of the deaths (23%) were due to A (H3N2) virus and only one death was due to virus B. During week 12, A (H1N1) was predominant and simultaneously the highest number of deaths was reported (10 deaths representing 26.3% of all influenza deaths).

Conclusion: Comparing to last season 2014-2015, the influenza epidemics of 2015-2016 is considered similar in terms of number of ILI cases and hospitalization rate. However, the lethality of severe cases was significantly higher with 38 deaths reported this season. The type A (H1N1) pmd09 virus was responsible of most of severe cases and deaths, confirming its known virulence.

Biography

Hind Bouguerra has completed her Medical studies from the Faculty of Medicine of Tunis, Tunisia. She has specialized in Preventive Medicine and Public Health. She has a Master of Biostatics, Epidemiology and Clinical Research degree from the Faculty of Medicine of Tunis. She has worked in the Laboratory of Epidemiology at Pasteur Institute of Tunis and in the National Observatory of New and Emerging Diseases of Tunisia, participating in many papers. She has worked mostly in epidemiological surveillance including influenza program in Tunisia which is supported by US/CDC, part of InPRIS project.

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Sophie Buffin, J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Quantification of the haemagglutinin in monovalent influenza vaccines by a latex agglutination assay (LAA) as an alternative to the single radial immunodiffusion (SRID) assay

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To formulate inactivated influenza vaccines, the concentration of haemagglutinin (HA) must be accurately determined. The standard test currently used to measure HA in influenza vaccines is the single radial immunodiffusion (SRID) assay. The SRID assay is a cumbersome technique presenting a number of drawbacks such as low sensitivity and interference by some adjuvants. We developed a very simple, sensitive and rapid alternative HA assay using latex agglutination. The LAA uses the Spherotest® technology, which is based on the agglutination of HA-specific immunoglobulin-coated latex beads, which bind to the HA. The amount of HA in a sample can then be calculated from the level of bead agglutination by a simple absorbance measurement. A standard curve is generated using serially diluted HA reference protein. The results show that for monovalent A/H5N1 and A/H1N1 vaccines, the LAA demonstrated equivalent linearity, accuracy and precision as compared to the SRID assay. Moreover, unlike the SRID assay, LAA enables HA quantification in AlOOH-adjuvanted vaccines and in emulsion-based adjuvanted vaccines without interference. In addition, LAA was found to be more simple, rapid and sensitive than SRID. In conclusion, LAA may be useful to rapidly and accurately quantify the influenza HA protein in monovalent vaccines, especially in those formulated with low amounts of HA in the presence of an adjuvant.

Biography

Sophie Buffin joined the Research department of Sanofi Pasteur in 2005 with a Master's degree. She is currently a Ph.D. student at the University of Lyon.

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Influenza

September 12-13, 2016 Berlin, Germany

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Barbara Camilloni et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Serological methods are able to determine how well influenza vaccines work

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In influenza vaccine efficacy studies, virus identification is considered the ideal end point. This approach, especially if performed in large populations could be difficult to carry out and the results could depend on the level of influenza viruses' circulation. This is why serological studies are often used as surrogate methods. Here we analyze the antibody response of 181 elderly volunteers (aged ≥65 years) to 2014-15 influenza vaccine to understand if serological data are able to predict the vaccine efficacy. We compared the response of those who have or have not had a serologically evidenced influenza infection after vaccination (the volunteers that had a seroconversion on comparing hemagglutination inhibiting (HI) titers found 1 and 6 months after vaccination were considered positive for serological evidence of recent infection). Before vaccination the infected group showed lower antibody levels than uninfected volunteers, after vaccination these differences increased. Dividing the infected volunteers according to the absence or the presence of influenza like illness (ILI) and to the severity of the ILI, we found that, 1 month after vaccination, 80-90% of volunteers with severe infections or with mild infections, respectively, were unprotected (HI<40). On the other hand, among the infected volunteers not showing ILI and the non-infected volunteers, more than half were found to be protected. Although the validity of using serologic confirmation of infection rather than virus identification to determine vaccine efficacy has been questioned, our results, though obtained analyzing a small population, confirm the validity of the serological approach.

Biography

Barbara Camilloni is a Researcher at the University of Perugia, Italy. She has completed her Postgraduate School in Microbiology and Virology and PhD in molecular pathogenesis, immunology and control of transmissible agents causing major illnesses associated with poverty (malaria, tuberculosis and AIDS). Her major research work includes virological monitoring of seasonal influenza and pandemic as part of coordinated Italian surveillance network (InfluNet), evaluation of the effectiveness of influenza vaccination in the elderly and surveillance of acute flaccid paralysis (national / international program of polio eradication). virological surveillance of rotavirus infections in children.

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Ya-tzu Chang et al., J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Influenza epidemic of 2015-16 influenza season in Taiwan

Ya-tzu Chang, Yu-Ju Lin, Yi-Chien Chih, Shu-Mei Chou and **Chang-Hsun Chen**
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The 2015-2016 influenza season, was a tough period for Taiwan, having 1932 confirmed severe and complicated influenza cases including 328 estimated deaths. Most severe cases (about 77%) were infected with influenza A (H1N1) pdm09 virus. The majority of severe complicated influenza cases and deaths were adult aged 50-64 years. The incidences among all age groups were highest compared to the same period in the last 3 years, especially in the 50-64 age group. The main attacked age group changed from 65 years above to 50-64 years, similar demographic pattern seen in 2009 H1N1 pandemic. The government-funded influenza vaccination program in 2015-2016, following the international consensus, mainly targeted the elders aged more than 65 years, children aged six months through elementary school students and people aged above 50 years with chronic medical conditions. As a result, most people aged 50-64 years have not received influenza vaccines. In addition, the coverage rate of people with chronic diseases was only about 9%. Due to these reasons, in 2016/17 season, we plan to increase the purchase of influenza vaccines and vaccination points, as well as the awareness of the public, to improve the vaccination coverage rates and subsequently lower influenza incidence among people with chronic diseases.

Biography

Ya-tzu Chang is a Public Health Officer of the Department of Division of Preparedness and Emerging Infectious Disease in Taiwan Centers for Disease Control. She is responsible for policy making of influenza prevention and control and has handled experiences on 2009 H1N1 pandemic influenza and H7N9 influenza in Taiwan.

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http://dx.doi.org/10.4172/2332-0877.C1.015

Flu pathogenesis proteolytic theory and its role in the improvement of flu's treatment

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Introduction: Interaction of virus and cell in the pathogenesis of viral diseases is insufficiently studied. The main point here is penetration of virus into a healthy cell with an obligatory virus' deproteinization. However the deproteinization of viruses is studied insufficiently. First of all it refers to the mechanisms of introduction of flu virus in the cells of mammals, including humans. In this regard in 1983 we offered the new theory of flu pathogenesis with participation of proteinases-inhibitory system.

Objective: To study the state and role antiproteinasis systems of the virus and recipient in the development of an influenza infection for receiving essentially new medical preparations on the basis of inhibitors of trypsin-like proteinases.

Methods: In work presented we used flu viruses, A/PR/8/34 (H1N1), AO/32(H1N1) strains, white mice, chicken embryos, white rats, waste of γ-globulin and albumin manufacturing, human interferon and immunoglobulin, herpetic, gonococcus and tularemia vaccines and medicines: Influvac, Fluarix, Vaxigrip: Anti-influenza vaccines, Avaxim: Vaccine for hepatitis A and blood preparations Fraxiparine, Solcoseryl.

Results: It has been established that cleaning and concentration of influenza virus A various by different methods does not exempt virus from cellular enzymes trypsin-like proteinases and their inhibitors. Both domestic (human immunoglobulin and interferon, anti-influenzal and herpetic vaccines) and foreign preparations (Influvac, Fluarix, Vaxigrip, Avaxim, Fraxiparine and Solcoseryl) had trypsin-like proteinase and its inhibitor in their structure. In the experiments on the white mice at infection with flu A virus there was a violation of proteinase-inhibitory balance, especially during the first hours after contamination. From the lungs of healthy mice six isoforms of trypsin-like proteinase have been allocated and antiproteinase immune serums were received to them. At the treatment of the animals infected with a lethal dose of flu A virus, only one serum (to the third isoform) has protected white mice from death. From the waste of γ-globulin manufacture of donor blood, inhibitor of trypsin-like proteinases which protected for 80% of white mice from death was emitted.

Conclusions: Endogenous inhibitors of human blood proteinases are perspective preparations in the fight with flu in humans.

Biography

V A Divocha was graduated from I. I. Mechnikov Odessa State University in 1967, Faculty of Biology (Department of Virology). In 1973 she continued her Postgraduate study at Odessa Institute of Virology and Epidemiology (specialty virology). In 1974 she was awarded her candidate degree with the thesis "Interaction of Coxsackie B viruses with sensitive cell cultures and their antigenic relationships". In 2009 she was awarded her doctoral degree with the thesis entitled "Biological basis antiprotease therapy of influenza". She has scientific experience of 35 years and has more than 186 scientific publications, 2011 monograph, textbook, 10 patents and 3 innovations. She is currently working as the Head of the Laboratory of Experimental and Clinical Pathology for Ukrainian Research Institute of Transport Medicine and the Supervisor of the nine research programs in virology and biochemistry.

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Hany Hamed Esmail Khalil, J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Novel and efficacious compounds disturb influenza A virus infection

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Influenza A virus is a negative RNA stranded virus of the family Orthomyxoviridae and represents a major public health threat, compounding existing disease conditions. Influenza A virus replicates rapidly within its host and the segmented nature of its genome facilitates re-assortment, whereby whole genes are exchanged between influenza virus subtypes during replication. Antiviral medications are important pharmacological tools in influenza virus prophylaxis and therapy. However, the use of currently available antiviral is impeded by sometimes high levels of resistance in circulating virus strains. Notably, the over use of existing antiviral drugs such as oseltamivir (Tamiflu) and zanamavir (Relenza) increases the likelihood of viral escape mutations. Here, we identified novel anti-influenza compounds through screening of chemical compounds that synthesized de novo and several naturally occurring products on human lung epithelial cells. Computational and experimental screening of extensive natural products and water soluble chemical compounds identified novel influenza virus inhibitors that can reduce influenza virus infection without any detectable toxic effects on host cells. Interestingly, the indicated active chemical compounds inhibit viral replication most likely via interaction with cell receptors and disturb influenza virus entry into host cells. Additionally, the selected natural product inhabits viral replication via increasing of interferon beta (IFN-β) production from infected cells. In conclusion, screening of new synthesis compounds and natural extractions on influenza A virus replication provides a novel and efficacious anti-influenza compounds that can inhibit viral replication and indicates that these compounds are attractive candidates for evaluation as a potential anti-influenza drugs.

Biography

Hany Hamed Esmail Khalil has completed his PhD from Humboldt University in collaboration with Max-Planck Institute for Infection Biology followed by 6 months Postdoctoral Fellowship at Max-Planck Institute for Infection Biology, Berlin, Germany and additional 4 months Postdoctoral Fellowship at Wexner Medical Research Center, Ohio State University, USA. He is the Assistant Professor at Genetic Engineering and Biotechnology Research Institute, Department of Molecular Biology, University of Sadat City Egypt. He is the Principle Investigator in two different projects supported by (STDF) projects ID, 6117 and project ID, 4694.

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Influenza

September 12-13, 2016 Berlin, Germany

Accepted Abstracts

J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Occurrence and spread of influenza A(H1N1)pdm09 virus infection in Norwegian pig herds based on active sero surveillance from 2010 to 2014

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The incursion of influenza A(H1N1)pdm09 virus was detected by Norway's active sero surveillance of its pig population in 2009. Since then, surveillance data from 2010 to 2014 revealed that 54% of 5643 herd tests involving 1567 pig herds and 28% of 23036 blood samples screened positive for antibodies against influenza A virus. Positive herds were confirmed to have influenza A(H1N1) pdm09 virus infection by hemagglutination inhibition test. In 50% of positive herd tests, ≥60% of the sampled pigs in each herd had antibodies against influenza A(H1N1)pdm09 virus. This within-herd animal seroprevalence did not vary for type of production, herd size or year of test. The overall running mean of national herd seroprevalence and annual herd incidence risks fluctuated narrowly around the means of 45% and 32%, respectively, with the highest levels recorded in the three densest pig-producing counties. The probability of a herd being seropositive varied in the five production classes, which were sow pools, multiplier herds, conventional sow herds, nucleus herds and fattening herds in descending order of likelihood. Large herds were more likely to be seropositive. Seropositive herds were highly likely to be seropositive the following year. The study shows that influenza A(H1N1)pdm09 virus is established in the Norwegian pig population with recurrent and new herd infections every year with the national herd seroprevalence in 2014 hovering at around 43% (95% confidence interval (40-46%).

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Burden of acute lower respiratory tract infection caused by influenza virus among children in Egypt

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Background: Influenza virus is one of the most important causes of acute lower respiratory tract infections (ALRTI) in children. We aimed to assess the burden of influenza among hospitalized children less than 5 years in Egypt.

Methods: We enrolled 3075 patients, of which 77.8% were children less than 5 years old diagnosed with ALRTI admitted to Cairo University Hospitals during five-year period from 2010 to 2014. Nasopharyngeal aspirates were obtained from the patients and tested for influenza among 16 respiratory viruses by mutliplex PCR.

Results: Patients had a mean age of 4 months, 53.4% were males. Average hospitalization duration was 5 days, 35% were positive for one or more virus. Influenza A and influenza B were detected in 6.2% and 3.2% of children respectively. All influenza patients presented with cough and fever. More than 80% had tachypnea and nasal flare. Complications were associated with chronic lung and heart conditions. The most common complications were ARDS (81.8%), requiring ICU admission (12%) and death in 8.2%; though seasonal distribution was not consistent, yet 80% of influenza cases occurred in winter and early spring seasons ($p<0.001$). Nosocomial transmission occurred in 2 outbreaks in a Surgical Pediatric Intensive care units, affecting 7 children.

Conclusion: Influenza is an important etiology of ALRTI in children below 5 years of age. As it is more prevalent in winter and tends to cause severe infection in high risk group, vaccination, rapid diagnosis and early start of antiviral therapy are essential.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Molecular analysis of influenza A/H3N2 and A/H1N1pdm viruses circulating in the Democratic Republic of Congo, 2014

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Introduction & Aim: Influenza is a common human respiratory infection and a cause of high morbidity and mortality. However, not much is known about influenza viruses circulating in Democratic Republic of Congo (DRC). This study aimed to characterize genetically and antigenically those strains affecting patients in this particular country.

Methods: Nasal, throat and nasopharyngeal swabs from patients presenting with severe acute respiratory infections (SARI) or influenza-like-illness (ILI) were collected from August to December, 2014 in various surveillance sites selected in DRC and delivered to the National Institute of Biomedical Research (INRB) using the viral transport medium for molecular work. Viral RNA extraction and amplification by reverse transcription polymerase chain reaction (RT-PCR) were done and positive influenza samples with a Cycle threshold (Ct<30) were sent to the World Health Organization (WHO) Collaborating Center for Surveillance, Epidemiology and Control of Influenza at the US Centers for Disease Control and Prevention (CDC) in Atlanta for further genetic and antigenic characterization.

Results: A total of 32 samples were tested at INRB and were found to be positive to influenza A with Ct<30. These samples were shipped to the US CDC in Atlanta for further sub-typing: 26 samples were influenza A (H3N2), 2 were influenza A (H1N1) pdm09, two samples were negative for influenza by RT-PCR and two samples contained insufficient volume for testing. The majority of influenza A (H3N2) viruses tested from DRC was antigenically related to the A/Switzerland/9715293/2013 vaccine virus, while two influenza A (H1N1) pdm09 virus isolates were antigenically characterized as A/California/07/2009-like. All A (H3N2) and A (H1N1) pdm09 virus isolates characterized in this study from DRC were sensitive to oseltamivir and zanamivir.

Conclusion: Two genetically distinct influenza subtypes, A (H3N2) and A (H1N1) pdm09, were found to be circulating in the DRC during the study period. Based on these results, effective measures against influenza should be advised, including prevention of infection by either vaccination or administration of antiviral drugs prophylactically or therapeutically.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Protection against influenza virus lethal challenge by HA2-M2e fusion protein in BALB/c mice

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The error-prone polymerase and segmented nature of influenza virus A genome cause antigenic drift and shift respectively. These phenomena make influenza vaccines inefficient along time and against different viral subtypes. In this study for the first time protection properties of a new recombinant fusion protein including HA2 and M2e proteins originated from influenza virus A/Brisbane/59/2007-like (H1N1) in BALB/C mice model, was determined via lethal challenge by homologous (mouse adapted, A/PR8/34 (H1N1)) and heterologous (mouse adapted, A/Brisbane/10/2007 (H3N2)) influenza virus subtypes. The protection properties of the recombinant HA2-M2e fusion protein determined by measurement of IgG class responses and neutralizing assay after immunization mice by the fusion protein and monitoring the lung viral titers, body temperature changes and survival rate of the immunized mice after lethal homologous and heterologous challenges. The study showed immunization by HA2-M2e caused a good protection against homologous challenge and a weaker protection against heterologous challenge. The results showed that HA2-M2e fusion protein can be recommended as a universal vaccine candidate, however more studies need to optimize this recombinant construction as a universal vaccine candidate.

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Limiting mutations in avian influenza viruses through effective poultry disease management

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Although avian influenza outbreaks occur periodically in poultry flocks, only recently we have considered avian influenza as a significant threat to human health and the global economy. The 1997 emergence of H5N1 first brought our attention to avian influenza's ability to cause disease in humans. More recently the H7N9 virus was reported in China that causes severe respiratory illness resulting in death in about one-third of infected patients. Other avian influenza subtypes, including H7N7 and H9N2, have also infected people. The 2015 outbreak of Highly Pathogenic Avian Influenza (HPAI) in the United States illustrates the economic impact of an avian influenza outbreak. 219 detections of HPAI resulted in the death of nearly 50 million birds and a total economic impact of $3.3 billion dollars U.S. The longer these viruses remain in circulation, the greater their potential to mutation into forms that can cause disease in humans or increased pathogenicity in poultry. Testing near the turkey farm infected with HPAI H7N8 in Indiana this year revealed 8 additional farms with LPAI H7N8, suggesting that the virus mutated into a more lethal form as it spread. Historically, poultry carcasses have been disposed of by a variety of methods including burial, incineration, land-filling and more recently, composting. The success of the composting method during outbreaks in Delaware in 2004 and Virginia in 2007 resulted in composting being a key carcass disposal method during the 2015 HPAI outbreak. In Minnesota, for example, 108 of the 109 commercial poultry operations successfully composted their flocks. Animal carcass disposal remains a significant weakness in many nations' comprehensive national strategy for biodefense. While incidents of high consequence foreign animal diseases are increasing, response plans often lack comprehensive carcass disposal considerations. Now is the time to revisit and update foreign animal disease response plans.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Impact of Umifenovir use on the reduction secondary bacterial pneumonia following influenza

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Pneumonia often occurs secondary to influenza infection and accounts for a large proportion of the morbidity and mortality associated with seasonal and pandemic influenza outbreaks. The antiviral drug umifenovir (Arbidol) is licensed in Russia for treatment and prophylaxis of acute respiratory infection including influenza A and B infection. In the present study, we investigated the efficacy of umifenovir or oseltamivir in a mouse model of secondary *S. aureus* pneumonia following A/California/04/2009 (H1N1) influenza virus infection. We also performed a clinical study on the effectiveness of umifenovir in reducing flu-associated pneumonia. Experiments in mice showed that oral treatment with oseltamivir (20 mg/kg/day) and umifenovir (40 and 60 mg/kg/day) improved survival in mice from 0% to 90%, significantly prolonged survival and abolished weight loss. The treatments also inhibited virus titer by ≥2 logs and viable bacterial counts in the lungs of mice. The lungs of mice treated with oseltamivir or umifenovir showed less-severe histopathologic findings compared to the control group. The observation case-control clinical study was set up in season 2010/2011 and 2014/2015 and included 5287 patients admitted to 88 hospitals with acute respiratory viral infections (ARVI) from 50 regions of the Russian Federation. The analysis showed that in high-risk groups of patients the incidence of bacterial complications (pneumonia) was higher than the average for the study population. Our observational studies suggest the benefit of early umifenovir treatment (i.e., within 48 hours after illness onset) in reducing pneumonia incidence in high-risk patients.

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Minimal requirements for high virulence of non-H5/H7 avian influenza viruses

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Avian influenza viruses (AIV) are classified as either low pathogenic (LP) or highly pathogenic (HP) due to their virulence in chickens. Highly pathogenic avian influenza viruses (HPAIV) exhibit a polybasic cleavage site (PCS) within the hemagglutinin (HA) protein and therefore the HA can be cleaved and activated by ubiquitous proteases causing severe systemic disease with high lethality. Naturally occurring HPAIV have always been of subtype H5 or H7 with very rare exceptions. Recently we showed that HPAIV can be created with other HA subtypes exhibiting an artificial PCS in a H5 HPAIV background and the introduction of a PCS within the HA in the parental background was not sufficient. Therefore, the objective of the study was to investigate the minimal requirement for exhibiting a highly pathogenic phenotype of non-H5/H7 LPAI viruses. Reverse genetics systems were established for LPAIV strains H4N6 and H8N4. Reassortants of LPAIV HA with artificial PCS and gene segments of a H5N1 HPAIV were generated and the virulence was ascertained in SPF chickens. In summary, the HPAIV H5N1 nucleoprotein (NP), neuraminidase (NA) and the matrix protein (M) segments conferred increased virulence. Whereas the impact on virulence of the NA and M gene segments differed, the NP gene of H5 HPAIV increased virulence in both H4 and H8 backgrounds. Furthermore, the impact of single NP amino acids was assessed.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Plant expression platforms for vaccine production

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Plant made biologics have elicited much attention over recent years for their potential in assisting those in developing countries who have poor access to modern medicine. Additional applications such as the stockpiling of vaccines against pandemic infectious diseases or potential biological warfare agents are also under investigation. Plant virus expression vectors represent a technology that enables high levels of pharmaceutical proteins to be produced in a very short period of time. Recent advances in research and development have brought about the generation of superior virus expression systems which can be readily delivered to the host plant in a manner that is both efficient and cost effective. The following presentation describes recent innovations in plant virus expression systems and their uses for producing biologics from plants.

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Construction of recombinant protein of influenza A virus neuraminidase gene expressed in baculovirus

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Two structural antigens, haemagglutinin (HA) and neuraminidase (NA) are attractive candidates for the development of a genetically engineered vaccine against influenza. Recombinant vaccines are produced by a simple and effective method, although expected to induce an immune response to a specific antigen, remain to be further improved for their high effectiveness. On the other hand, a potent and effective vaccine against influenza should be able to induce both humoral and cellular immune responses. In the present study, the NA gene, which is more stable than the HA one was amplified by Polymerase Chain Reaction (PCR) and then cloned into a eukaryotic expression vector pFastBac HTA. The purity of the expressed NA protein was analyzed on SDS-PAGE electrophoresis. Western blot was carried out to examine the expression of NA using the commercial anti-NA polyclonal antibody. Additionally, an immunofluorescence assay was used to qualitatively assess the antigenicity and biological activity profiles of the recombinant protein, NA, on infected Sf9 cell surface by using immunized rabbit antiserum.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Molecular characterization of influenza viruses circulating in Cuba April 2009 to August 2010

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Influenza is a respiratory disease with high epidemic behavior; the main etiologic agents are influenza viruses A and B. The virus influenza A are primarily responsible for annual epidemics and the only causing pandemics. Fighting these viral agents is based mainly in the use of vaccines and drugs that inhibit viral proteins M2 and NA. Currently, the use of antiviral drugs has been limited by the emergency and circulation of influenza virus variants resistant to adamantane worldwide. The neuraminidase inhibitors have been the drug of choice available for the treatment and prophylaxis of influenza virus before the availability of influenza vaccine. The aim of this work was the molecular characterization of influenza virus circulating in Cuba in the period April 2009-August 2010. Phylogenetic analysis of seasonal influenza viruses and pandemic virus showed that both viruses were genetically similar to the strains included in the vaccine recommended by 'WHO'. Molecular characterization of these agents circulating in Cuba showed the necessity of systematic monitoring of these Cuban genetic variants. In the present work we identified genetic variants of influenza A resistant to oseltamivir. It was detected for the first time in Cuba the circulation of influenza A (H1N1) viruses with resistant markers to the antiviral drugs available.

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Epidemiologic pattern and diseasome exploration for physical performance: A new horizon for genetic and environmental cross-talk in health and disease

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Both genetic and environmental factors contribute to human diseases. Most common diseases are influenced by a large number of genetic and environmental factors, most of which individually have only a modest effect on the disease. Though genetic contributions are relatively well characterized for some monogenetic diseases, there has been no effort at curating the extensive list of environmental etiological factors. However, considering the interaction between the factors, a network of association and clustering would explain the influencing factors on health and disease. In this study we evaluated association of factors on physical performance. From a comprehensive search of the MeSH annotation of MEDLINE articles, NIH Genetic Association Database (GAD) and OMIM database, genetic and environmental etiological factors associated with physical performance were identified. Clustering of both genetic and environmental etiological factors puts genes in the context of environment in a quantitative manner. After extraction of genetic factors, associated diseases with those genes were searched. Finally a matrix of association was formed. The degree of associations was determined by pooling the published data and the network of "etiome" was constructed by Gephi. A 22 by 22 gene-gene interaction showed ACE gene with the highest centrality. Also 600 cells gene-disease matrix were illustrated including the degree of associations and 95% CIs. The diseasome of physical performance demonstrated interesting clusters of diseases and risk factors with an average degree of 7.4 and average clustering coefficient of 0.60. The network principally included two main clusters around diabetes and neoplastic diseases, while diabetes had the highest strength and centrality. The diseasome helps a better understanding of genetic and environmental factors attributed to physical performance in order to find effective treatments for linked factors. Diabetes and ACE gene polymorphism should take a paramount attention in this regard.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Evaluation of immunogenic properties recombinant fusion protein 4xM2e-HA influenza A virus expressed in MDCK cell line

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Background & Aim: The recent pandemic swine H1N1 influenza (2009) outbreak demonstrated that egg-based vaccine manufacturing does not adequately respond to pandemic strains. Recent study has established an alternative for subunit vaccine by the use of the recombinant. We try produced universal vaccine 4M2e-HA that can be produced in large scale in reasonable time.

Methods: In this study a recombinant 4xM2e-HA gene of influenza A virus was designed and expressed in MDCK cell which could be secreted out of cells. Immunized mice with this protein induced both humoral and cellular response against influenza A virus.

Result: The immunized mice showed increased immunological indicators such as IFN-γ and IL-2, IL-12, IL-4 and induced suitable CTL response, also antibody against fusion protein can be neutralized both heterologous and homologues influenza virus.

Conclusion: These findings suggest that 4xM2e-rHA expression in MDCK cell may provide a new approach for developing a novel universal vaccine that may protect not only specifically against a new circulating strains but is expected to protect broadly against new virus strains possessing common epitopes with conserved sequences. The 4xM2e-rHA protein is a highly purified single protein that might enhance tolerance against the antigen and allows administration of higher doses and produce stronger immunological response and protection against the mentioned virus.

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Comparison between MDCK and MDCK-SIAT1 cell lines as preferred host for cell culture-based influenza vaccine production

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Increasing demands for seasonal influenza vaccine and the need for faster methods of vaccine production during flu pandemics and the threat posed by highly pathogenic avian influenza viruses, have made cell culture a suitable substrate for influenza vaccine manufacturers. Cell-adapted viruses replicate with high fidelity, which are expected to have potent vaccine immunogenicity. The aim of this study was evaluating MDCK and MDCK-SIAT1 cell lines for their ability to produce the yield of influenza virus. Yields obtained for influenza virus H1N1 grown in MDCK-SIAT1 cell was almost the same level as MDCK; however, H3N2 virus grown in MDCK-SIAT1 showed lower peak of viral titers in comparison with MDCK cells. The optimized MOI to infect the cells on plates and microcarrier was 0.01 and 0.1 for H1N1 and 0.001 and 0.01 for H3N2, respectively. MDCK-SIAT1 cells have the capacity to be considered as an alternative mean to manufacture cell-based flu vaccine, especially for the human strains (H1N1), due to its antigenic stability and high titer of influenza virus production compared to egg inoculation.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

2nd International Conference on

Influenza

September 12-13, 2016 Berlin, Germany

Immunobioinformatic analysis of the chimeric model of influenza A M2e antigen fused with molecular adjuvant of FliC: Designing, construction & its expression in *E. coli*

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Influenza virus makes a large impact on public health. Annual influenza epidemics cause of death worldwide by almost 250 thousand is considered. Due to permanent mutations in the genome of the virus and the perpetual possibility of producing new viruses that occur as seasonal or pandemic flu, producing a vaccine for this virus is very important. According to the research and understanding of the genome of this virus and the use of genetic engineering techniques, universal vaccine produce is not out of reach. M2e is a conserved epitope that exists among the epitopes candidates for the vaccine against influenza. In addition to that this influenza virus region is antigenic, it is similar in the majority of flu strains and it is protected in some strains with minor differences in amino acid. It does not count appropriate stimulus to the immune system because this peptidic region is too short. For this reason, a molecular adjuvant called FliC was used. In this study, the piece consists of three sequence repeats of the M2e epitope attached to FliC, the molecular adjuvant, (3M2e.FliC) then transferred the recombinant plasmid to *E. coli* strains (BL21 and ER2566), we compare the protein expression in two strains. Immunoinformatics analyzes confirmed that in this recombinant protein, M2e and FliC epitopes are recognized by the immune system and they are existing at the protein surface and available for the immune system. From other activities performed in this study was Three-dimensional modeling of 3M2e.FliC recombinant protein that in this section, a new modeling method was introduced for recombinant protein modeling that provides better results than usual modeling methods.

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Design and evaluation of a multi-epitope universal peptide against influenza virus infection in BALB/c mice

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Human infection with the new subtype influenza A virus is associated with a high mortality and morbidity and causes worldwide pandemic. There is necessity to improve a universal vaccine against influenza pandemic and produce protective immunity by inducing strain-specific neutralizing antibodies to the viral hemagglutinin. For this purpose we have designed a novel multiple linear epitopes (B-cell, CTL and T_h) immunogenic based on the hemagglutinin proteins backbone containing human T cell epitopes for H1 & H3 subtype. In this study, we use the epitope-based vaccine design by using immunoinformatics approach in order to predict the binding of B-cell and T-cell epitopes (class I and class II human leukocyte antigen [HLA]). BCPREDS was used to predict the B-cell epitope. Propred, Propred I, netMHCpan and netMHCIIpan, were used to predict the T-cell epitope. All epitopes were checked by epitope mapping, NCBI ORF Finder, ExPASy, Swiss-Pdb Viewer and Protean. This sequence was cloned into the prokaryotic expression vector peT41a. BALB/c mice were immunized with different dosages of recombinant protein and the immune responses were determined in the form of protective response against influenza virus, antibodies titers (IgG1 and IgG2a), spleen cell lymphocyte proliferation and the levels of interferon-γ and interleukin-4 cytokines. We observed an increase in the number of influenza virus-specific IFNγ-secreting splenocytes, composed of populations marked by $CD4^+$ and $CD8^+$ T cells producing IFNγ or TNFα. Upon challenge with influenza virus, the vaccinated mice exhibited decreased viral load in the lungs and a delay in mortality. These findings suggest that human multi-epitope recombinant influenza virus proteins are a valid approach for a general T-cell vaccine to protect against influenza virus infection.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Molecular epidemiology of virus influenza B in Parana state, Southern Brazil from 2000 to 2015: Implications in immunizations strategy for influenza

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Influenza (flu) is an acute infectious respiratory disease caused by a global spread of influenza virus type A, B and to a lesser extent type C. Children, the elderly and immunocompromised patients with chronic diseases are the most likely groups to severe disease (severe acute respiratory syndrome), responsible for high rates of hospitalization and death that occur annually in 10% of the world population. Epidemiological indicators have shown how the impact of influenza B is substantial, both on the number of childhood deaths but also in the development of severe disease with high numbers of admissions in ICU. In Brazil, the vaccine provided by the National Immunization Program is trivalent, consisting of only one of the two influenza B lineages, which co-circulate annually. In this cross-sectional study, we have characterized by molecular methods the influenza B strains detected from clinical samples stored at the Virology Laboratory/HC-UFPR from 2000 to 2015 and evaluated a possible mismatch between annual prevalent lineage and vaccinal lineage. B lineages (Victoria & Yamagata) were identified by qRT-PCR. From a total of 7,258 respiratory samples investigated for flu B in the period of the study, 74 were positives. Of these, 64 samples were differentiated by lineage. We have observed in 2000 (n=2) and 2001 (n=8) 100% Yamagata; in 2003 (n=7) 43% Yamagata and 28% Victoria; in 2003 (n=5) 80% Victoria and 20% Yamagata; in 2004 (n=2) 50% each lineage; in 2006 (n=6) 66% Yamagata and 34% Victoria; in 2008 (n=17) 41% Yamagata and 29% Victoria; in 2009 (n=2) 100% Yamagata; in 2010 (n=3) 66% Yamagata and 33% Victoria; 2012 (n=3) and 2013 (n=7) 100% Victoria; 2015 (n=6) 100% Yamagata. In the years 2005, 2007, 2011, 2014 none flu B was identified. Two of the years with a high number of cases (2001 and 2008) have presented Yamagata prevalence, while in 2013 there was Victoria lineage prevalence. However, only in 2013 there was a substantial vaccine mismatching. In general, we have also observed that the lineages Yamagata and Victoria co-circulated in an incidence of 60% and 40% respectively. Studies on epidemiological and molecular characteristics of influenza infections are essential for the introduction of preventive and therapeutic intervention by health surveillance units. The identification of strains circulating in the community is a great benefit, providing the information needed for the definition of the annual composition of vaccines.

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J Infect Dis Ther 2016, 4:6(Suppl)
http://dx.doi.org/10.4172/2332-0877.C1.015

Influenza vaccination of medical residents and nurses at the three major teaching hospitals in Iran: across-sectional survey

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Objectives: Health care workers (HCWs) who are unimmunized against influenza put through patients to unnecessary risk of infection.

Objectives: The aim of this study was to evaluate the vaccination status of HCWs, knowledge of and attitudes towards influenza vaccination.

Study design: A cross-sectional survey.

Methods: This cross-sectional study was performed in 459 HCWs of three hospitals between October 2006 and February 2007. They received a username and password to enter in the "queries.tums.ac.ir" website and filled self-administered online questionnaire.

Results: The influenza vaccination coverage for the 2006-2007 seasons was 14.4% (range, 11.2% to17.6%). In logistic regression model of variables, only taking the vaccine in the future year (OR=2.44, CI 95%: 1.21-4.89) was significantly associated with influenza vaccination uptake. The mean knowledge score of residents were 24.0±4.4 (range, 9-34) and nurses were 24.1±4.9 (range, 10-33; P=0.9). Resident and nurses who taking the vaccine in the future year, residents who recommend the vaccine to coworkers or family and nurses who having children less than 16 years at home had significantly higher knowledge scores (P-value<0.0001).

Conclusion: Our data showed that influenza vaccination coverage is low. We will need education and communication strategies to overcome the lack of knowledge and interest.

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The neuraminidase universal epitope of influenza A virus induces a protective immune response in mice

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Human infection with influenza A virus is associated with a high mortality and morbidity and causes worldwide pandemics. There is essential to improve a universal vaccine against influenza pandemic. We identified a total of 12 conserved epitopes in viral neuraminidase proteins containing human T-cell epitopes for N1 & N2 subtypes. In this study, we use the epitope-based vaccine designed by immunoinformatics tools to predict the binding of B-cell and T-cell epitopes (class I and class II human leukocyte antigens [HLA]). BCPREDS was used to predict the B-cell epitopes. Propred, Propred I, netMHCpan and netMHCIIpan were used to predict the T-cell epitopes. The 3D molecular model was constructed by Swiss Model server and N-Glycosylation sites excluded from estimated regions. Important parameters like antigenicity and hydropathicity analyzed by Protean program. This sequence was cloned into the prokaryotic expression vector Pet-41b(+). BALB/c mice were immunized with different dosages of recombinant protein and the immune responses were determined in the form of protective response against influenza virus, antibodies titers, spleen cells lymphocyte proliferation and the levels of interferon-γ and interleukin-4 cytokines. We observed an increase in the number of influenza virus-specific IFNγ-secreting splenocytes, composed of populations marked by CD4+ and CD8+ T cells producing IFNγ or TNFα. Upon challenge with influenza virus, the vaccinated mice exhibited decreased viral load in the lungs and a delay in mortality. T-cells recognizing conserved epitopes were significant contributor to decreasing viral load and controlling disease severity during heterosubtypic infection in animal models.

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