

Aerosol delivery, but not intramuscular injection, of adenovirus-vectored tuberculosis vaccine induces respiratory-mucosal immunity in humans

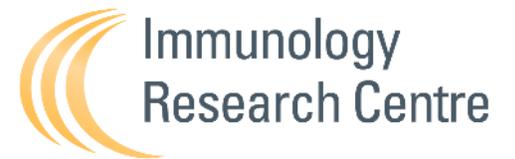
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CIHR IRSC

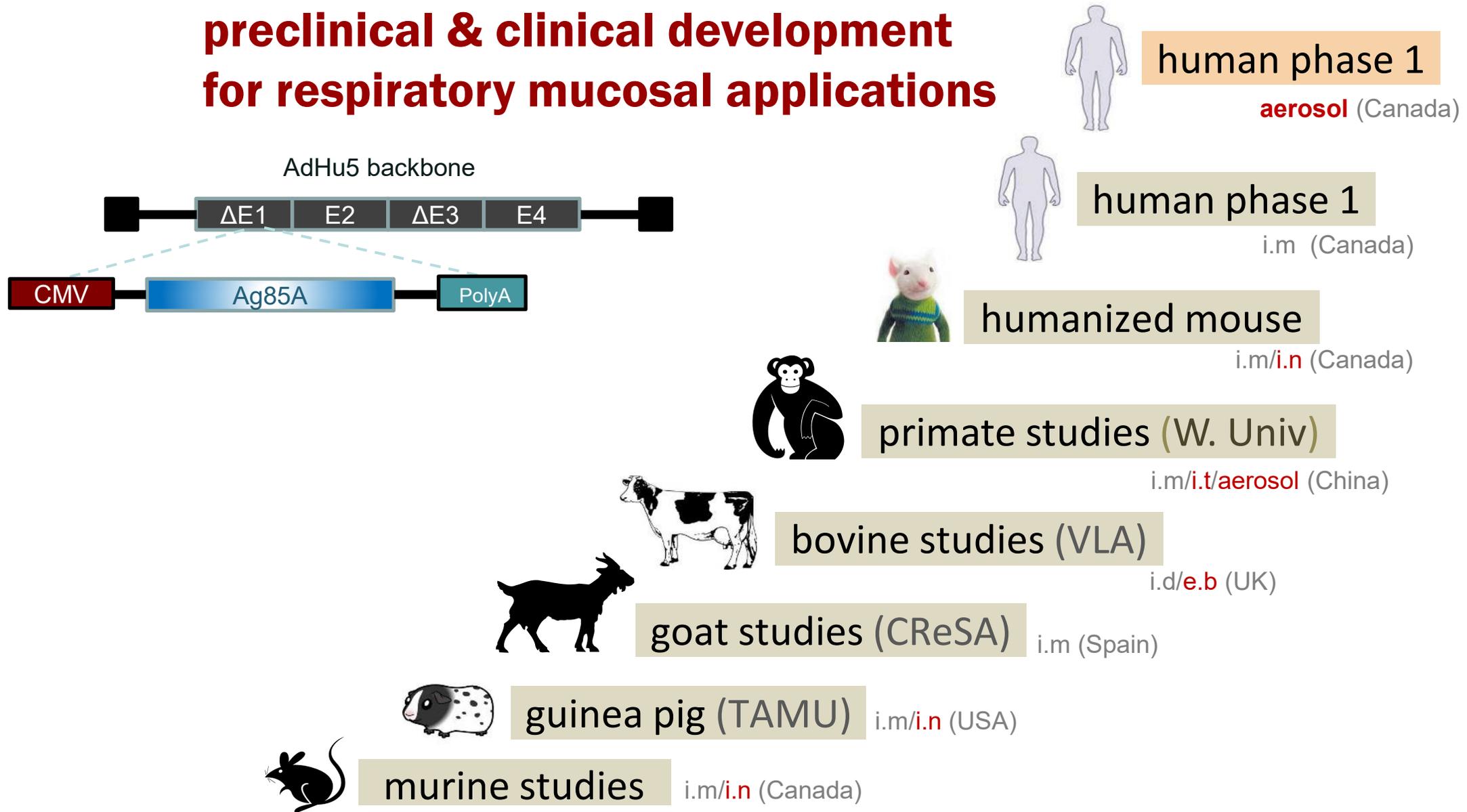
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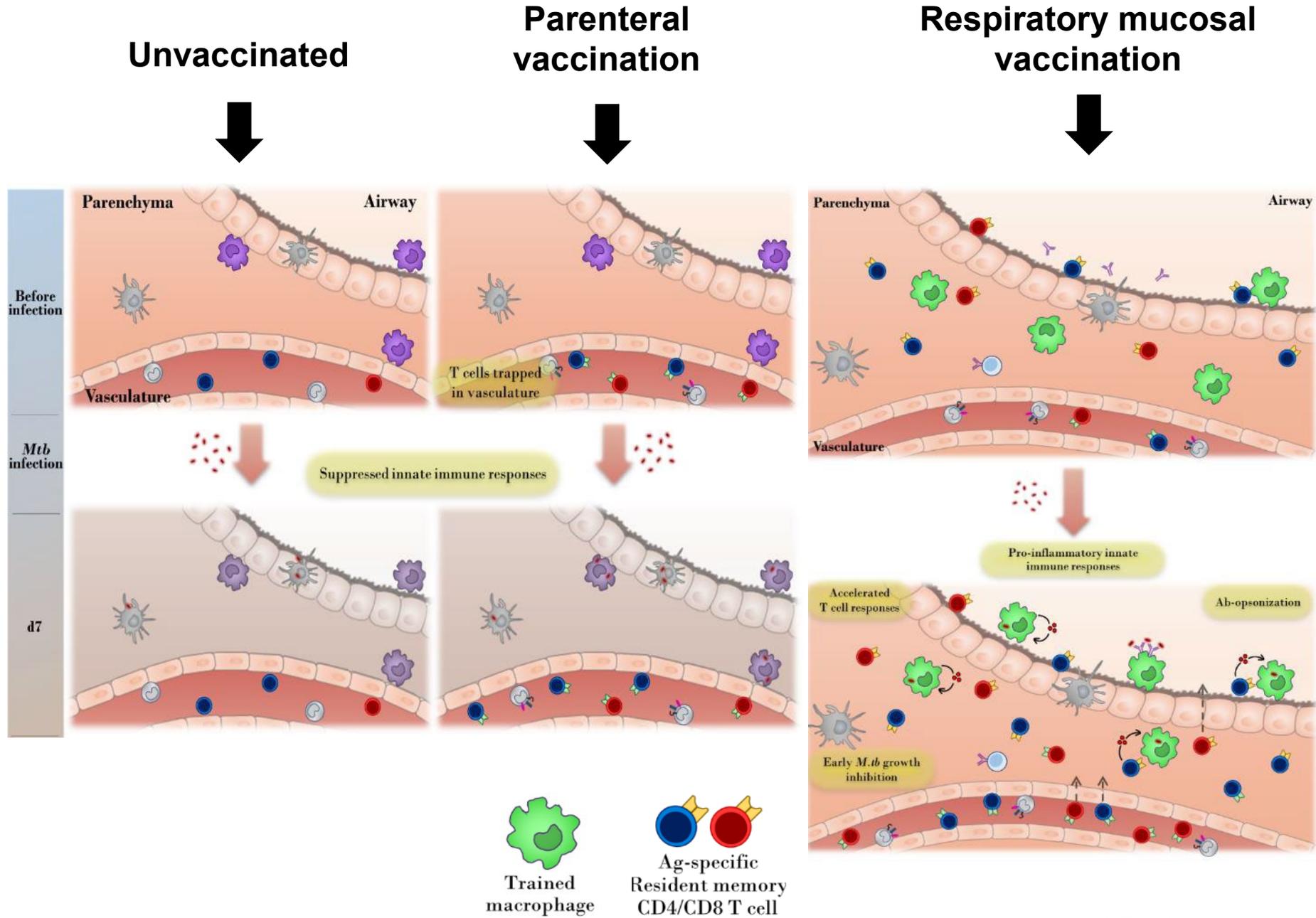


Conflict of Interest

- License Agreement (#L011-050) of Technology Transfer to CanSino Biotech Inc. of China “Recombinant human type 5 adenovirus-based TB vaccine (AdHuAg85A) and its preparation and use for clinical trials” (Inventors Z. Xing, F Smail, M. Medina, et al). Filing Date: 2011/07/22

AdHu5Ag85A – preclinical & clinical development for respiratory mucosal applications

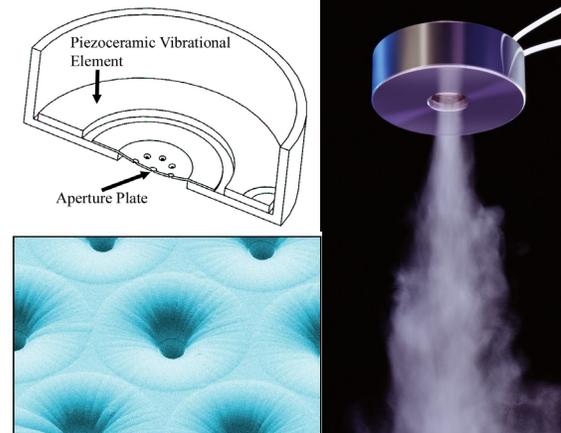
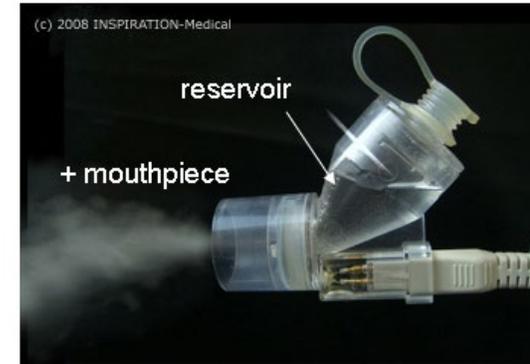




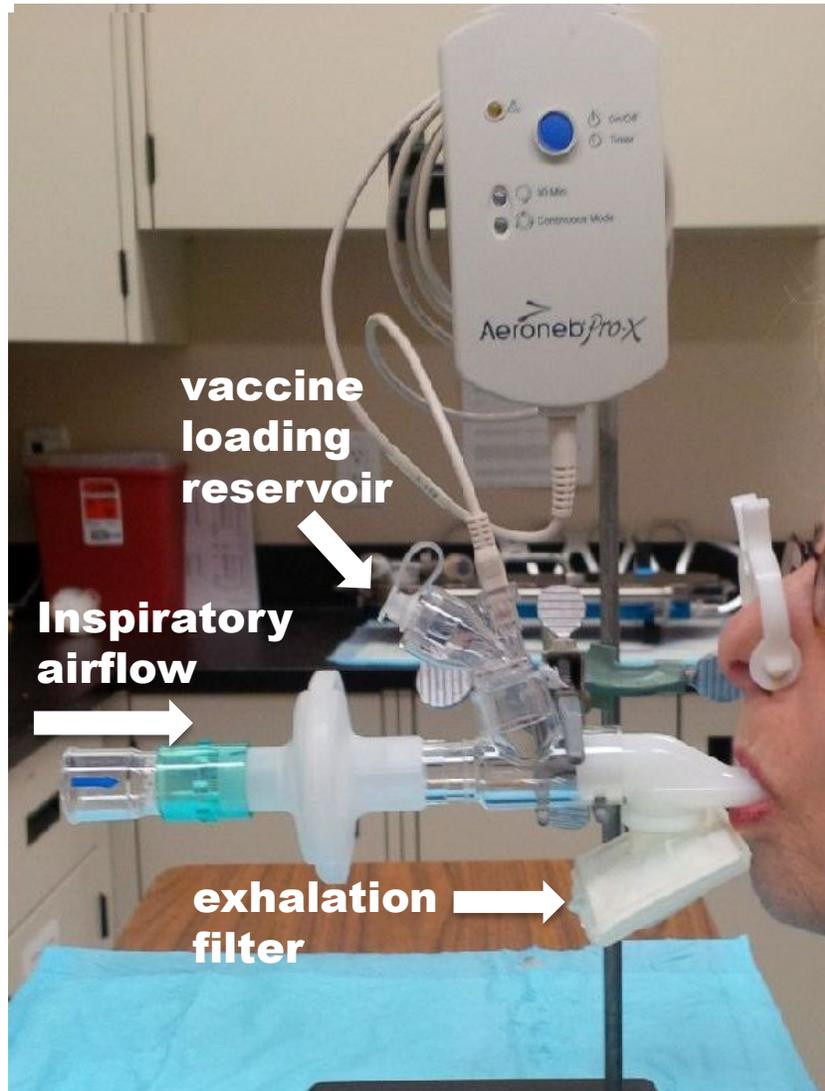
Respiratory mucosal delivery of AdHu5Ag85A by AeroNeb® nebulizer



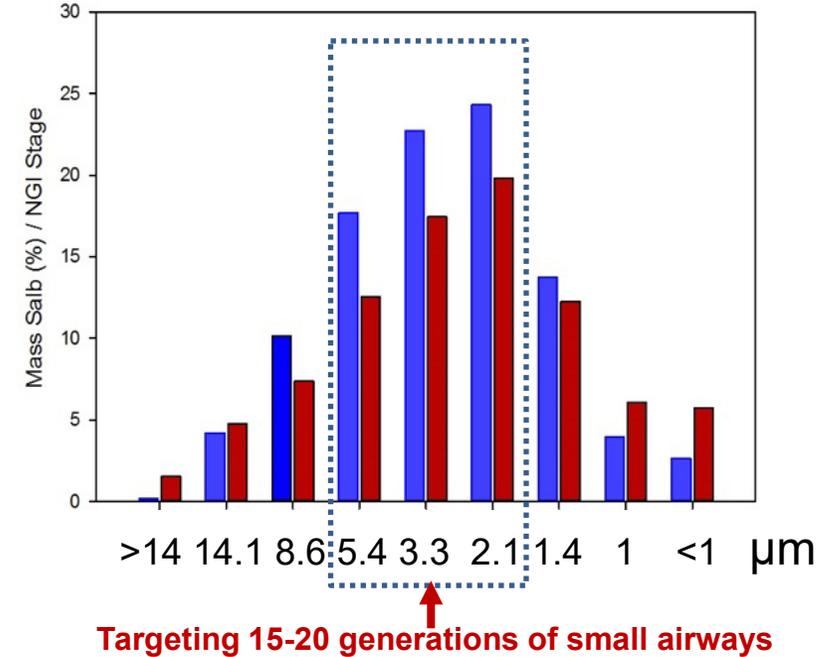
Aeroneb® Solo
Single Patient Use Vibrating Mesh
Nebulizer



Assembled inhaled aerosol delivery system

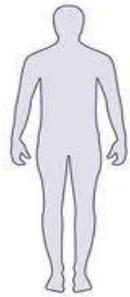


aerosol particle size distribution -salbutamol+vaccine vs salbutamol (red)-



- loading volume: 0.5 ml
- delivery time: 2 min
- loading vs. emitted dose: 50%
- droplet size: 85% <5.39 µm
- viability of aerosolized vaccine: 20%

Phase 1b Aerosol Trial Design



32 BCG+
volunteers
(18-55 yrs)

{ Inhaled aerosol
or i.m (10^8 pfu)

Baseline
tests

Ag-specific blood/BAL PBMC
Anti-AdHu5 Ab
Blood hematology/chemistry

AdHu5Ag85A vaccine
(1×10^6 or 2×10^6 pfu dose-escalation)



Consent
BCG history
HIV antibody
QFT test*
Chest x-ray
Spirometry
DLCO



BAL

BAL

BAL

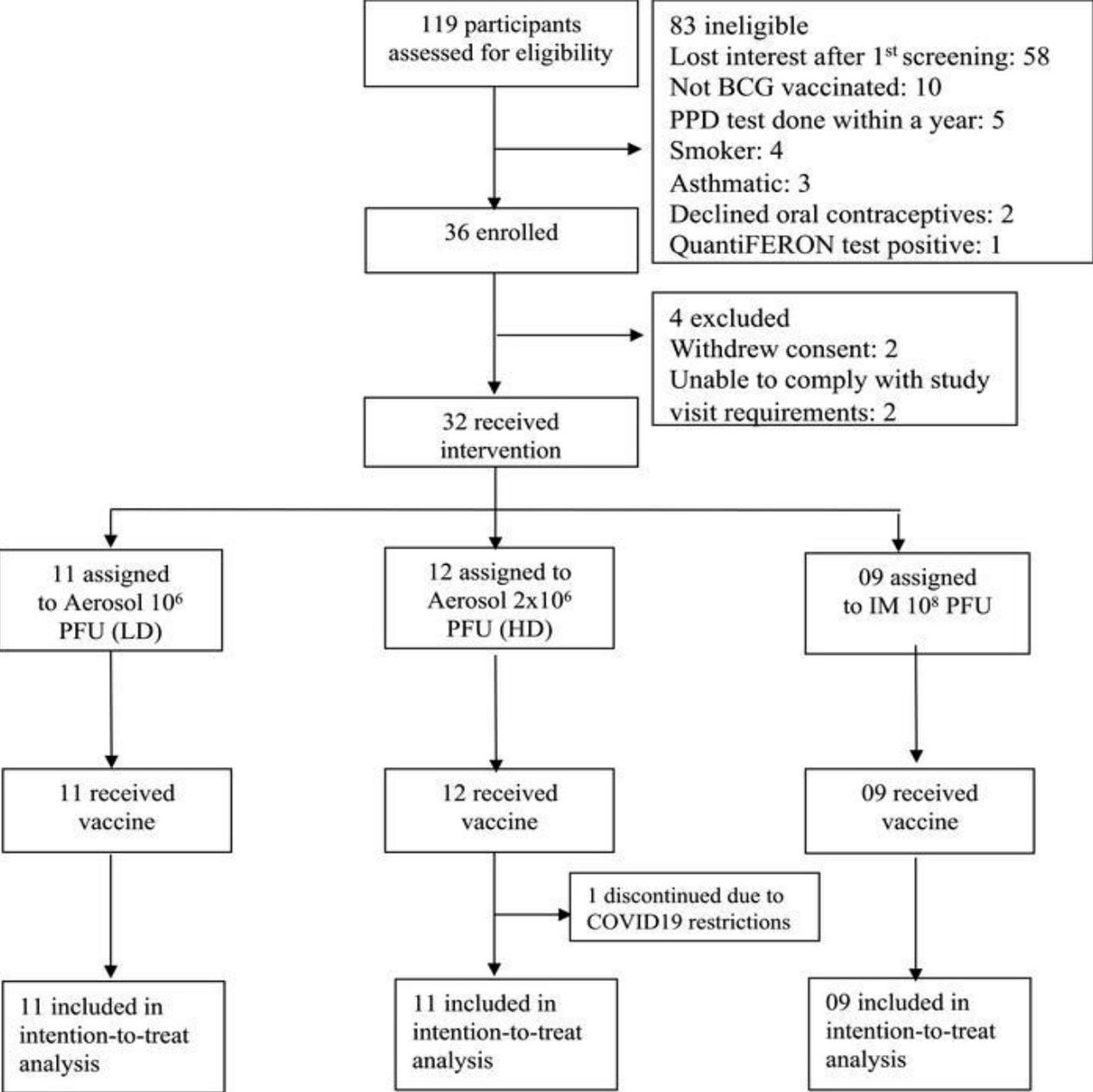
Safety evaluation
Spirometry
Blood/PBMC assays

Safety
evaluation

*QFT –Quantiferon TB test used to screen out latent TB

*BronchoAlveolar Lavage

TRIAL PROFILE

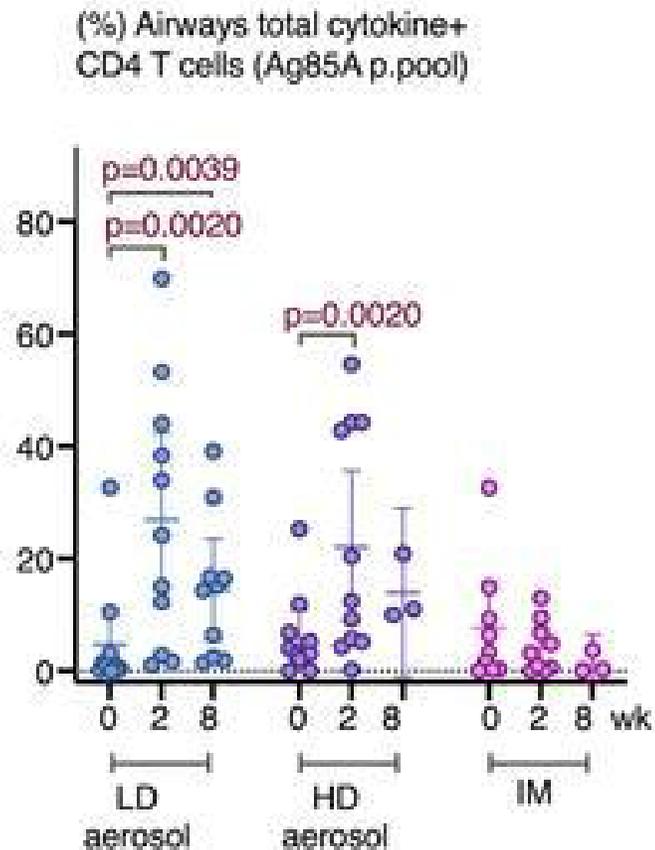


ADVERSE EVENTS

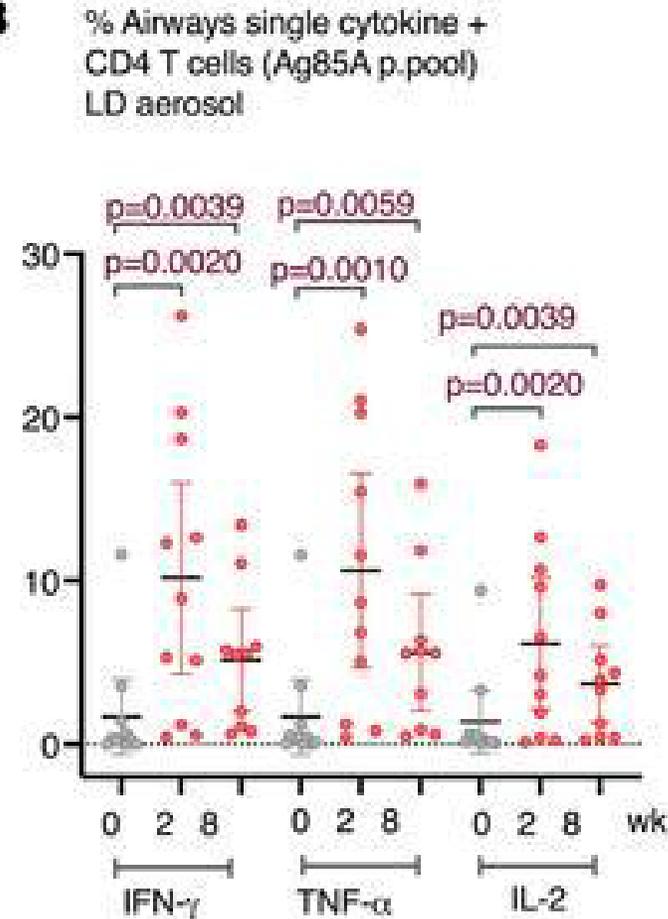
Adverse event	Low dose (n = 11)	%	High dose (n = 12)	%	i.m. (n = 9)	%
Injection site reaction						
Local pain	n/a	n/a	n/a	n/a	0	0
Redness	n/a	n/a	n/a	n/a	1	11.1
Swelling	n/a	n/a	n/a	n/a	1	11.1
Cough	2	18.1	2	16.6	4	44.4
Runny nose	3	27.7	2	16.6	2	22.2
Fatigue	4	36.3	3	25.0	3	33.3
Myalgia	3	27.7	0	0	0	0
Headache	3	27.7	7	58.3	2	22.2
Joint pain	1	9.0	0	0	1	11.1
Chest pain	1	9.0	0	0	0	22.2
Sneezing	1	9.0	1	8.3	2	0
Sinus pain	1	9.0	0	0	0	0
Abdominal pain	1	9.0	1	8.3	1	11.1
Shortness of breath	0	0	1	8.3	0	0
Nose bleed	1	9.0	0	0	0	0
Itchy throat	0	0	1	8.3	0	0
Shivers	2	18.1	0	0	0	0
Dizziness	0	0	0	0	2	22.2

Induction of multifunctional **CD4+ T cells in the airways** following aerosol (LD and HD) or intramuscular (IM) vaccination

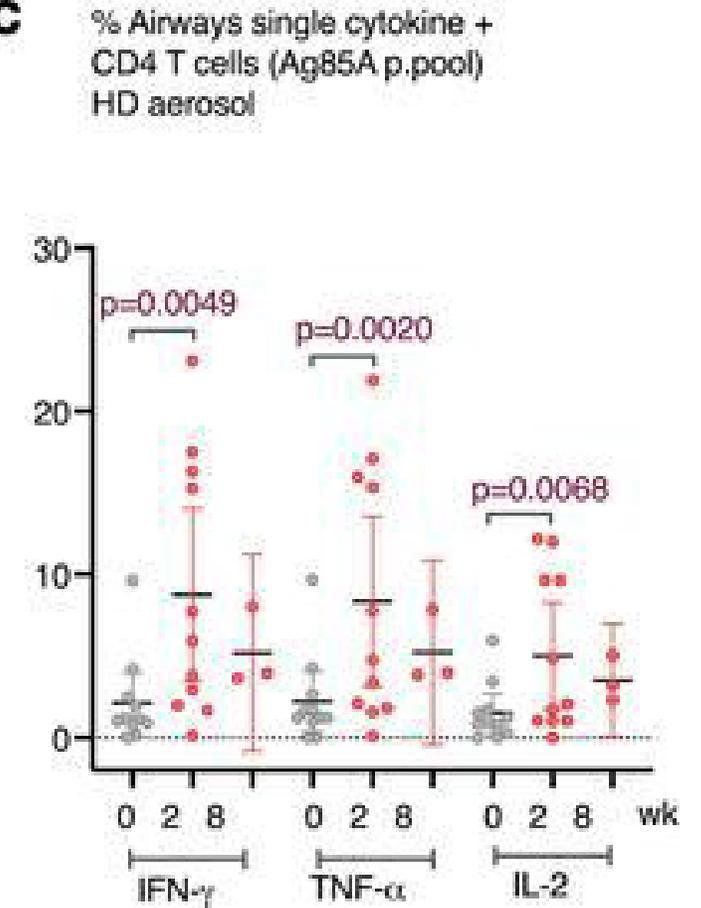
A



B

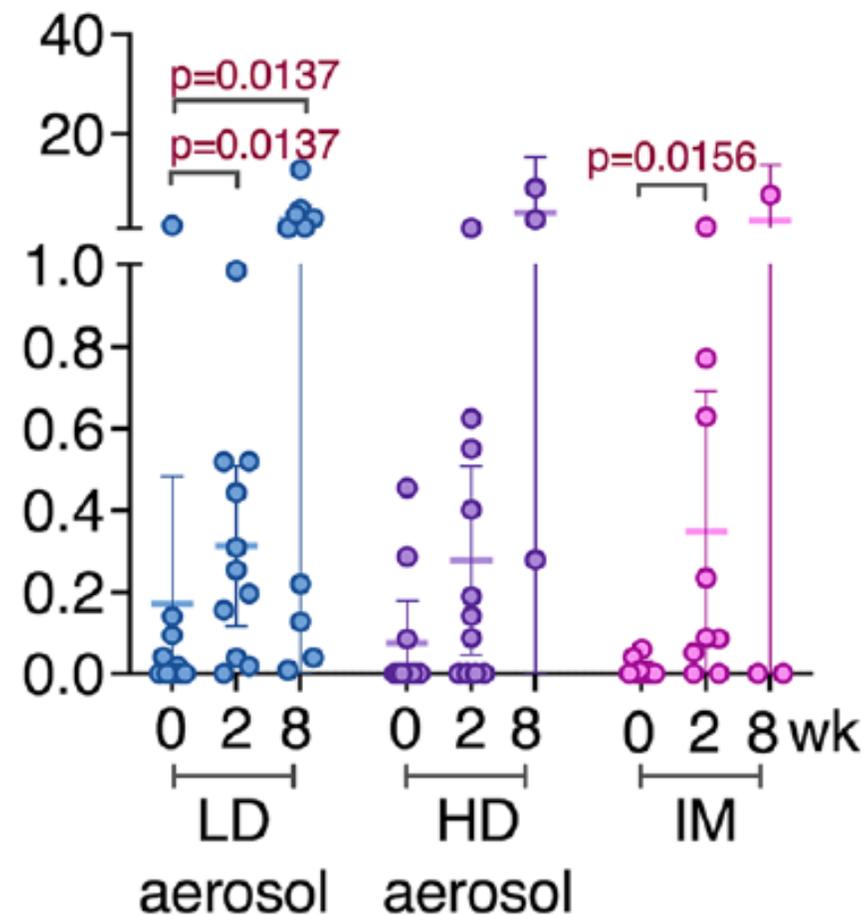


C



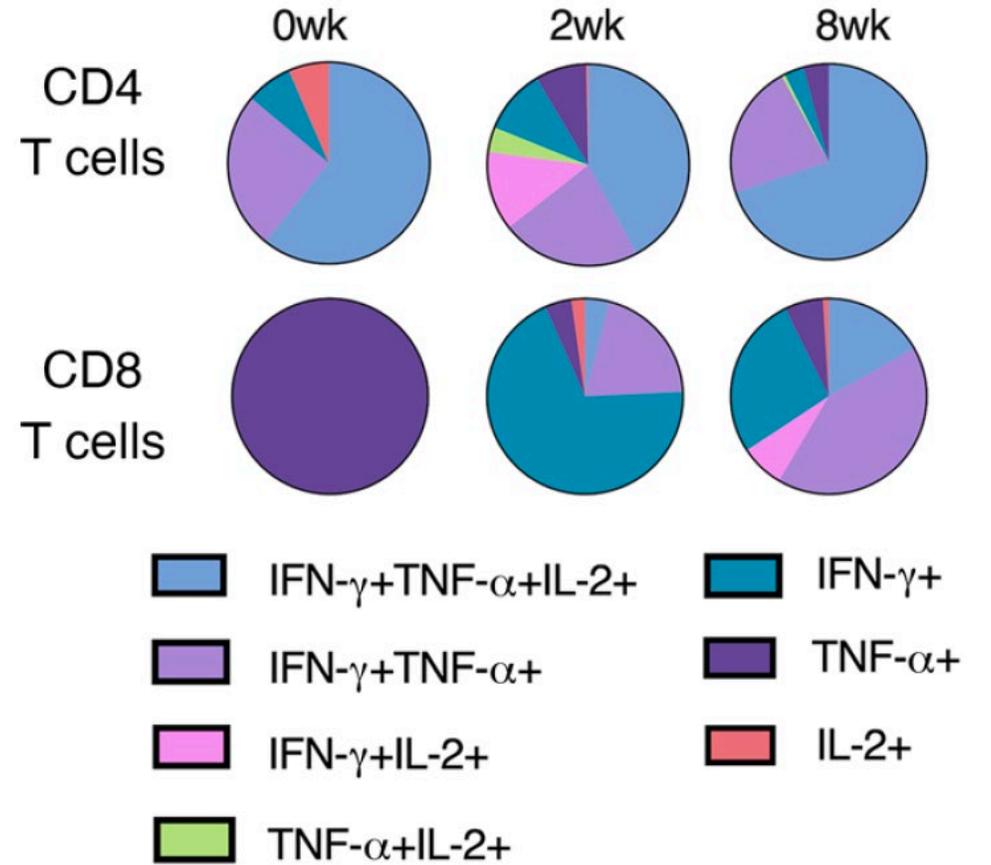
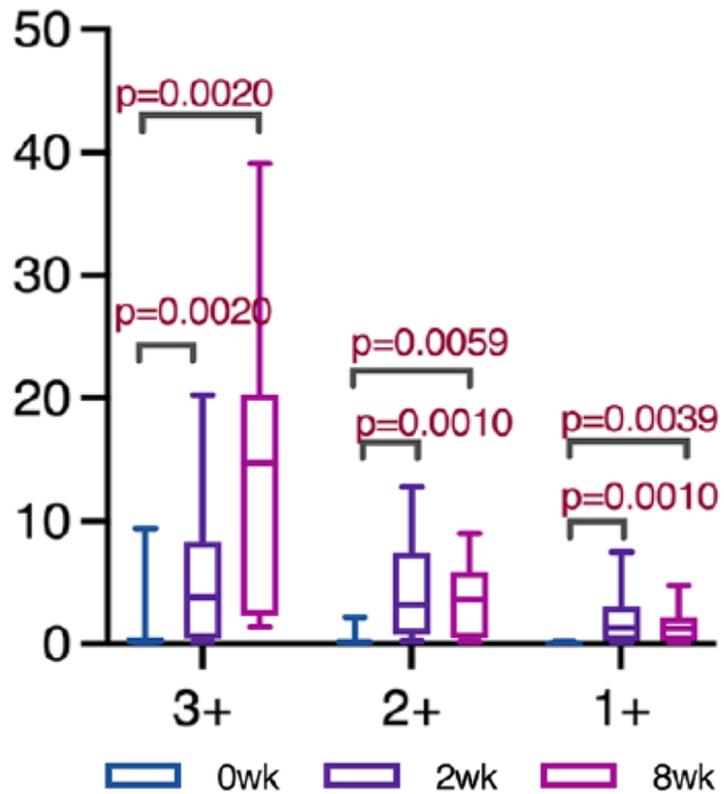
Data in dot plots are expressed as the mean value (horizontal line) with 95% CI. Box plots show mean value (horizontal line) with 95% CI (whiskers), and boxes extend from the 25th to 75th percentiles. Wilcoxon matched pairs signed-rank test was used to compare various time points with baseline values within the same vaccination group.

Frequencies of **airway** antigen–specific combined total cytokine–producing **CD8⁺ T cells** at various time points in LD aerosol, HD aerosol, and i.m. cohorts.



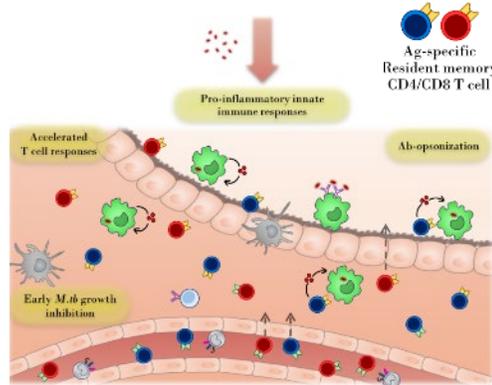
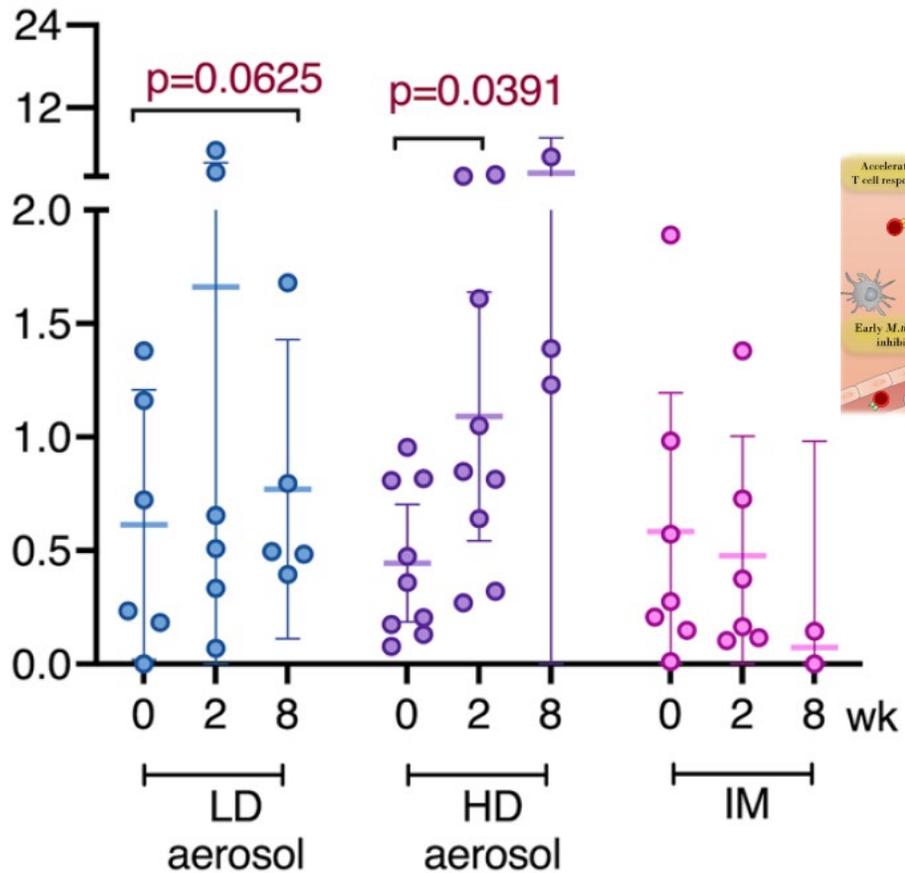
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Frequencies of airway polyfunctional (triple/3+, double/2+, and single/1+ cytokine⁺) antigen-specific CD4⁺ T cells at various time points in LD aerosol group.

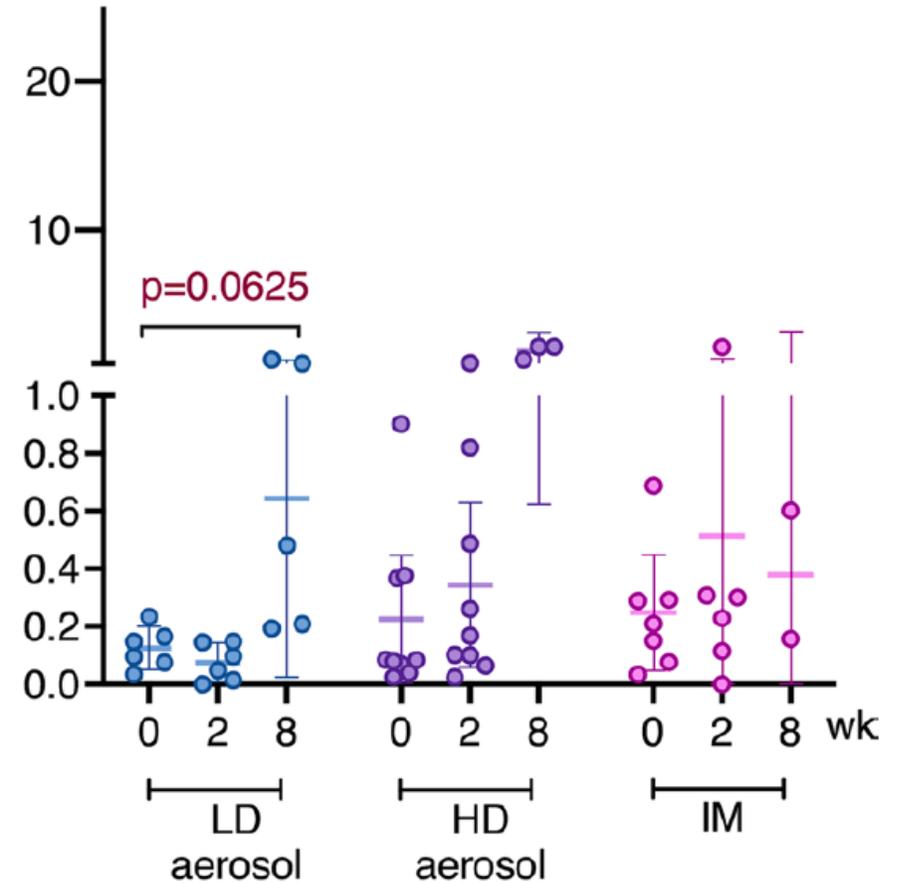


Pie chart of median proportions of antigen-specific airway CD4⁺ and CD8⁺ T cells expressing a specific single or combination of 2 or 3 cytokines at various time points in LD aerosol group.

Frequencies of airway antigen-specific IFN- γ^+ **CD4⁺ T_{RM}** co-expressing CD69 and CD103 surface markers at various time points in LD aerosol, HD aerosol, and i.m. vaccine cohorts.

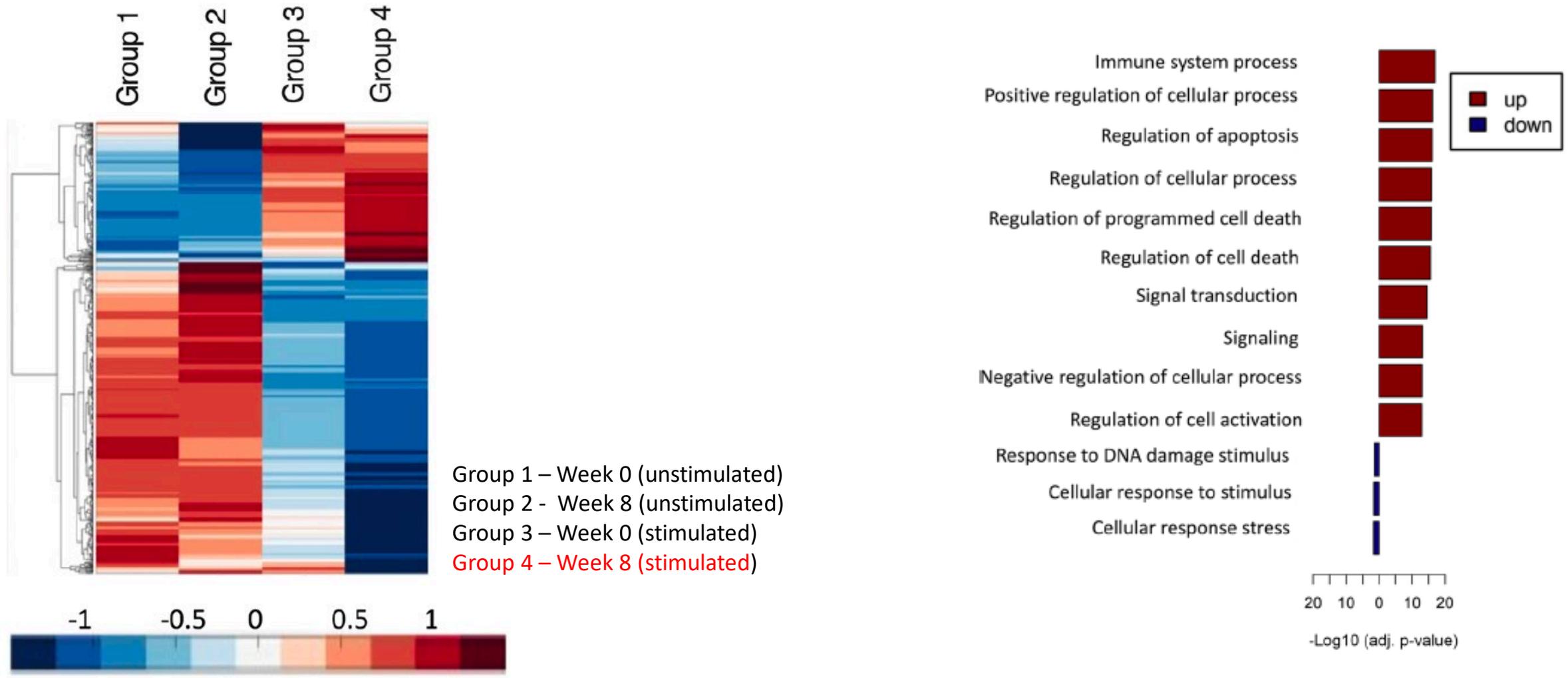


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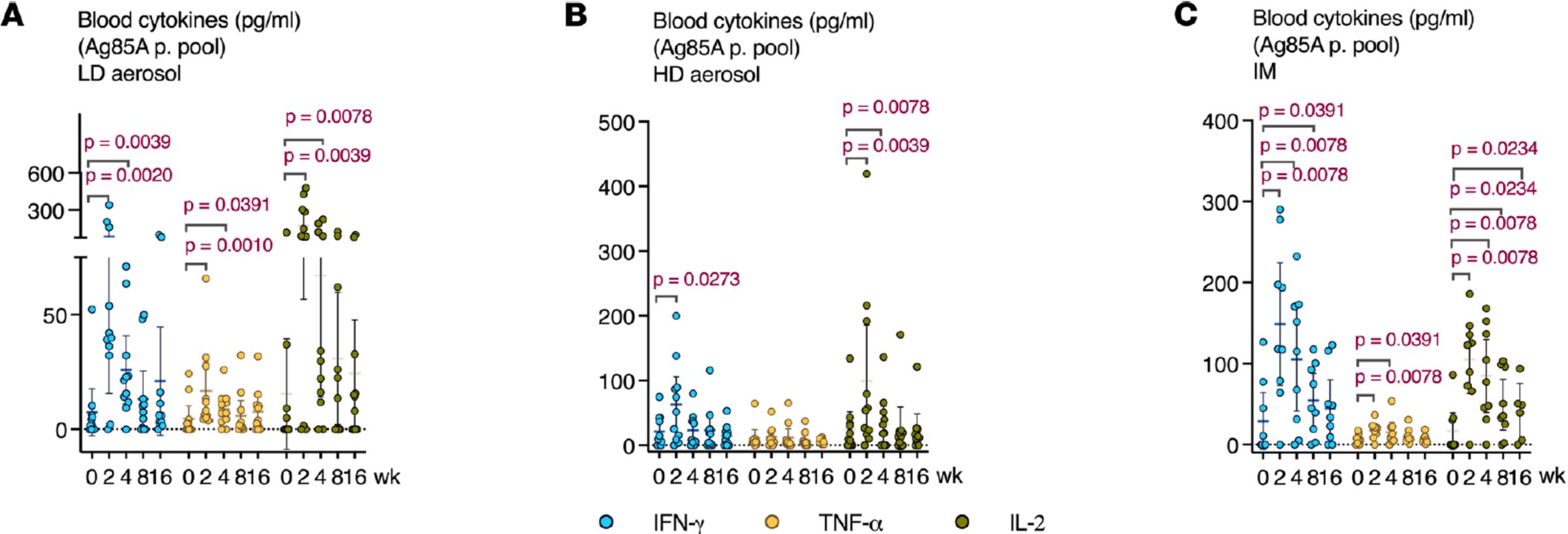


Data in dot plots are expressed as the mean value (horizontal line) with 95% CI. Wilcoxon matched pairs signed-rank test was used to compare various time points with baseline values within the same vaccination group.

Transcriptomic analysis of alveolar macrophages following low dose aerosol vaccination



Induction of antigen-specific T cell responses in the peripheral blood following aerosol or intramuscular vaccination.



Antigen-specific cytokine production in whole blood culture at various time points after LD aerosol, HD aerosol, and i.m. vaccine groups. The measurements were subtracted from unstimulated control values.

Anti-Ad5 antibody titres before and after low dose, high dose and intramuscular vaccination

Sample	Ad5 humoral immunity	Study time (week)		LD aerosol		HD aerosol		i.m.
			<i>N</i>		<i>N</i>		<i>N</i>	
Serum	Anti-Ad5 total IgG titre	0	11	9513 (700, 11,5520)	11	5695 (932, 39,080)	9	14257 (4974, 67,200)
		4	11	4974 (611, 326,600)	11	9384 ^A (1161, 68960) <i>P</i> = 0.0010	9	20350 ^A (5744, 61,200) <i>P</i> = 0.0017
	Ad5 neutralizing antibody titre	0	11	22 (2, 7937)	11	130 (2, 7519)	9	203 (2, 11,110)
		4	11	32 (3, 7692)	11	134 (2, 7634)	9	2311 ^A (25, 19,231) <i>P</i> = 0.0039
BALF	Anti-Ad5 total IgG titre	0	11	469 (222, 2855)	11	522 (84, 3441)	9	281 (24, 3290)
		8	10	502 (115, 1188)	3	213 (98, 859)	3	147 (84, 194)
	Ad5 neutralizing antibody titre	0	11	2.13 (1, 55)	11	13 (1, 93)	9	5.9 (1-139)
		8	10	2.8 (1, 46)	3	14 (1-79)	3	6.4 (1-30)

^A*P* values obtained by comparing 4-week time point values with baseline values within the same vaccination group using Wilcoxon matched-pairs signed-rank test. Units of measure within table are as follows: Anti-Ad5 total IgG titre: arbitrary units/mL. Ad5 neutralizing antibody titre: reciprocal value of the serum dilution corresponding to 50% of inhibition in the frequency of GFP⁺ cells.

