Mucosal immunity:
What do we need for protection?

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Host and virological factors contributing to breakthrough infection following vaccination

Waning immunity

Antibody

B cell

T cell
Mucosal immunity: sterilizing protection and rapid recall responses

Problems and solutions to nasal vaccines
Current status on mucosal vaccines

- Only a handful of licensed mucosal vaccines
- Live attenuated vaccines require significant R&D for safety and are not usable in immunocompromised
- Only one is available for respiratory pathogens (FluMist)
- FluMist only approved for 2-49 yo and not in pregnancy due to adverse events

Cautionary tale of adjuvanted nasal vaccines

Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland

Margot Mutsch, Ph.D., M.P.H., Weigong Zhou, M.D., Ph.D., Philip Rhodes, Ph.D., Matthias Bopp, Ph.D., Robert T. Chen, M.D., Thomas Linder, M.D., Christian Spyr, Ph.D., and Robert Steffen, M.D.

-1996-1999: 1218 volunteers during four winter seasons in clinical trial: no AE

-In 2000, the first licensed inactivated intranasal IAV vaccine approved for use in Switzerland

-Between Oct 2000 and April 2001: 46 cases of Bell’s palsy reported in vaccinees

-Retrospective Case control of Bell’s palsy cases in Switzerland Oct 2000 to April 2001
-773 cases identified->250 with 722 controls

<table>
<thead>
<tr>
<th>Vaccine and Bell’s Palsy Onset Interval</th>
<th>Case Patients (N=250)</th>
<th>Controls (N=722)</th>
<th>Adjusted Odds Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Inactivated vaccine</td>
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<tr>
<td>Onset interval ≤91 days</td>
<td>63 (25.2)</td>
<td>7 (1.0)</td>
<td>84.0 (20.1–351.9)</td>
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<tr>
<td>Onset interval &gt;91 days</td>
<td>5 (2.0)</td>
<td>1 (0.1)</td>
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<tr>
<td>Parenteral vaccine</td>
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<tr>
<td>Onset interval ≤91 days</td>
<td>10 (4.0)</td>
<td>41 (5.7)</td>
<td>1.1 (0.6–2.0)</td>
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<tr>
<td>Onset interval &gt;91 days</td>
<td>17 (6.8)</td>
<td>49 (6.8)</td>
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Solution: Prime and Spike

We found a way to safely and robustly induce protective immunity in the respiratory mucosa with a nasal booster

Ben Israelow
Tianyang Mao
“Spiking” respiratory immunity via intranasal boosting of prime-induced systemic immunity

Parenteral mRNA-LNP prime

CD8^+ T cells
IgG^+ B cells
CD4^+ T cells
IgA^+ B cells
IgG
IgA
IN Spike boosting elicits mucosal spike-specific IgA and IgG production in the airway
IN Spike boosting confers complete mucosal protection against lethal SARS-CoV-2 infection.

**Parenteral Prime**
0.05 μg mRNA-LNP IM

**Mucosal Boost**
1 μg SARS-CoV-2 Spike IN

**SARS-CoV-2 Challenge**
6×10⁴ PFU SARS-CoV-2 IN

Day 0
Day 14
Day 56
Day 70

Weight loss & Survival
IN Spike boosting reduces viral titer and alleviates lung pathology in the respiratory tract.
IN Spike boosting prevents severe inflammatory infiltration in the lower respiratory tract
IN SCV1 boosting induced mucosal and systemic antibody responses against SARS-CoV-2

Parenteral Prime
1 µg mRNA-LNP IM

Parenteral Boost
1 µg mRNA-LNP IM

Mucosal Boost
5 µg SARS-CoV-1 Spike IN

or

BALF and blood collection for anti-SARS-CoV-2 antibody analysis

K18-hACE2

Day 0

Day 14

Day 45

Anti-SCV2 S1 IgA

Anti-SCV2 S1 IgG

Anti-SCV2 S1 IgA

Anti-SCV2 S1 IgG

SCV2 Neut

Absorbance (nm)

BALF

Serum

IC_{50} (log)

Naive

mRNA-LNP Prime/Boost

Prime and SpikeX

mRNA-LNP Prime/Boost + SpikeX

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ns

ns

ns

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ns

ns

ns

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ns

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Conclusions

Prime and Spike leverages existing memory cells to stimulate robust mucosal immunity in the upper and lower respiratory tract.

Prime and Spike induces robust local T and B cell immunity at the respiratory mucosa.

Prime and Spike protects mice with partial immunity from lethal SARS-CoV-2 infection.

Intranasal boosting with SARS-CoV-1 spike elicits pan-sarbecovirus immunity without invoking original antigenic sin.