Development of Novel Mucosal Adjuvant

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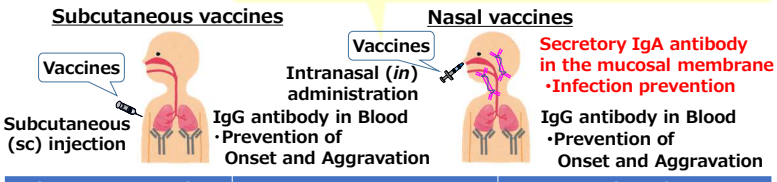
Objective: Development of a Novel Mucosal Adjuvant for Nasal Vaccines

Mucous membranes, which are in constant contact with the outside world, have physical and chemical barrier functions, such as mucociliary movement to eliminate foreign substances and pathogens, making it difficult to induce immune responses.

Useful mucosal adjuvants are necessary for mucosal vaccines to effectively induce mucosal immune responses.



Subcutaneous vaccines		Nasal vaccines
General infections	<Target of vaccines>	Respiratory tract infections (influenza, etc.)
Blood (systemic)	<Antibody induction site>	Airway mucosa (local) Blood (systemic)
Low	<Antibody cross-reactivity>	High
Blood: IgG	<Antibody type>	Mucosa: Dimeric IgA Blood: IgG
Prevention: Onset, Aggravation	<Expected effects>	+Infection preventive effect Prevention: Onset, Aggravation

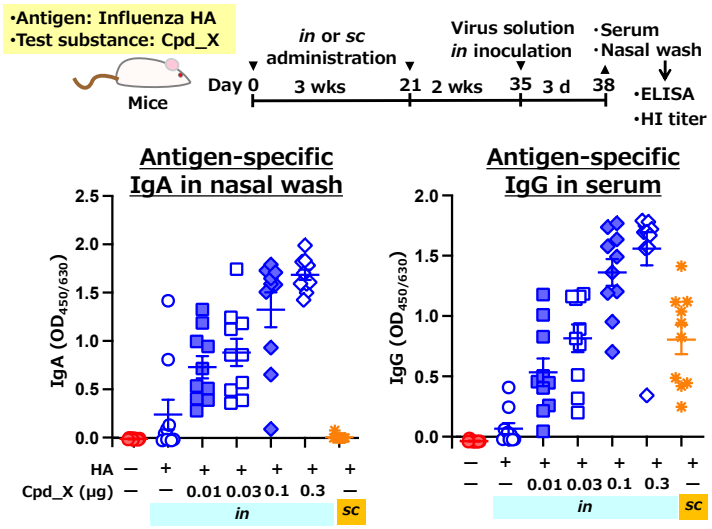
Development Process & Data Package

Construction of *in vitro* evaluation systems → Screening of compounds (Commercial library) → *In vivo* efficacy → Viral infection in mice and cynomolgus monkeys (・MOA analysis ・Safety evaluation) → 3 candidate compounds → Studies for practical application 1. Safety 2. Pharmaceuticals 3. Synthesis methods → Novel mucosal adjuvant: Compound X (Cpd_X) (dual TLR agonist structure)

Data Package (under CDA)

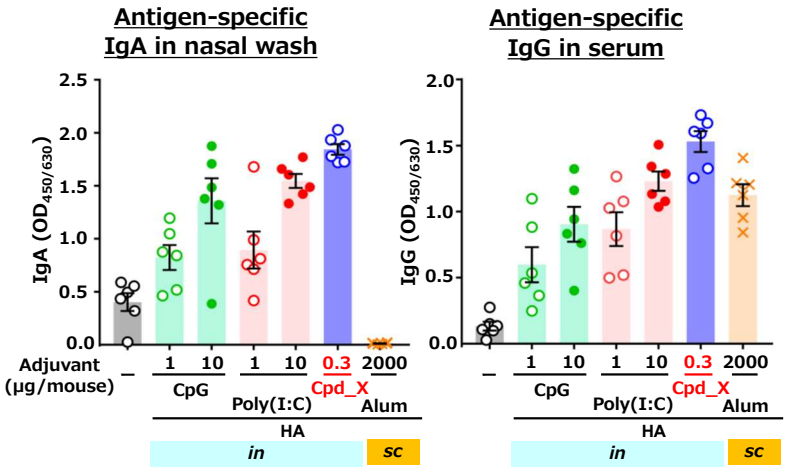
- [Substance information] ・Synthesis method, Purity, Physicochemical properties ・Stability
- [Intellectual property information] ・Patent application filed for Cpd_X
- [Safety studies] <Non-GLP preliminary study> ・Single-dose preliminary study ・*In vitro* genotoxicity preliminary study
- [Pharmacokinetics, etc.] <Non-GLP preliminary study> ・Plasma concentration measurement method ・Stability test of compounds in plasma
- [Efficacy] Adjuvant activity in mice administered intranasally. ・Influenza vaccine HA antigen ・SARS-CoV-2 Spike protein antigen

Intranasal administration of HA+Cpd_X induced IgA in the nasal mucosa and IgG in blood, and protected against viral infection

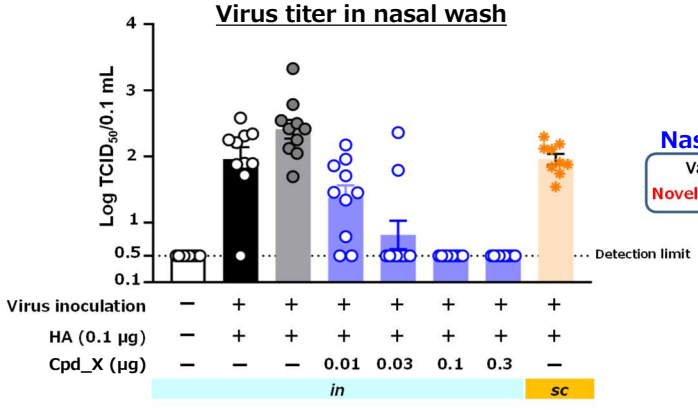


Serum HI titer								
	HA (μg)	—	0.1	0.1	0.1	0.1	0.1	0.1
	Cpd_X (μg)	—	—	0.01	0.03	0.1	0.3	—
	Route	—	*in*					*sc*
Geometric mean Ab titer (GMT)	5.0	6.6	15.2	17.4	26.4	42.9	42.9	
GMT change rate (>2.5)	—	1.3	3.0	3.5	5.3	8.6	8.6	
Seroconversion rate (≧titer; 1:40, GMT change rate≧4)	—	0/10 0%	1/10 10%	2/10 20%	5/10 50%	9/10 90%	6/10 60%	

Cpd_X induced antibody production at lower doses compared to CpG ODN (TLR9 agonist) and Poly(I:C) (TLR3 agonist)



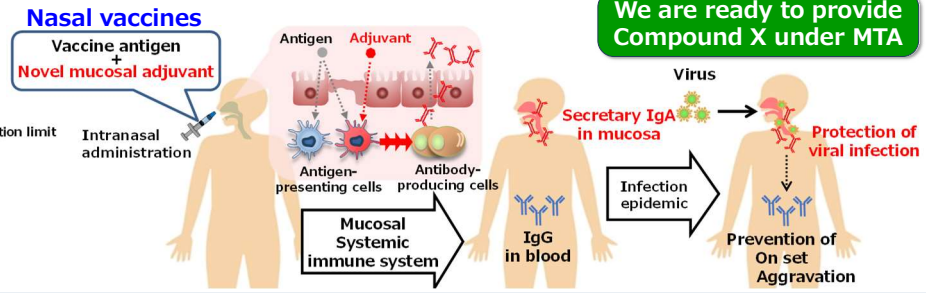
Virus titer in nasal wash



Summary

- Intranasal administration of Cpd_X with an influenza HA antigen:
  1) induces antigen-specific IgA antibody in nasal mucosa and IgG antibody in serum, and additionally enhances serum HI titer.
  2) exhibits the protective ability against influenza virus infection that is not seen with the HA subcutaneous vaccine (conventional type).
- Cpd_X was found to induce antibody production at lower doses compared to CpG ODN (TLR9 agonist) and Poly(I:C) (TLR3 agonist).

Nasal vaccine using the mucosal adjuvant Cpd_X shows superior vaccine efficacy compared to subcutaneous vaccine.
Cpd_X is a synthetic organic compound with TLR dual agonist structures. It is expected to be effective not only for split and subunit vaccines, but also for mRNA vaccines, etc. It is believed that it may become a useful mucosal adjuvant for nasal vaccines, etc.



We are ready to provide Compound X under MTA

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