Combined use of live-attenuated and inactivated influenza vaccines to enhance heterosubtypic protection

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Protection from commercial influenza vaccines is far from optimal when the vaccine strains *antigenically do not match* with the circulating viruses.

Currently licensed influenza vaccines have their limitations.

- live attenuated influenza vaccine (LAIV), inactivated influenza vaccine (IIV), and recombinant influenza vaccine (RIV)

Novel vaccination approaches.
Hierarchical clusters of HA subtypes

Aim of study

Subtype-specific influenza vaccines (Group 1 HA: H1 or H5)

Broadly cross protections

Level of cross protections induced by different combinations of vaccination regimens.

Highlights

I. Sequential vaccination can generate heterosubtypic protection against IAV.

II. Combined use of LAIV + IIV induces good cross protection.

III. Different vaccination regimens can induce different immune profiles.
Wyeth/IL-15/5Flu (5Flu)

- A novel vaccinia-based live-attenuated pentavalent vaccine
  1) HA, NA and NP (H5N1/A/Vietnam/1203/2004)
  2) M1 and M2 (H5N1/A/CK/Indonesia/PA/2003)
  3) Adjuvant human IL-15

- Previous studies revealed:
  a) Trigger both MHC I and II antigen processing machineries
  b) Elicit robust CD4 and CD8 T cell responses
  c) Induce good cross-protection.

Publications:

5Flu might be a promising candidate to serve as a universal vaccine.
4-dose sequential vaccination regimens in Balb/c mouse model

- 8-week old Balb/c mice.
- After sequential vaccination, either scarificed for No Challenge (NC)
- Or challenged (i.n.) with a lethal dose of heterologous IAV.

Sequential vaccinations generate strong cross-protection against infections caused by different subtypes

- For heterosubtypic protection, LAIV is more potent than IIV.
- Repeated immunization can lead to better protection.
Sequential vaccinations reduce severity of illness of infected mice

• Viral loads in the lungs, at 3 and 7 dpi

• Total protein concentration in BAL, at 7 dpi

➢ Group inH1/V: superior to IIV alone.

➢ Group inH1/V mice had the least lung injury.
**Sequential vaccinations induce efficient cross-protective antibodies**

- Serum, No Challenge

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<tr>
<th>Antigen</th>
<th>IgG1</th>
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<td>V</td>
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<td><strong>Group 1 HA</strong></td>
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<td>sH1</td>
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<td>pdmH1</td>
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<td>1280</td>
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<td><strong>Group 2 HA</strong></td>
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<td>H3N2/HK68</td>
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- Group inH1/V: ↑↑↑↑ IgG1.

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<th>Antigen</th>
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- IIV: ↑↑ IgG2α against Group 1 HA
Sequential vaccinations induce efficient cross-protective antibodies

- Influenza-NP specific IgG1 Ab profiles.
  - Serum, NC Vs at 7 dpi.
  - Group inH1/V: ↑↑↑ IgG1.
Sequential vaccinations induce efficient cross-neutralizing antibodies

- In serum, with Geometric mean titers (GMT).

- At 7 dpi

  - Group inH1/V: most potent regimen after infections.

  - NO pre-existing cross-nAbs induced by sequential vaccination regimens.
Sequential vaccinations improve influenza-specific T-cell responses

- Influenza immunodominant NP or HA epitope-specific CD8 T-cell responses.
- For Type-1 cytokines (IFN-γ, TNF-α, IL-2) and Type-2 (IL-4).

 Group inH1/V: type 1 CKs against NP and HA, including mono-functional and poly-functional (IFN-γ+TNF-α+)

 Group inH1/H5: NP-specific responses.

 No good IL-2 and IL-4.
Influenza immunodominant NP or HA epitope-specific CD4 T-cell responses.

For Type-1 cytokines (IFN-γ, TNF-α, IL-2) and Type-2 (IL-4).

Sequential vaccinations improve influenza-specific T-cell responses

- Group inH1/H5: TNF-α against NP and HA.
- Group V: TNF-α against NP.
- Different vaccine compositions induce different biases in T cell responses.
Sequential vaccinations exert effectively localized recall of CD8 T cell responses against heterologous IAV

- In BAL, at 7 dpi.
  - Good Tc1 CKs were detected.
  - Group inH1/V: ↑↑↑ against HA after H1N1 or H3N2.
  - Groups inH1 and inH1/H5: ↑↑ NP-induced responses after a H1N1, but not H3N2.
Sequential vaccinations exert effectively systemic recall of CD8 T cell responses against heterologous IAV

- In spleen, at 7 dpi.
  - Good Tc1 CKs were detected.
  - Group inH1/V: ↑↑ against HA after H1N1 or H3N2.
  - Groups V: ↑ NP-induced responses after a H1N1, but not H3N2.
Summary

1. All studied 4-dose vaccinations could induce some degrees of heterosubtypic protection in mice.

2. Combined use of LAIV + IIV vaccines could achieve the best heterologous protection.
Conclusion

• Potential benefits of combined use of LAIV + IIV vaccines.

• Best protection against lethal challenge of heterologous IAV in mice.

• Developing alternative vaccine strategies for universal protection.

• Relevant immunologic information.
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