A Novel Influenza Vaccine Based on Deletion of M2

Pamuk Bilsel
January 24, 2013
WHO Influenza Meeting
THE COMPELLING NEED FOR GAME-CHANGING INFLUENZA VACCINES

AN ANALYSIS OF THE INFLUENZA VACCINE ENTERPRISE AND RECOMMENDATIONS FOR THE FUTURE

EXECUTIVE SUMMARY

CIDRAP

Center for Infectious Disease Research & Policy

UNIVERSITY OF MINNESOTA

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**Single Replication Influenza Vaccine**

\[ \text{M2KO} = \text{Live attenuated vaccine} + \text{inactivated vaccine} \]

M2KO stimulates mucosal immunity in the respiratory tract, and is therefore ideal for disease prevention.
M2 protein is not made in cells infected with M2KO

Wild-type M2 ORF

Ectodomain

Transmembrane domain

Cytoplasmic Tail

M2KO M2 ORF

Ectodomain

Stop, Stop

Transmembrane domain

Cytoplasmic Tail

Wild-type M2

Outside cell

Cytoplasm

M2KO M2
M2 protein is membrane protein
Influenza Virus Life Cycle

M2 – ion channel activity

No M2 = No Infectious Virus

Subbarao et al., Immunity 24, 5-9 (2006)
M2KO is grown in M2 expressing cells

Production Cells: express M2

M2KO

Enter cell

Express viral proteins

Progeny vaccine virus

Normal Cell

No progeny virus
M2KO is attenuated \textit{in vivo}.

![Graph showing % body weight over days post-inoculation for PR8, M2KO, and PBS groups.](image)
Vaccine Study Design

PR8 virus

M2KO

Inactivated PR8 virus

FluGen
M2KO Generates Strong Antibody Response

A. Sera: Systemic

B. Trachea-Lung Washes: Local

ELISA titer (log_{10})

Wild-type | M2KO | Inactivated | PBS
---|---|---|---
Wild-type | | | |
M2KO | | | |
Inactivated | | | |
PBS | | | |

ELISA titer (log_{10})

Wild-type | M2KO | Inactivated | PBS
---|---|---|---
Wild-type | | | |
M2KO | | | |
Inactivated | | | |
PBS | | | |

IgG | IgA

FluGen
Challenge with ‘Homologous Virus’ (‘matched’ vaccine and virus)

H1N1 Vaccine

H1N1 Challenge Virus

6 weeks post-immunization
M2KO Protects Animal from Homologous Virus Challenge

Days post-challenge vs % body weight graph showing the protection effect of M2KO against homologous virus challenge. The graph compares the body weight percentage of animals exposed to different treatments over 14 days post-challenge. The treatments include wild-type virus, M2KO Flu, inactivated IN, inactivated IM, PBS, and no challenge. The graph highlights M2KO Protect's protective effect.
Challenge with ‘Heterologous Virus’
(‘mismatched’ vaccine and virus)

H1N1 Vaccine

H3N2 Challenge Virus

6 weeks post-immunization
H1N1 M2KO Flu Protects Mice from H3N2 Virus Challenge

% Survival

Days post-challenge

- Wild-type virus
- M2KO
- inactivated IN
- inactivated IM
- PBS
M2KO as H5N1 pandemic vaccine

- M gene does not encode M2 gene
- 6:2 reassortant
  - Internal genes are from PR8
- H5N1 HA is ‘avirulent’
  - no multi–basic cleavage site
- Does not shed/transmit virus

Diagram:
- Airflow
  - Inoculated Donor
  - Direct contact
  - Aerosol contact
SUMMARY

• M2KO vaccine:
  • does not shed virus
  • elicits systemic, mucosal and cell-mediated responses
  • protects against homosubtypic and heterosubtypic flu virus
  • induces long-lasting protective responses
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