DOWNLOAD PDF THE ISCOMATRIX ADJUVANT DEBBIE DRANE AND MARTIN J. PEARSE

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Find articles by Steven Rockman Lorena E. Brown Find articles by Lorena E. Barr Find articles by Ian G. Address correspondence to Steven Rockman, ua. Received Sep 6; Accepted Dec This article has been cited by other articles in PMC. Abstract In preparing for the threat of a pandemic of avian H5N1 influenza virus, we need to consider the significant delay 4 to 6 months necessary to produce a strain-matched vaccine. As some degree of cross-reactivity between seasonal influenza vaccines and H5N1 virus has been reported, this was further explored in the ferret model to determine the targets of protective immunity. We confirmed that vaccination with seasonal influenza vaccine afforded partial protection against lethal H5N1 challenge and showed that use of either AlPO4 or Iscomatrix adjuvant with the vaccine resulted in complete protection against disease and death. The protection was due exclusively to the H1N1 vaccine component, and although the hemagglutinin contributed to protection, the dominant protective response was targeted toward the neuraminidase NA and correlated with sialic acid cleavage-inhibiting antibody titers. Purified heterologous NA formulated with Iscomatrix adjuvant was also protective. These results suggest that adjuvanted seasonal trivalent vaccine could be used as an interim measure to decrease morbidity and mortality from H5N1 prior to the availability of a specific vaccine. The data also highlight that an inducer of cross-protective immunity is the NA, a protein whose levels are not normally monitored in vaccines and whose capacity to induce immunity in recipients is not normally assessed. INTRODUCTION The recent announcement of the engineering of avian H5N1 influenza virus to become readily transmissible by air in ferrets 1 , 2 has caused considerable concern and refocusing on issues regarding how vulnerable we are to infection with such a virus and whether we have the tools available to lessen the impact should this virus become pandemic. Although vaccination is considered the best approach to prevent disease and limit transmission, the effectiveness of vaccination in the face of a pandemic is dictated by the length of time taken to produce a pandemic strain-matched vaccine in sufficient quantities for mass vaccination 7. Cross-reactive immunity, particularly against influenza virus of a heterologous hemagglutinin HA subtype, as would be expected to emerge as a severe pandemic, is efficiently induced by prior infection through the action of cytotoxic T cells to the conserved internal components of the virus, but such immunity is much less demonstrable after vaccination with current inactivated vaccines 8. Nevertheless, a number of groups have investigated the ability of a seasonal influenza vaccine or components thereof to induce protection against H5N1 infection. Thus far, partial protection has been demonstrated in the mouse model 9 , 10 and in pigs 11 following parenteral delivery of a seasonal trivalent vaccine in the absence of an adjuvant. Cross-reactive responses to seasonal influenza vaccines that could potentially confer this partial benefit have been attributed to antibodies against HA 12 or neuraminidase NA 13 â€” To fully appreciate the targets of cross-reactive immunity, the individual components of seasonal influenza vaccines were used to examine heterologous protection in this setting. These studies have provided further insight into the immune mediators of heterologous protection and suggest that an adjuvanted seasonal influenza vaccine could be deployed immediately after an H5N1 pandemic is declared to afford protection before the pandemic strain-matched vaccine becomes available. Healthy juvenile ferrets less than 12 months old and weighing to 1, g were obtained from the Institute of Medical and Veterinary Science, Adelaide, South Australia. Ferrets were allocated to groups in a manner to minimize the potential impact of age and weight on the response to vaccination and challenge and were determined to be seronegative for the currently circulating seasonal strains H1N1, H3N2, B viruses using standard hemagglutination inhibition HI tests prior to the commencement of the study. Real-time PCR assays specific for H3 and N1 were used to confirm the identity of the gene segments contained in the resulting reassortant virus. This vaccine was recommended for the Northern Hemisphere to influenza seasons and the Southern Hemisphere season. The

concentration of viral antigen, expressed in terms of HA protein content, was determined by a standard single radial immunodiffusion assay and compared to that of a known standard of the relevant strain. Vaccination and viral challenge of ferrets. Vaccination and challenge were performed under ketamine-medetomidine anesthesia General clinical observations were made prior to and following challenge, and a detailed clinical signs sheet and an evaluation of activity based on a five-level score 16 were recorded at each inspection. Animals were weighed while under sedation at the time of vaccination and challenge and on days 3, 5, 7, and 14 postchallenge. Rectal temperature was also determined at sedation. Blood samples were collected immediately prior to each vaccination and prior to viral challenge. A further blood sample was taken 14 days postchallenge or at the time of euthanasia for serology. Blood collections were performed on anesthetized animals ketamine-medetomidine, Nasal washes were collected into 1 ml of phosphate-buffered saline PBS , on days 3, 5, and 7 postchallenge for virus isolation. Immunological and virological evaluation. The samples were assessed by a hemagglutination inhibition HI test using chicken red blood cells and virus neutralization VN by standard methods. Enzyme-linked immunosorbent assays ELISAs were performed on wells coated with detergent-solubilized purified virus preparations Fluorescent -COOH beads no. The coating was performed using carbodiimide-based linking of the -COOH groups on the bead surface with primary amino groups of the antigen according to the Bio-Rad protocol modified to slow down the reaction in order to reduce undesired cross-linking of the HA. Reading of the control and tested samples was performed using a BioPlex bead array reader Bio-Rad. The individual sensitivity of the beads coated with various HAs was determined by comparing the results to those of standard antibody solutions using the bead array in the BioPlex reader and using ELISAs with the same HA antigens that were used for coating the beads. The standard antibody for such calibration was ViroStat anti-influenza A polyclonal biotinylated antibody. Fluorescence in BioPlex readings was measured as the mean fluorescent index MFI , which is proportional to the level of the antibody binding to the influenza virus strain-specific bead. All serum samples were diluted 1: The ferret model was used to investigate the ability of seasonal influenza vaccines to protect against a lethal H5N1 challenge. All four PBS control ferrets rapidly lost weight Fig.

Chapter 2 : ISCOMATRIX adjuvant: a potent inducer of humoral and cellular immune responses.

Debbie P. Drane,2 Max Schnurr,1 Thuy T. T. Le,3 Martin J. Pearse,2 Francois A. Lemonnier,4 ESO-1 and ISCOMATRIX adjuvant was confirmed by flow.

The mechanisms by which ISCOMATRIX adjuvant facilitates its immune effects are the scope of significant study and indicate that ISCOMATRIX adjuvant i rapidly traffics antigen into the cytosol of multiple dendritic cell subsets, ii induces the induction of an array of cytokines and chemokines and iii links the innate and adaptive immune responses in vivo in a Toll-like- receptor-independent but MyDdependent manner. The newer generation of vaccines are, typically, derived from purified pathogen subunits to reduce Prophylactic vaccination against pathogens has contributed overt reactogenicity, but as a result are also less efficacious greatly to improving human health. No better examples and require the addition of exogenous adjuvants to reinstate can be demonstrated than the effective control of polio, immunogenicity. How- ever, there is still an urgent need for vaccines against several Adjuvants provide additional signals during the induction pathogens that cause serious human infections and increased of immune responses to the vaccine antigen with the aim of morbidity. In addition, Roels, Adjuvanted vaccines also provide a rational strategy through pattern recognition receptors PRRs. Although to induce protection in individuals whose immune system efficacious, such vaccines are also associated with increased is waning or dysfunctional due to senescence or immune suppression. Immune protection during a pandemic out- Abbreviations: Ab, antibody; APC, antigen presenting cells; AS, adjuvant break requires the rapid induction of immunity. C , old of activation of the immune system, so that it will polyinosinic: Wed, 14 Jun Baz Morelli and others and facilitates broader vaccination. Adjuvant development achieve protection and whether the type of immune is an active area of research driven by the need to improve response induced by the adjuvant fulfils these parameters. Approved and novel adjuvants Very few adjuvants are currently licensed for human Mechanism of defence against infection vaccine use. The most common are the aluminium salts The initiation of the immune response against pathogens which have been used as vaccine adjuvants for over involves recognition of PAMPs and activation of innate 80 years in a very large number of individuals, dem- cells and dendritic cells DCs through PRR signalling. Although aluminium salts These include cell-surface and endosomal Toll-like recep- are effective for induction of Ab responses, generation of tors TLRs , surface C-type lectin receptors and the Th2 responses and, more recently, activation of the cytosolic NOD-like receptors and RIG-I-like receptors inflammasome Kool et al. Th1, Th2, Th17 differing in their Kuroda et al. The adjuvant MF59, developed by cytokine profile and effector functions. The production of Novartis, is an oil-in-water emulsion that is believed to interleukin IL by DCs promotes differentiation of stimulate chemokine production by monocytes, macro- Th1 cells [secreting interferon IFN -c, IL-2 and tumour phages and granulocytes and activates an array of cytokines necrosis factor TNF -a], which activate natural killer NK and host defence pathways at the injection site Seubert cell and macrophage functions and induce IFN-c-regulated et al. MF59 has been licensed for Ab isotypes that enhance phagocytosis, Ab-dependent cell an influenza vaccine for the elderly Fluad, Novartis and cytotoxicity and complement activation. In general, Th1 responses reactive immune responses among different viral clades, play critical roles in the protection against intracellular which might be important during pandemics Banzhoff pathogens, whereas Th2 responses are involved in the et al. They are also associated with in- The need for more potent Ab responses, as well as flammatory immunopathologies in some individuals e. The discovery of PRRs and their Evasion of the immune response by pathogens role in the initiation of immune responses has led to the development of PRR agonists as either individual adjuvants Pathogens have evolved mechanisms to evade the immune or as components of adjuvant combinations. Clinical trials are in progress with AS01 presentation, reducing the magnitude of the adaptive res- vaccines for HIV and tuberculosis. A Phase III clinical trial ponse. Furthermore, certain HCV proteins induce T regu- with AS01 vaccine showed protection against clinical and latory cells that suppress emerging effector T-cell responses

severe malaria in children Agnandji et al. AS03 has Li et al. Porphyromonas gingivalis and Listeria been included in a pandemic influenza vaccine Leroux- monocytogenes avoid detection by being retained within Roels et al. Therefore, the with antigen formulated with aluminium salts alone Beran selection of adjuvants for any given disease must take et al. Bacterial unmethylated into consideration the immune evasion mechanisms of the CpG oligodeoxynucleotide ODN is a TLR-9 agonist that pathogen, the immunological mechanisms required to induces Th1 cytokines Bode et al. We have addressed influenza virus, measles virus, lymphocytic choriomenin- these issues with the development of the ISCOMATRIX gitis virus, orthopox virus and hepatitis B virus infections adjuvant which does not require antigen to be incorporated Klinman et al. All the components used in the manufacture of Brichard, C] capable of meeting the stringent needs for human vaccines induces T-cell responses in animal models, although data in the 21st century. C by serum proteases Li et al. Derivatives of poly I: Liposome encapsulation of poly ICLC Understanding the mode of action of novel adjuvants is now reduces its toxicity and enhances the duration of protection essential in defining adjuvant safety and potential applica- of an influenza virus vaccine in mice, highlighting the link tions to support registration of the final vaccine product. We between vaccine formulation and its efficacy and safety have used a wide range of in vivo and in vitro approaches profile Li et al. A summary of our findings is represented in Fig. TLR-8 agonists can also enhance immunogenicity in mice to recombinant hepatitis B antigen in comparison to aluminium-containing adjuvants Du et al. The classical ISCOM technology, however, required incorporation of vaccine antigens into the structure, which not only restricted the Fig. During acidification of these compartments, measured by intracellular cytokine staining ICS. Antigen presentation within the DLN is sustained for up to 7 days intracellular depot Wilson et al. Generation of high- DCs , ensuring continuous and prolonged antigen presentation. Lymph nodes shut down leukocyte weakly at best detected with other adjuvant systems. The co-expression of these two functional facets increase in the number of NK cells, B-cells, T-cells, DCs ensures the generation of robust adaptive immune responses. This is a adjuvant system. The activation of NK cells appears to be under the regulation of DCs and specific cytokines, Although some of the features depicted in Fig. Activation of innate cells may those observed with other adjuvants e. The activation of the inflammasome has reported for other adjuvant systems. Furthermore, presenting cells APCs. In parallel, antigen presentation is IL-1b is induced in vivo Wilson et al. We are currently Wilson et al. Effector responses et al. Broad responses including, Ab, Pam3Cys Duewell et al. This is also shown in Fig. Vaccination responses as compared to aluminium hydroxide or the of patients with recombinant HPV 16 early gene proteins TLR-3 agonist poly I: In vitro experiments with human individuals Anderson et al. Prophy- fold less antigen Sanders et al. Enhanced immuno- lactic vaccines need to induce high-titre Ab responses that genicity at a low dose of antigens was also observed using are long-lived, of high affinity and of isotypes capable of recombinant gp in guinea pigs Boyle et al. We have The route of inoculation is an important consideration shown that, in mice, an OVA-ISCOMATRIX vaccine in vaccine development and immunization protocols as it induces formation of persistent germinal centres and can determine the type and quality of the immune res- plasmocytes, both of which explain the long-lasting Ab ponse. Furthermore, the induction of high and persistent both parenteral and non-parenteral routes. Ab titres is detectable in blood up to 1 year after one or showed that the Ab responses induced by an two vaccinations, as well as significant affinity maturation ISCOMATRIX influenza vaccine delivered intranasally, unpublished data. Similar findings were reported by were higher than the responses induced by the unadju- Clements et al. Such versatility was at a very low dose of antigen, either in mice or non-human also observed in a mouse model for Helicobacter pylori primates Clements et al. It is of note that subsequent analyses of the humoral alternate routes in specific cases. These isotypes are cytophilic and complement ling pathways. In this regard, Jacobs et al. These studies were completed as part of three separate development References programs for a therapeutic HPV vaccine, a therapeutic HCV vaccine and a prophylactic influenza vaccine. A compre- Agnandji, S. First results of phase 3 trial of adjuvant has recently been reported McKenzie et al. N Engl J Med , Briefly, clinical evaluation of the local and systemic re- â€” A randomized, placebo-controlled, dose- studied

and in all antigenâ€”adjuvant combinations. Local escalation study to determine the safety, tolerability, and immuno- reactions were predominantly mild to moderate and re- genicity of an HPV therapeutic vaccine in HIV-positive partici- solved within 4 days, and a flu-like syndrome was the most pants with oncogenic HPV infection of the anus. J Acquir Immune common unsolicited systemic adverse effect. No evidence Defic Syndr 52, â€" Expert Opin Ther Pat 20, â€" MFadjuvanted H5N1 vaccine induces immuno- logic memory and heterotypic antibody responses in non-elderly and A study to determine safety, tolerability and immuno- elderly adults. A study to determine safety, Birmingham, C. Nature , â€" adjuvant in healthy adults and the elderly. Expert Rev Vaccines 10, â€" Cancer Immun 5 Suppl. Efficacy of a conjugate vaccine containing with the younger adults, suggesting that ISCOMATRIX polymannuronic acid and flagellin against experimental Pseudomonas adjuvant has the potential to overcome immune senescence aeruginosa lung infection in mice. Infect Immun 79, â€" Development of a recombinant tetravalent dengue virus Conclusion vaccine: CPG , an persistent effector and memory Ab and cellular responses. J Clin Immunol 24, â€" TLR agonists that should Clinical studies will provide information as to responses in humans. Baz Morelli and others Dorn, B. J Exp Med , Porphyromonas gingivalis traffics to autophagosomes in human â€" Infect Immun 69, â€" Expert Rev Vaccines 6, â€" Unmet needs in modern vaccinology: Hum Vaccin 5, â€" Antigen sparing and cross-reactive immunity with an adjuvanted Du, J. TLR8 agonists stimulate newly recruited monocyte-derived trial. Immune evasion by Duewell, P. J Immunol , 55â€" A long, naturally presented immunodominant Pathog 5, e

Chapter 3 : ISCOMATRIX adjuvant for antigen delivery | Read by QxMD

Martin J Pearse Debbie Drane. H Arnold Martin J Pearse Debbie P Drane Trina J Stewart in ISCOMATRIX adjuvant is a potent anticancer vaccine inducing both.

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The ability of the ISCOMATRIX adjuvant to induce these broad immune responses is due to the combination of antigen presentation by both MHC class I and class II pathways, and the powerful immunomodulatory capability of the saponin.

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