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

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CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

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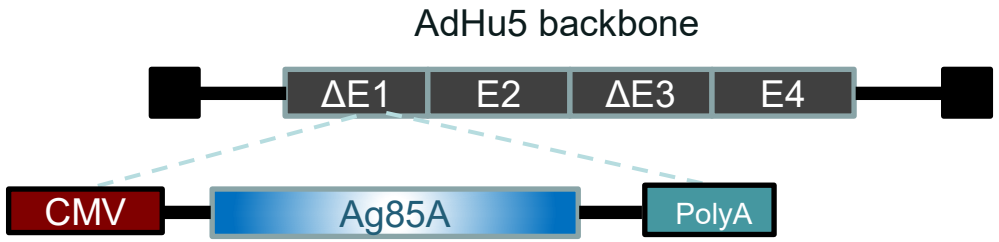
Conflict of Interest

- 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 Smaill, M. Medina, et al). Filing Date: 2011/07/22

AdHu5Ag85A –
preclinical & clinical development for respiratory mucosal applications



human phase 1

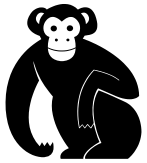
aerosol (Canada)

human phase 1

i.m (Canada)

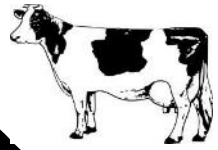
humanized mouse

i.m/i.n (Canada)



primate studies (W. Univ)

i.m/i.t/aerosol (China)



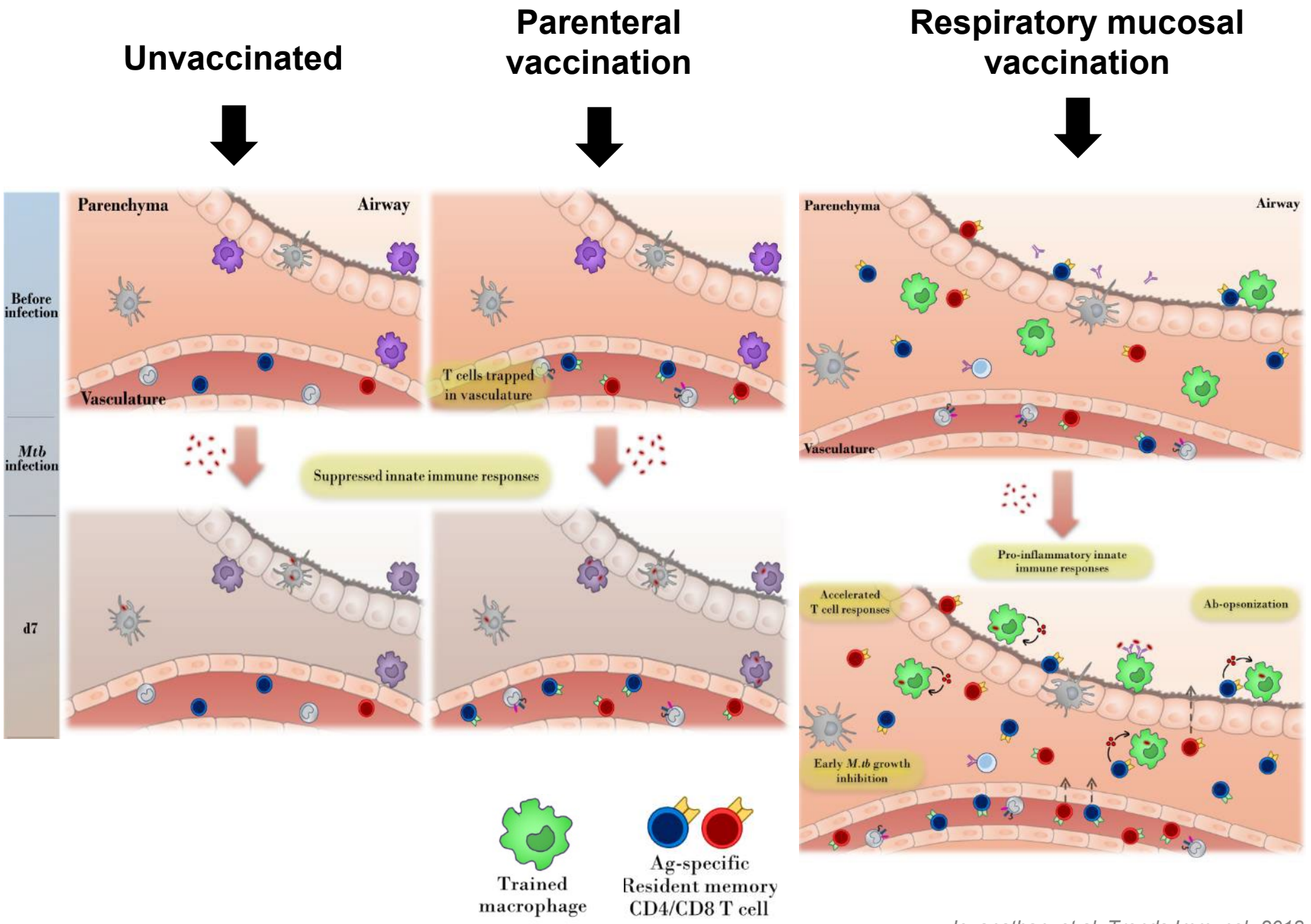
bovine studies (VLA)

i.d/e.b (UK)

goat studies (CReSA) i.m (Spain)

guinea pig (TAMU) i.m/i.n (USA)

murine studies i.m/i.n (Canada)

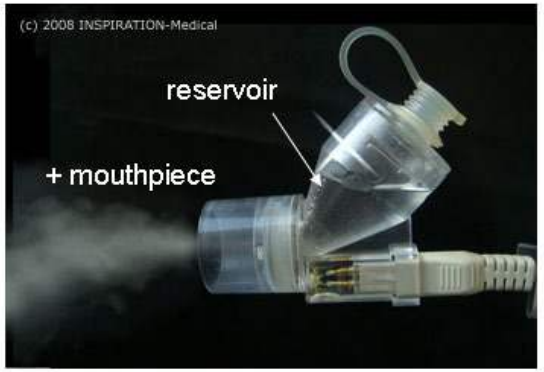


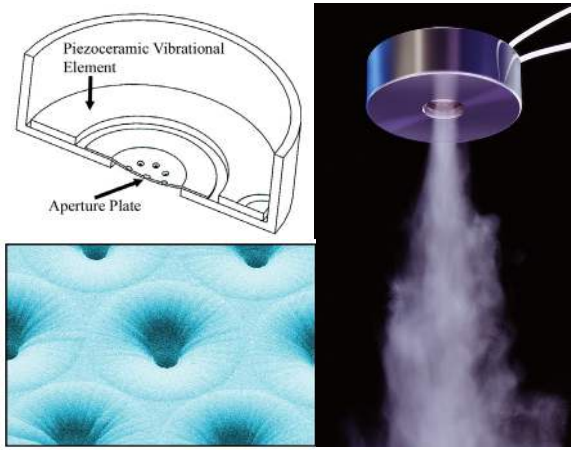
Jeyanathan et al, Trends Immunol, 2018

Respiratory mucosal delivery of AdHu5Ag85A by AeroNeb® nebulizer

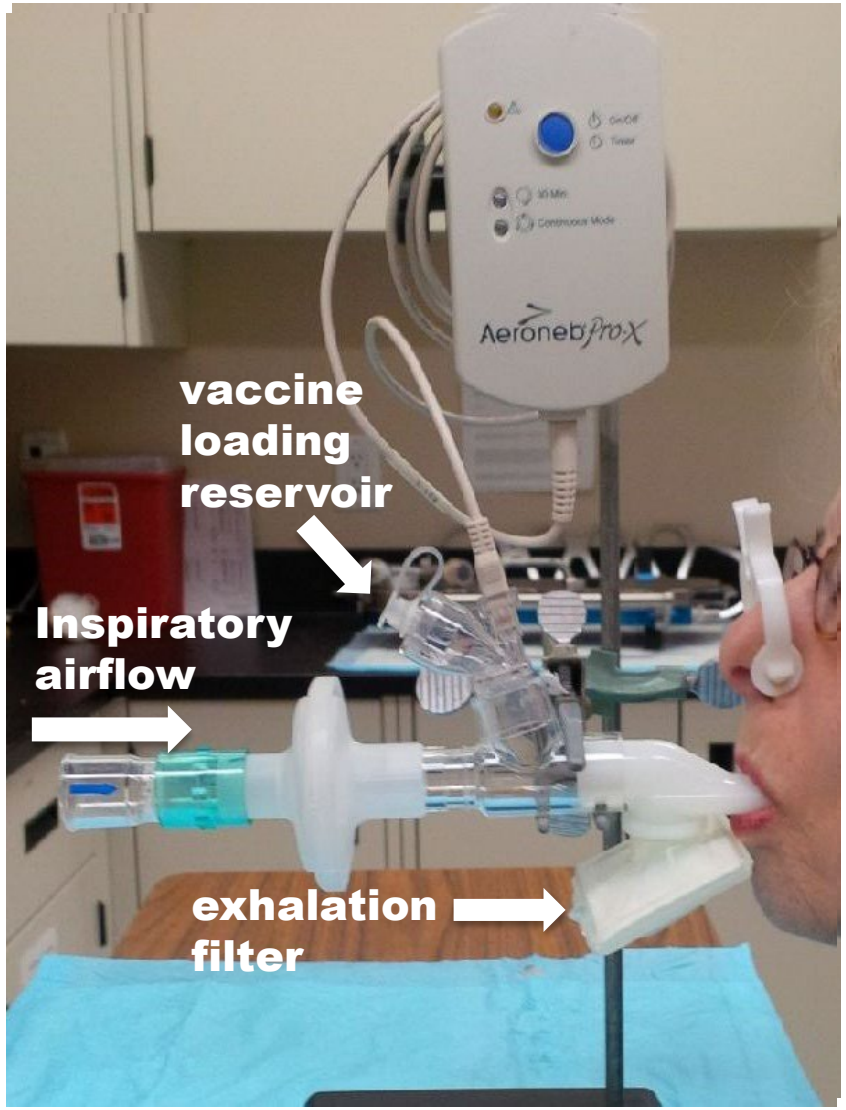
Aeroneb® Solo
Single Patient Use Vibrating Mesh Nebulizer

Aerogen



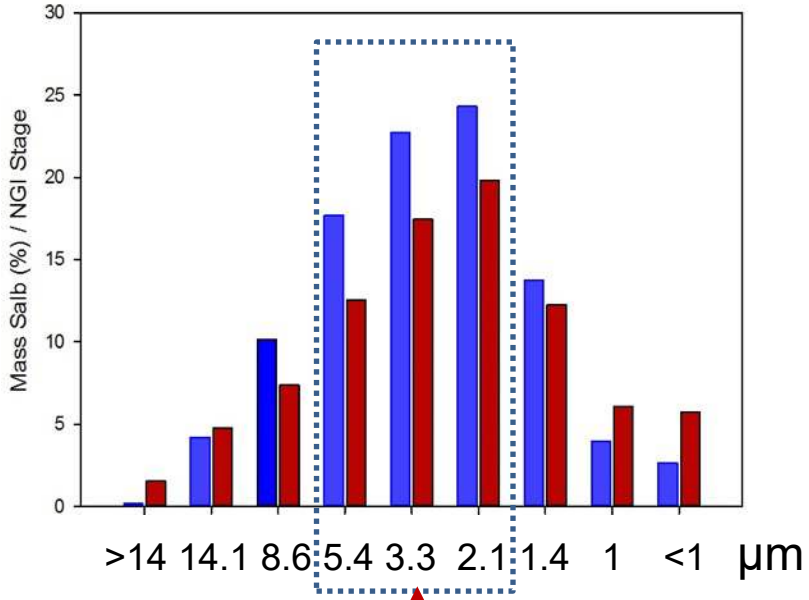


Assembled inhaled aerosol delivery system



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
($1x10^6$ or $2x10^6$ pfu dose-escalation)

screening | baseline | wk 2 | wk 4 | wk 8 | wk 16 | wk 24

BAL

BAL

BAL

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

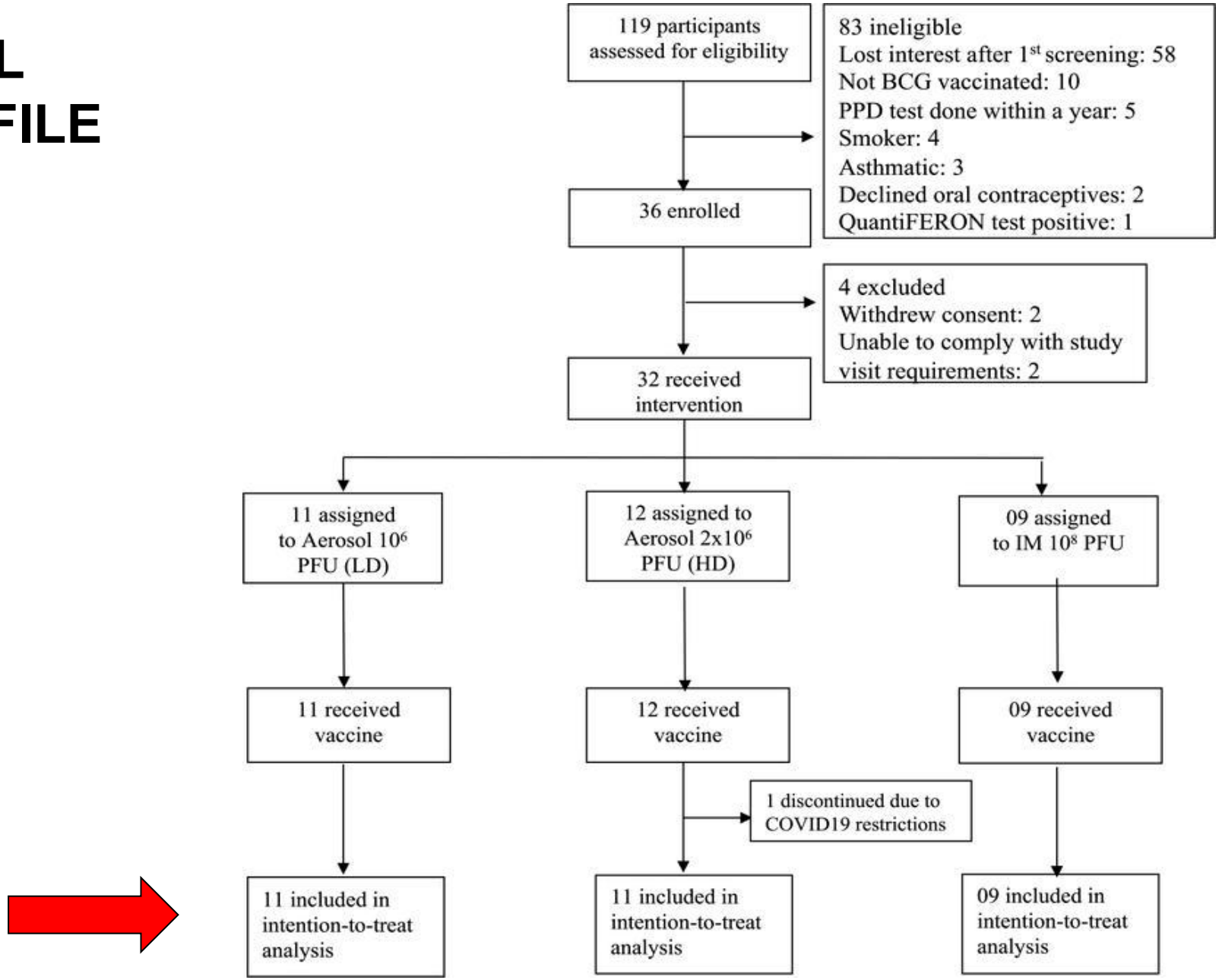
Safety evaluation
Spirometry
Blood/PBMC assays

Safety evaluation

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

*BronchoAlveolar Lavage

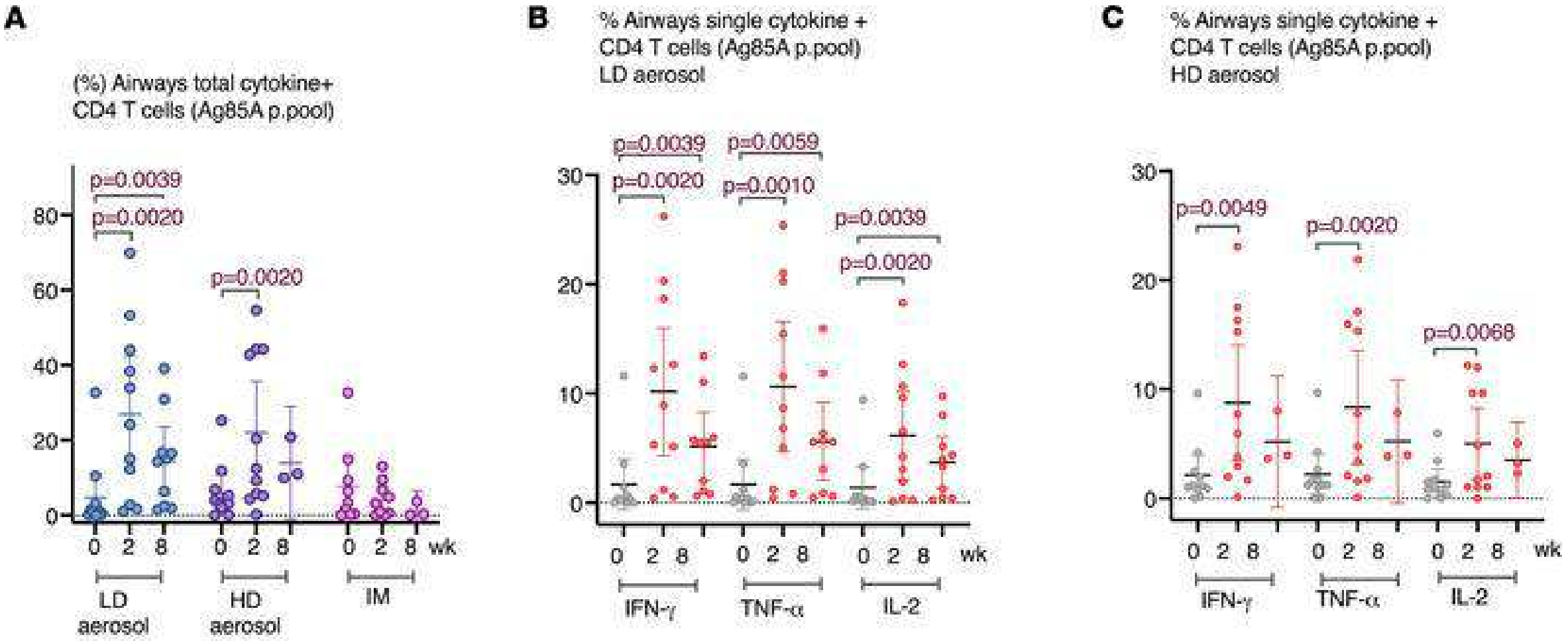
TRIAL PROFILE



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



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.

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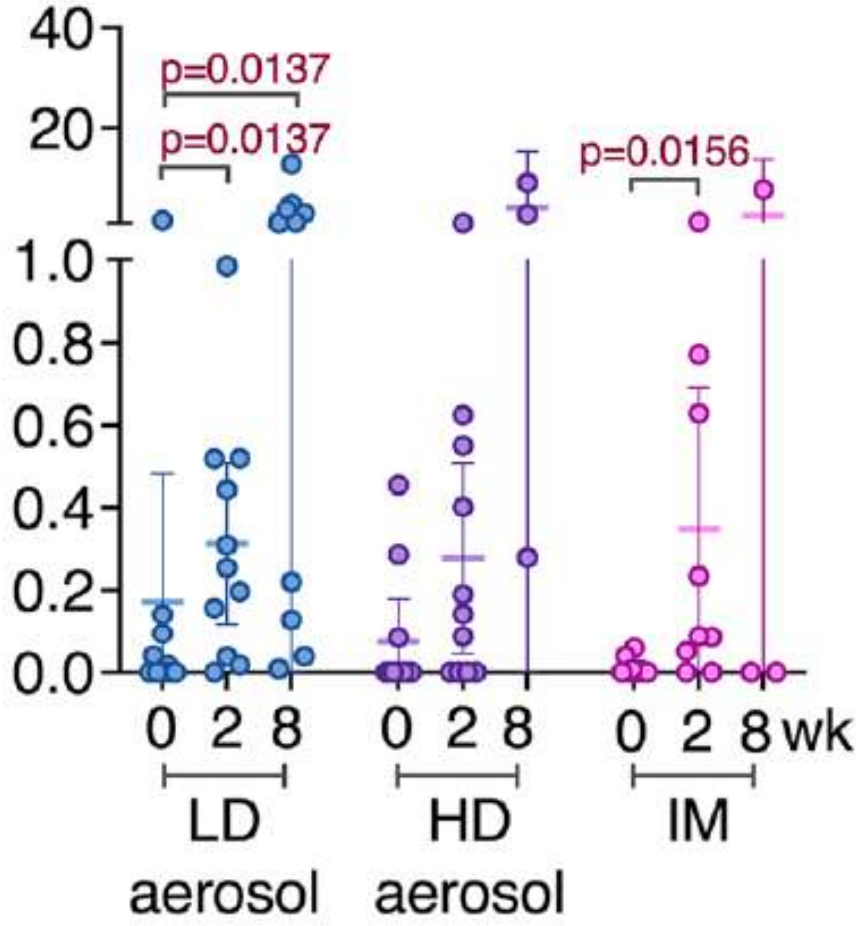
Frequencies of airway antigen–specific combined total cytokine–producing CD8$^+$ T cells at various time points in LD aerosol, HD aerosol, and i.m. cohorts.



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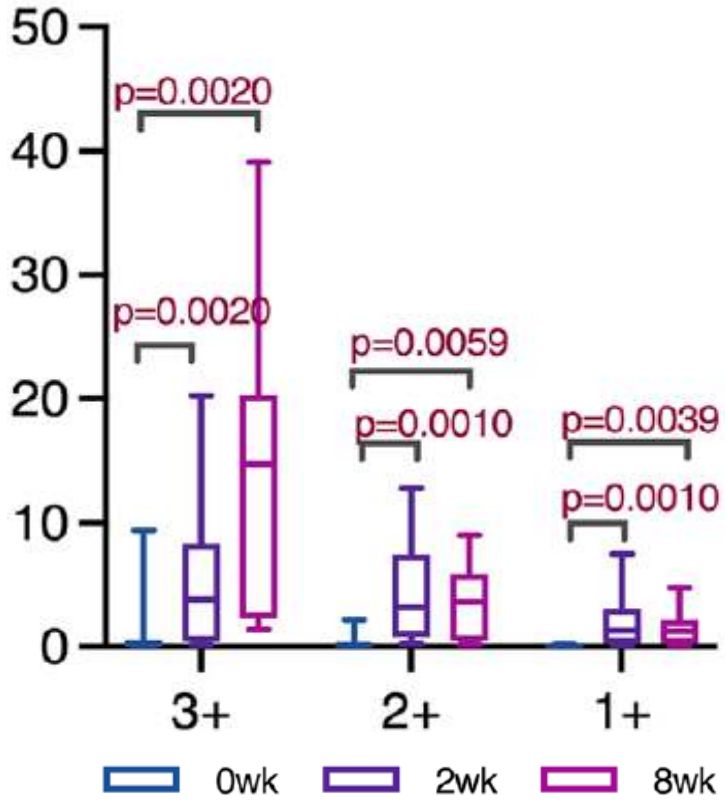
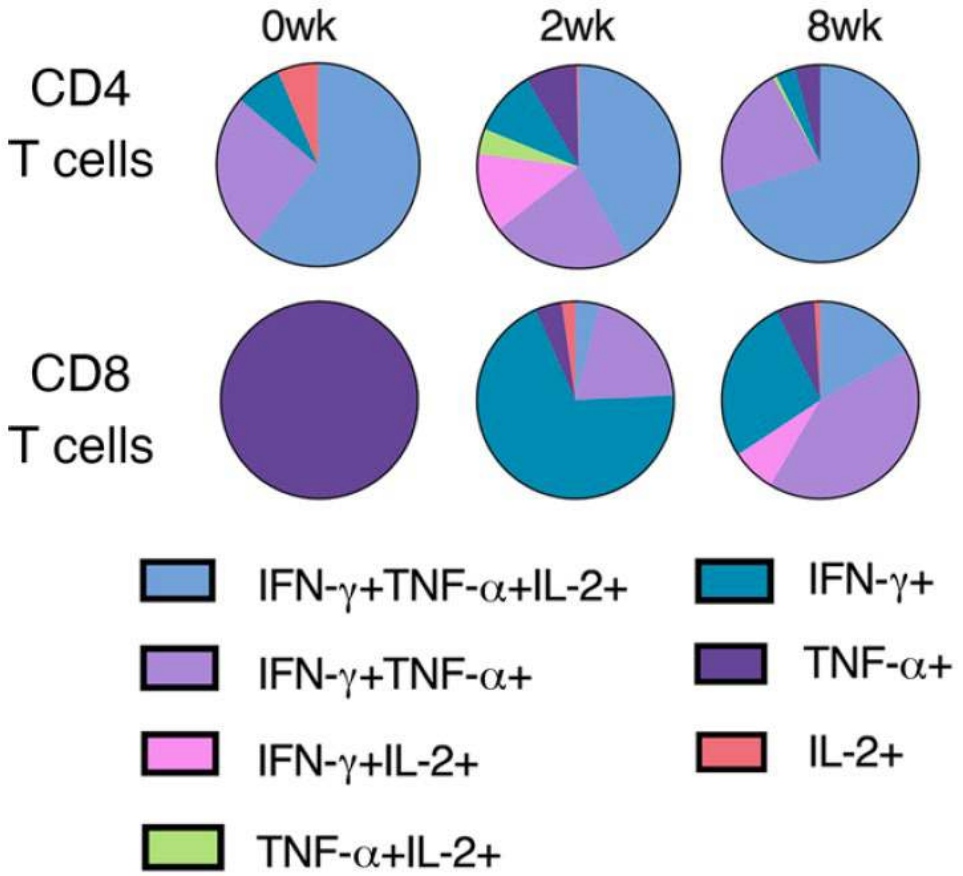
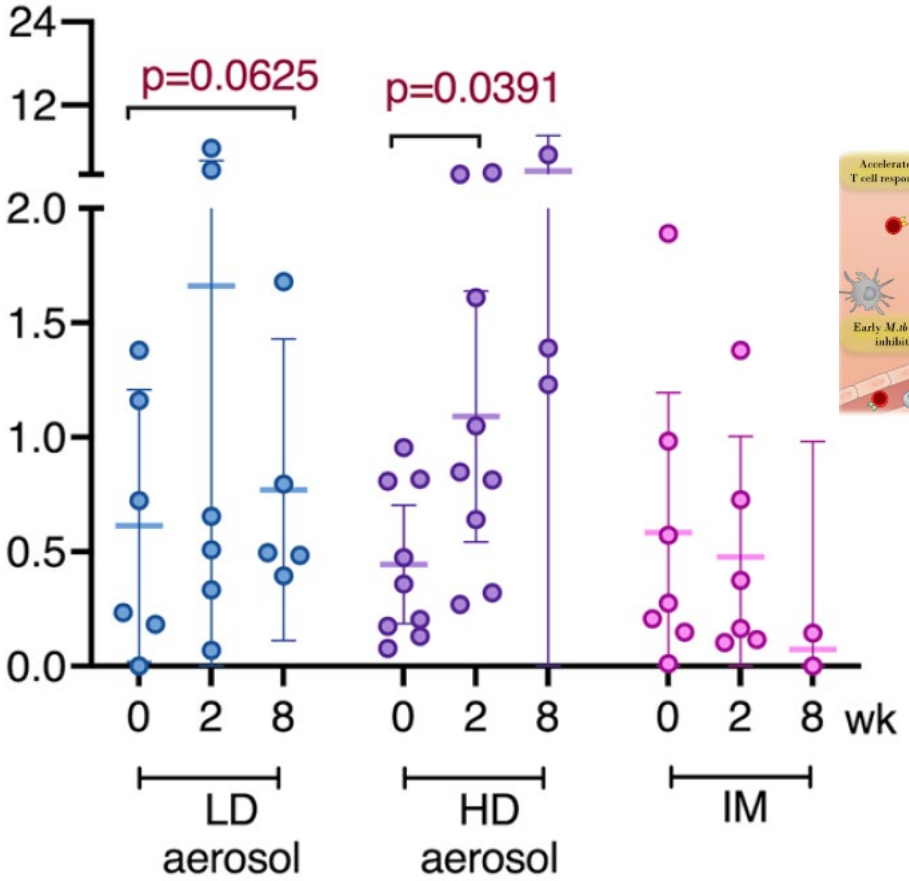
Frequencies of airway polyfunctional (triple/3+, double/2+, and single/1+ cytokine$^+$) antigen-specific CD4$^+$ T cells at various time points in LD aerosol group.

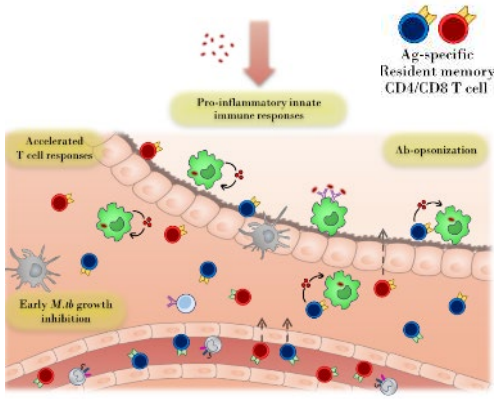




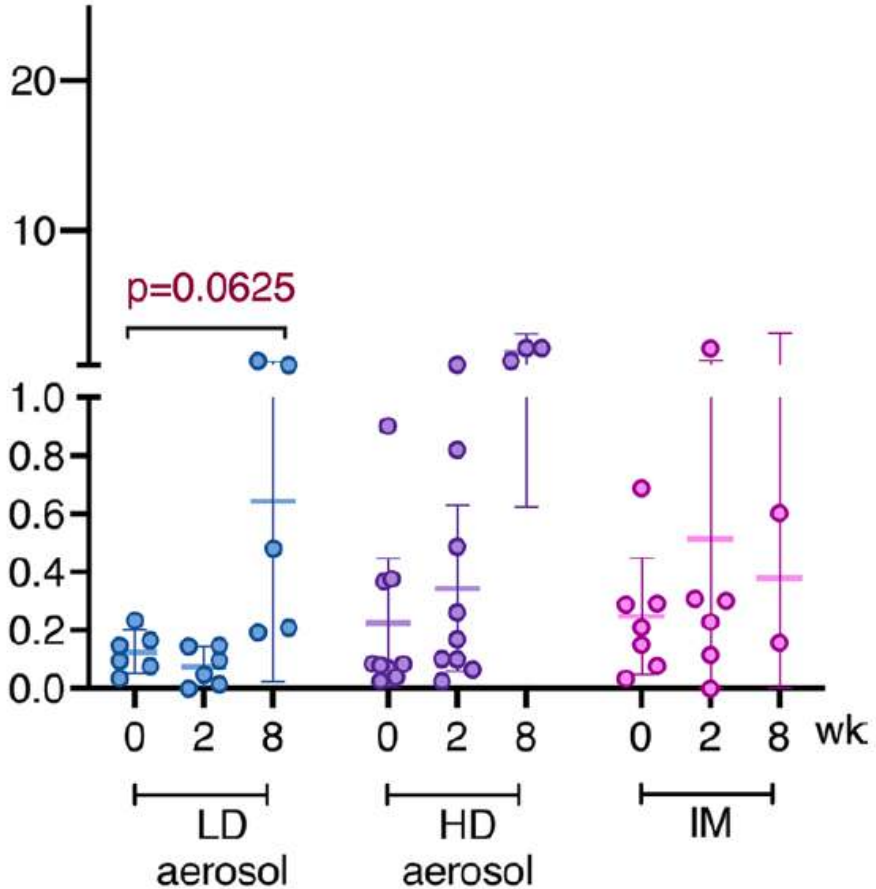
Pie chart of median proportions of antigen-specific airway CD4$^+$ and CD8$^+$ T cells expressing a specific single or combination of 2 or 3 cytokines at various time points in LD aerosol group.

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.



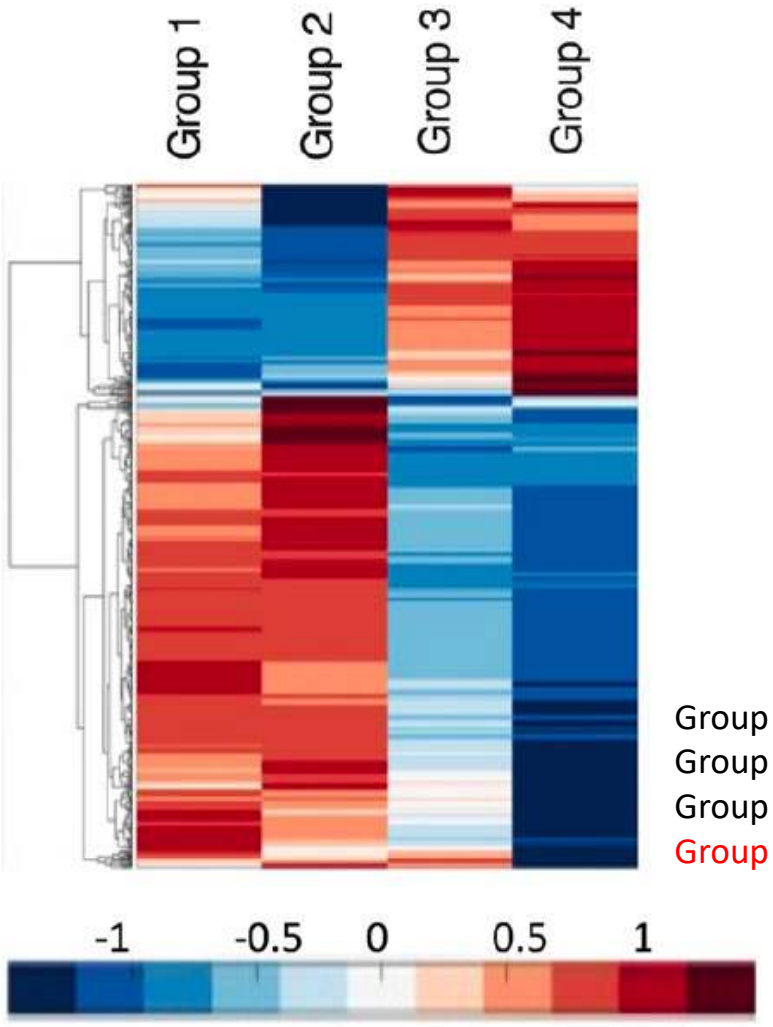


Frequencies of airway antigen–specific IFN-γ$^+$ **CD8$^+$ T_{RM}** co-expressing CD69 and CD103 at various time points in LD aerosol, HD aerosol, and i.m. vaccine cohorts.

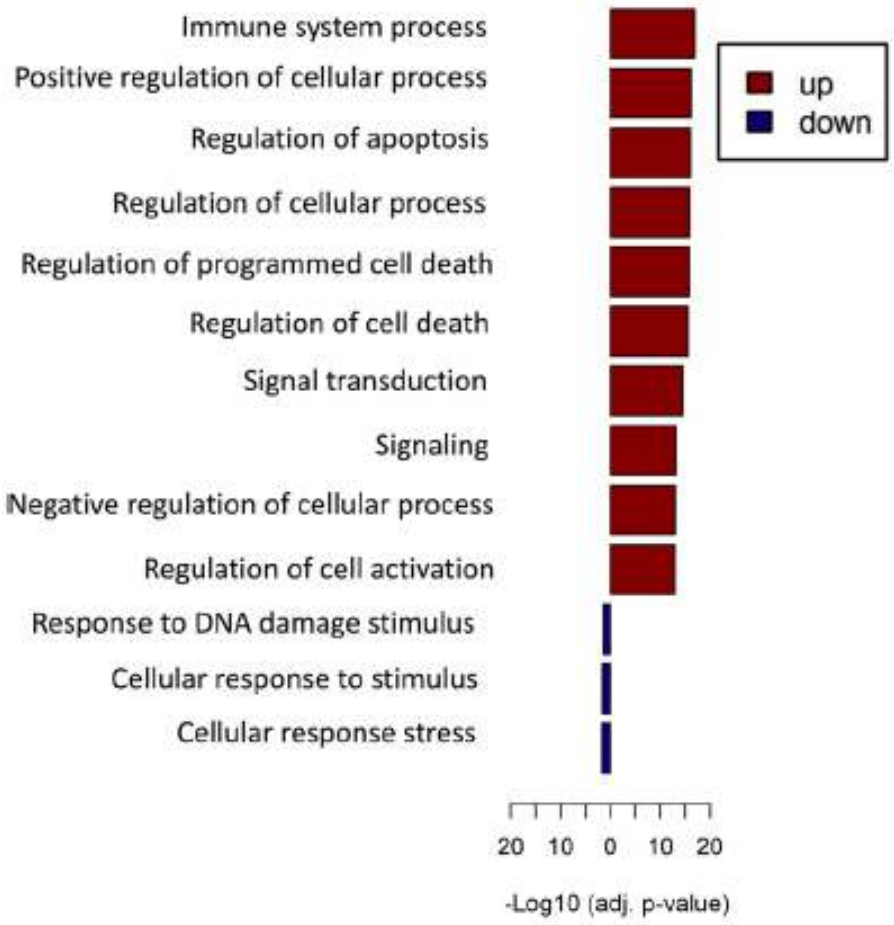


Data in dot plots are expressed as the mean value (horizontal line) with 95% CI. Wilcoxon matched pairs signed-rank test was used to compare various time points with baseline values within the same vaccination group.

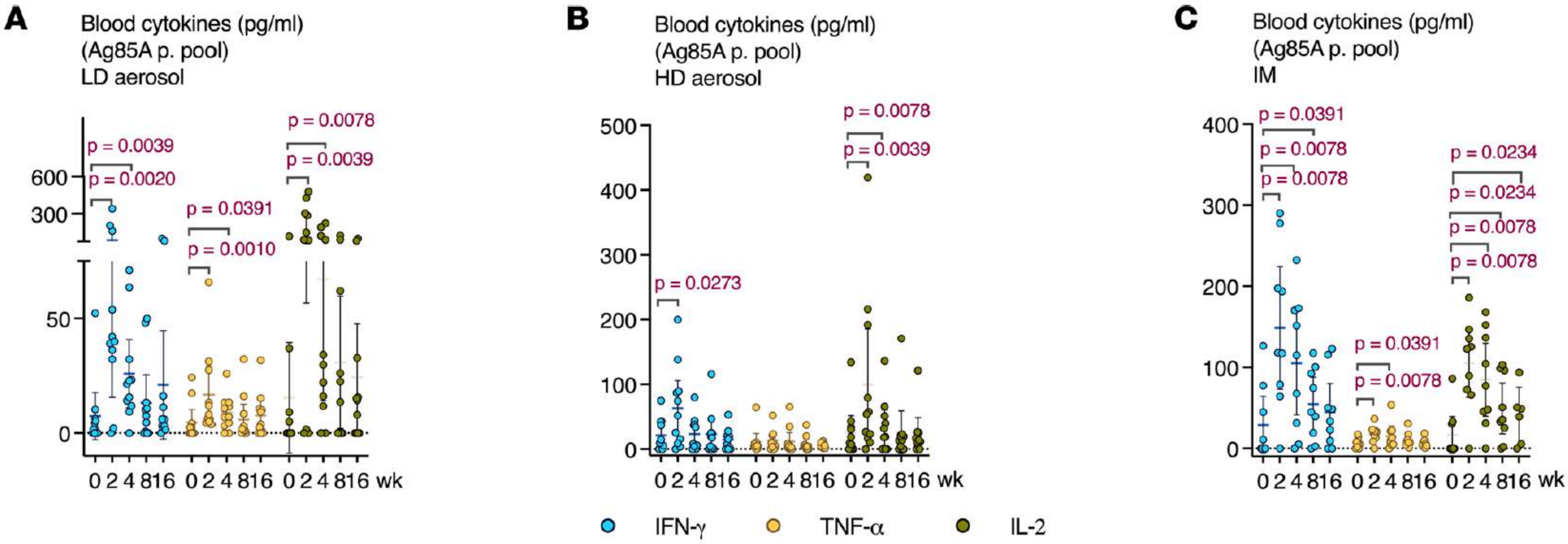
Transcriptomic analysis of alveolar macrophages following low dose aerosol vaccination



Group 1 – Week 0 (unstimulated)
Group 2 - Week 8 (unstimulated)
Group 3 – Week 0 (stimulated)
Group 4 – Week 8 (stimulated)



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

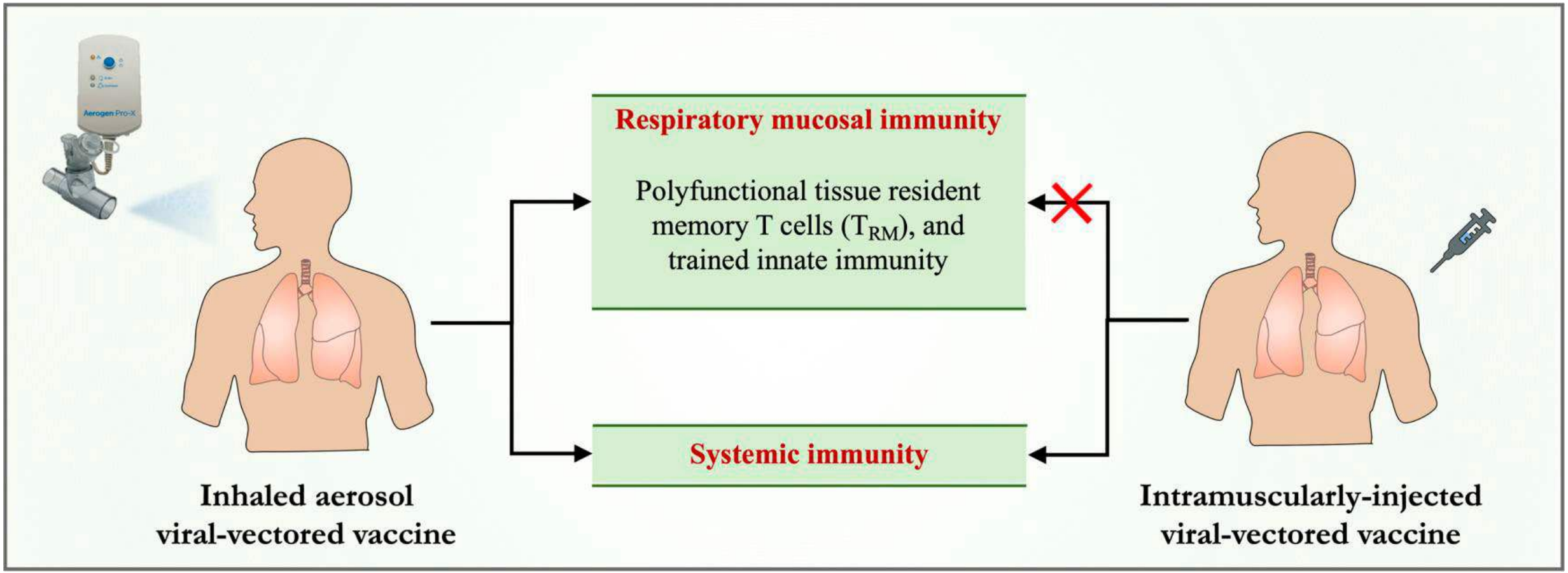


Antigen-specific cytokine production in whole blood culture at various time points after LD aerosol, HD aerosol, and i.m. vaccine groups. The measurements were subtracted from unstimulated control values.

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.
			N		*N*		*N*	
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) *P* = 0.0010	9	20350[A] (5744, 61,200) *P* = 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) *P* = 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 tire: arbitrary units/mL. Ad5 neutralizing antibody titre: reciprocal value of the serum dilution corresponding to 50% of inhibition in the frequency of GFP^+ cells.



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