How can development of new vaccine platforms, such as mucosal vaccines, be encouraged?

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Worldwide Deaths Annually from Mucosal Infections

- **COVID-19** (6.5 million and counting/32 month)
- Acute respiratory infections (4 million)
- Diarrheal diseases (2.2 million)
- HIV/AIDS (2 million)
- Tuberculosis (1.5 million)
- Measles (400,000)
- Whooping cough (294,000)
- Hepatitis B (103,000*)
- Roundworm and hookworm (6,000)

Adapted from Janeway’s Immunology, 8th ed. (© Garland Science 2012)
Why are mucosal vaccines better than intramuscular vaccines?
Waning immunity

- Antibody
- B cell
- T cell
Mucosal immunity: sterilizing protection and rapid recall responses

Problems and solutions to nasal 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)

• Proximity of nasal cavity to the CNS via olfactory bulb requires extra safety precautions

Modified from Nature Reviews Immunology volume 22, pages236–250 (2022)
Solution: Prime and Spike

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

Circulation
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**
6×10^4 PFU SARS-CoV-2 IN

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**Weight loss (Average)**

Weight loss (% of weight at day 0)

Days post infection: 0 2 4 6 8 10 12 14

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**Weight loss (Individual)**

Weight loss (% of weight at day 0)

Days post infection: 0 2 4 6 8 10 12 14

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**Survival**

% Survival

Days post infection: 0 2 4 6 8 10 12 14

- Naïve
- IM Prime
- Prime and Spike

Survival:

- ****
- ns
IN Spike boosting reduces viral titer and alleviates lung pathology in the respiratory tract.
IN SARS-CoV-1 Spike boost induces mucosal and systemic antibody responses against SARS-CoV-1.
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.

• Prime and Spike reduces mucosal viral replication and transmission.
How can development of new vaccine platforms, such as mucosal vaccines, be encouraged?

• More resources and government support are needed to develop and translate mucosal vaccines -> Operation nasal vaccines at lightning speed (Eric Topol)

• Develop correlates of protection that better reflect mucosal immunity. This may require new methods of collection and measurements.

• Make existing vaccines available for research purposes. We need to be able to compare new vaccine strategies to existing vaccines.
Acknowledgement

**Unadjuvanted intranasal spike vaccine booster elicits robust protective mucosal immunity against sardbecoviruses**

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