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DNA vaccine based on genes from pandemic influenza A viruses induces broadly protective immunity in swine

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STATENS SERUM INSTITUT

INFLUENZA DNA VACCINE

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INTRODUCTION

We have developed an influenza DNA vaccine expressing different influenza proteins of pandemic and seasonal origin and demonstrate protection in swine against infection with both heterologous and homologous H1N1 virus infection.

- Influenza vaccines inducing broad cross-reactive immune responses would be of great advantage for protection against both seasonal and emerging influenza viruses.
- DNA vaccines trigger both humoral and T-cell immunity which induce a broad and long-lived protection
- Intradermal (i.d.) delivery of DNA vaccines has been the most effective way of immunisation using less antigen.
- New-generation DNA vaccines perform well, also in larger animals.

CONCLUSIONS

The influenza DNA vaccine based on the surface glycoproteins of pandemic H1N1v-09, seasonal H3N2 influenza viruses and internal proteins from the pandemic 1918 H1N1 virus induced protection against homologous and heterologous virus infection in pigs.

- DNA vaccinated pigs were protected from infection or able to clear the virus infection more rapidly than the control group
- The influenza DNA vaccine induced broadly protective haemagglutination inhibition (HI) and HA specific IgG antibodies able to cross-react with heterologous H1N1 and H3N2 viruses
- Vaccine induced antibody levels were increased upon challenge with homologous and heterologous virus infections.

Protection against heterologous H1N1 challenge – Pilot study

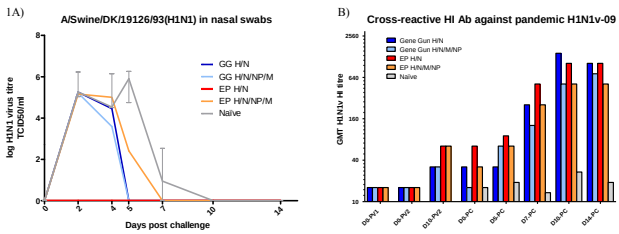

Figure 1: DNA vaccine based on the HA+NA genes of H1N1v-09 virus, with or without the M + NP genes of H1N1 1918
Challenge: Classical swine H1N1 virus from 1993. (DNA vaccine groups n=1, Naïve group n=4)

- DNA vaccinated pigs clear the virus infection, heterologous to the vaccine component, more rapidly than unvaccinated pigs. Sterile immunity observed for the pig vaccinated with HA+NA by EP (Fig. 1A).
- HI titre >40 at day 10 post 2.nd vaccination by EP. Higher levels of HI antibodies in DNA vaccinated pigs compared to non-vaccinated pigs (Fig.1B).
- Heterologous challenge trigger vaccine-generated H1N1v-09 HI antibodies.
- EP was chosen as the gene delivery method for the following study.

DNA vaccine induces high antibody levels in pigs and protects against H1N1v-09 infection

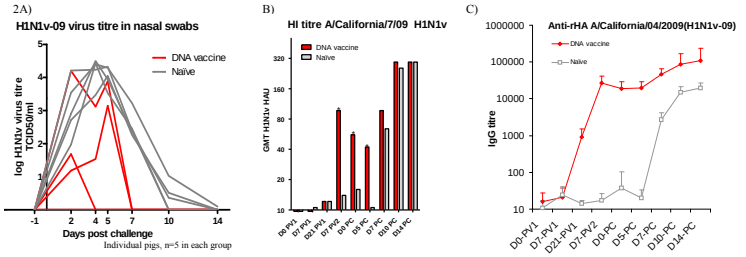

Figure 2: DNA vaccine based on the HA+NA genes of H1N1v-09 +HA and NA of H3N2-05 + M + NP genes of H1N1 1918
Challenge: H1N1v-09 virus. (DNA vaccine group n=5, naïve group n=5)

- Pigs vaccinated by DNA EP are either protected from infection or clear the virus infection more rapidly than un-vaccinated pigs. Sterile immunity observed for 2 of 5 DNA vaccinated pigs (Fig. 2A).
- H1N1v-09 HI titre >40HAU at 7 days post 2.nd vaccination. Significant higher HI antibodies compared to un-vaccinated pigs (Fig. 2B)
- The DNA vaccine induce high HA specific IgG antibodies after first vaccination which is increased after challenge (Fig. 2C)

DNA vaccine induces high cross-reactive levels of HI and IgG antibodies in pigs

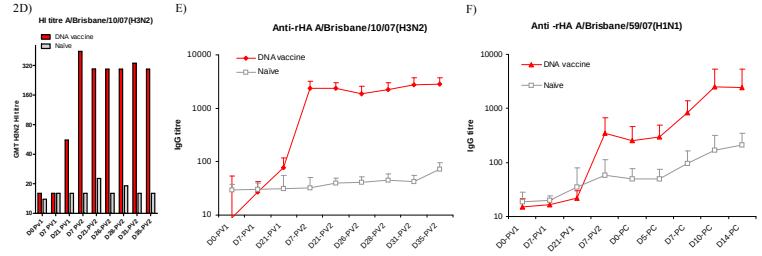

Figure 2: DNA vaccine based on the HA+NA genes of H1N1v-09 +HA and NA of H3N2-05 + M + NP genes of H1N1 1918
Challenge: H1N1v-09 virus. (DNA vaccine group n=5, naïve group n=5)

- Antibodies against the H3N2 components in the DNA vaccine (included in the 2006 to 2008 protein vaccines) cross-reacted with the H3N2 components included in the 2009-10 protein vaccine (A/Brisbane/10/07) (Fig. 2D and E).
- Cross-reactive H3N2 HI titre >40HAU at 21 days post 1.st vaccination (Fig. 2D)
- The DNA vaccine based on the H1N1v HA and NA genes induce HA specific IgG antibodies that cross-react with the genetically and antigenetically different H1N1 virus from previous seasons (A/Brisbane/59/07). In addition, challenge by H1N1v induce an increase in antibodies against the seasonal H1N1 (Fig.2F)

Objectives/Study design

Objectives
Study 1 – Fig. 1A, B, Fig. 3:
•Pilot study, epidemal delivery of DNA vaccine: comparison of gene gun (GG) and electroporation (EP)
•Determine cross-protection from classical swine H1N1 infection by human H1N1v-09 DNA vaccine in swine.
Study design: Influenza genes were codon-optimised and cloned in an expression vector. Four pigs were vaccinated twice, three weeks apart with either HA and NA genes from H1N1v-09 (A/California/7/09) alone or in combination with NP and M genes from the 1918 H1N1 virus, dorsal side of each ear and on inner side of each thigh. Each GG shot contained 2 µg DNA, EP used 100 µg DNA each i.d. injection. The pigs were challenged with A/swine/DK19126/93(H1N1) ten weeks after last immunisation (Fig.3). One pig was included for each DNA vaccine group and four pigs were included in the un-vaccinated naïve group.

Study 2 – Fig. 2A, B, C, D, E, F, Fig. 4:
•Evaluate the protection from H1N1v-infection in swine immunised with an H1N1v/H3N2 DNA vaccine based on the 2009 H1N1 pandemic HA and NA + 2007 H3N2 HA and NA + 1918 H1N1 pandemic NP and M genes.
Study design: Influenza genes were codon-optimised and cloned in an expression vector. Five pigs were vaccinated by EP (200 µg total DNA in one injection, ~66.4 µg HA DNA, each injection), twice, three weeks apart with HA and NA genes from H1N1v-09 and A/Wisconsin/67/05(H3N2) in combination with NP and M genes from the 1918 H1N1 virus, dorsal side of each ear and on inner side of each thigh. The pigs were challenged with A/California/07/09(H1N1v) three weeks after last immunisation (Fig. 4).