Unlocking Universal Immunity The future of broadly protective influenza vaccines

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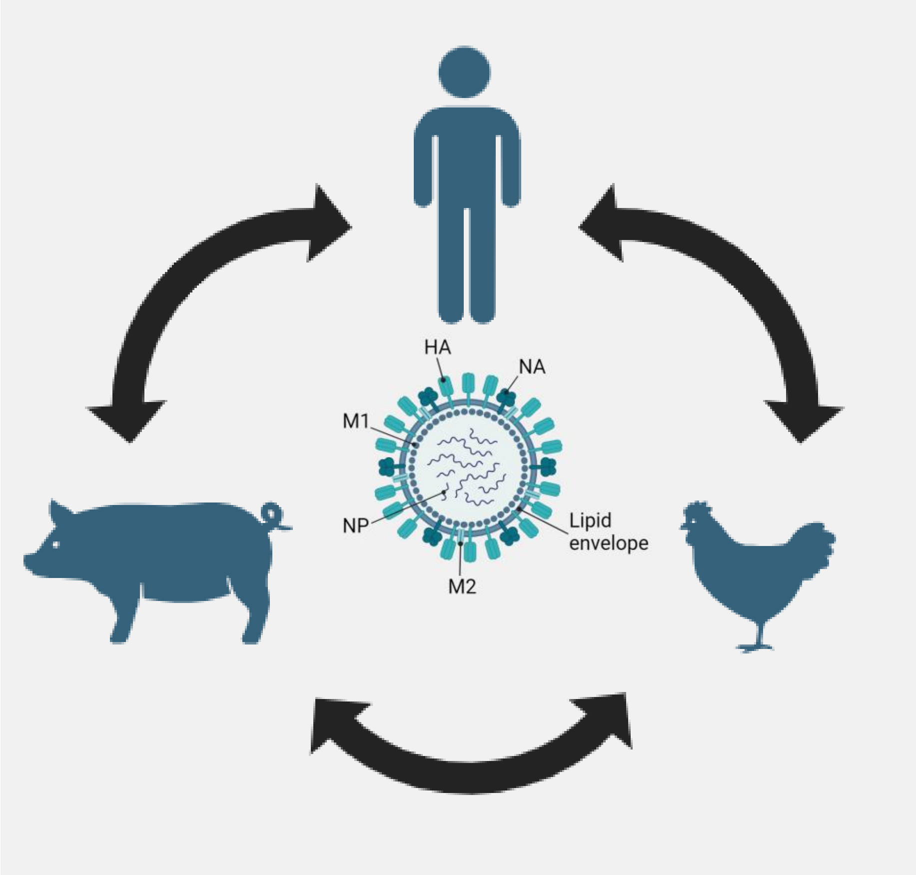
Influenza – a global health threat

Humans

- 290,000 – 650,000 deaths annually
- Young and elderly most at risk

Pigs

- Economic losses
- Zoonotic threat and source of new pandemic viruses



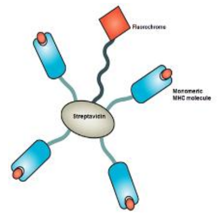
Better control strategies are urgently needed
Novel therapeutics and vaccines to stop transmission

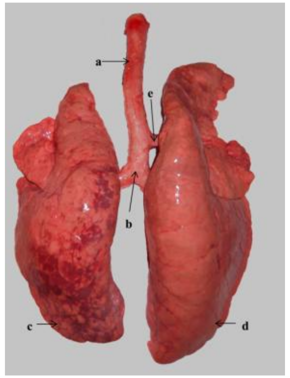
The pig is an excellent model to study immunity to influenza

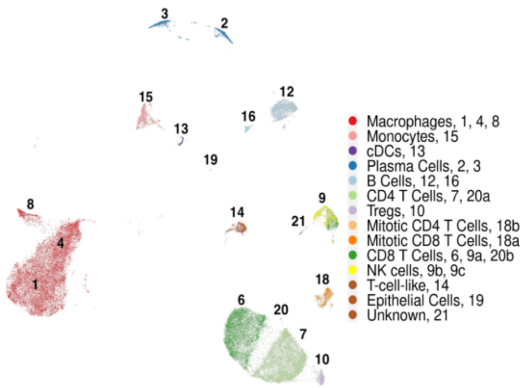
Immunologically, anatomically, genetically and physiologically similar to humans

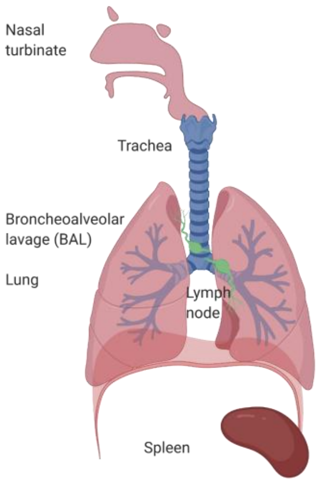
Large natural host for influenza A viruses

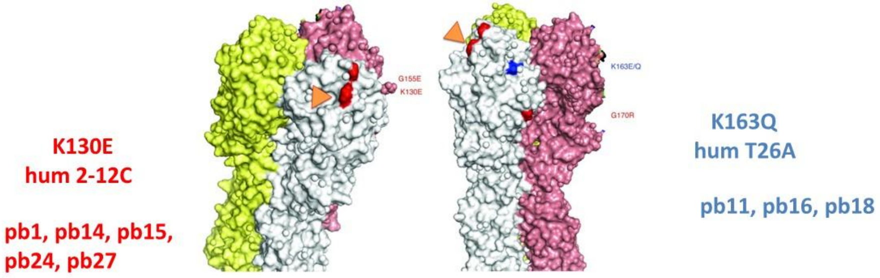
- Infected with similar influenza viruses (pH1N1)
- Display similar clinical signs and lung pathology
- Tracheobronchial tree lung structure and airway morphology similar to humans
- Extensive toolbox to study porcine immune responses
- Generated the first porcine mAbs
- Unrestricted access to the respiratory tract











Tungatt et al PLoS Pathogens 2018
Holzer et al PLoS Pathogens 2021
Martini et al Mucosal Immunology 2022
Muir *et al* PloS Pathogens 2024
Sedaghat-Rostami et al J Immunol 2025

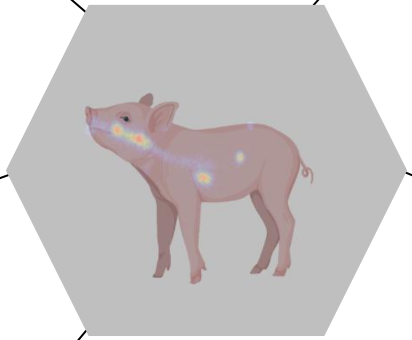
The pig – large natural host for influenza and coronaviruses

Spatial and temporal dynamics of influenza immune response

- Tungatt et al, PloS Pathogens 2018
- Martini et al, Front Immunology 2020
- Edmans et al, Front Immunology 2021
- Maritni et al, J Immunology 2021
- Martini et al, Mucosal Immunol 2022
- Muir et al, PLoS Pathogens 2024
- Vatzia et al, Discovery Immunology 2025

Vaccine induced protective responses - differ from small animals

- Morgan et al, J Immunology 2016
- Holzer et al, J Immunology 2018
- Holzer et al, Front Immunology 2019
- Vatzia et al, Front Immunology 2021
- Schmidt et al, Front Immunol 2023
- Vatzia et al, NPJ Vaccines 2023
- Vatzia E et al, NPJ Vaccines 2024
- Gubbins S et al Front Immunol 2024



Transmission dynamics

- Canini et al, PLoS Pathogens 2020
- Everett et al, J Virology 2020

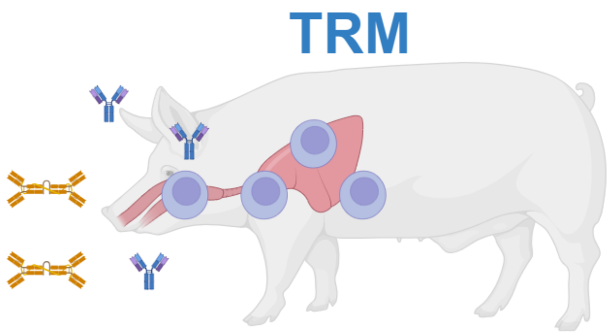
Porcine mAbs – therapy, Fc functions, virus evolution

- Morgan et al, Front Immunology 2018
- McNee et al, J Immunology 2020
- Holzer et al, PLoS Pathogens 2021
- Paudyal et al, Front Immunology 2021
- Paudyal et al, Front Immunology 2022
- McNee et al, Front Immunol 2023
- Paudyal et al, Front Immunology 2024
- Hatton et al, NPJ Vaccines 2025

Porcine coronavirus model

- Graham et al, NPJ Vaccines 2020
- Tan et al, Nature Comm 2021
- Keep et al, Front Immunol 2022
- Sedaghat-Rostami E et al, J Immunol 2025

Harnessing mucosal immunity for protection against respiratory viruses is essential



Questions?

- **How best to target the respiratory tract?**
- **How best to prevent transmission by mucosal therapeutics?**
- **How best to induce broadly protective immunity?**

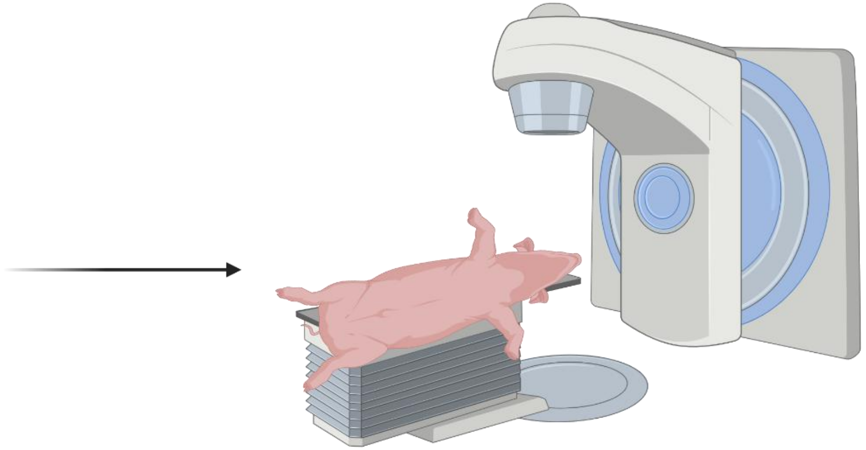
Humans
- Mucosal respiratory vaccine - Flumist
- No mAbs approved for mucosal delivery

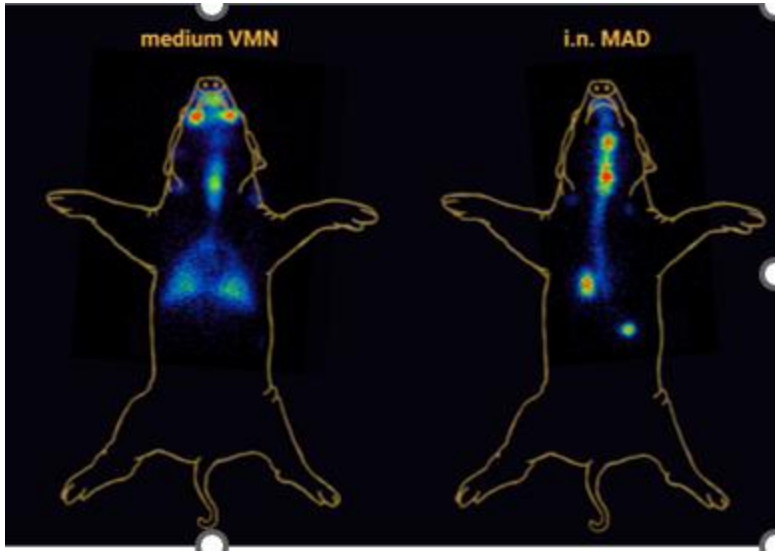
Which part of the RT to target for optimal protection?

In vivo scintigraphy in pigs using ^{99m}Tc DTPA

vibrating mesh nebuliser (VMN) < 2-5 μm

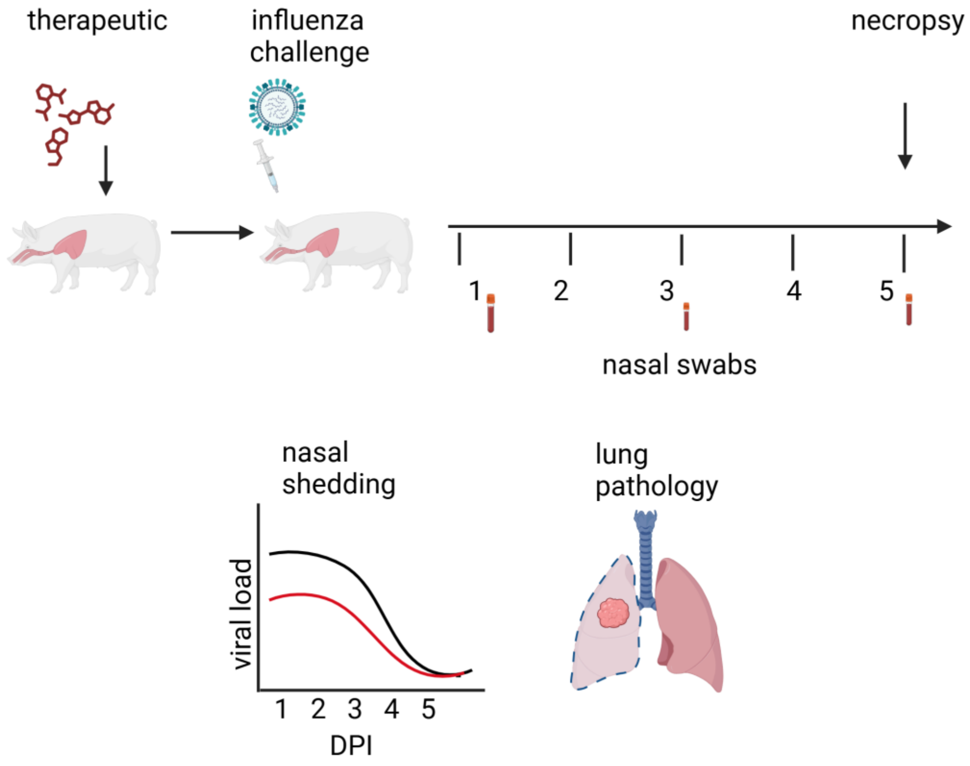
I.N. – using MAD > 80μm





- Aerosol delivers uniformly 20% of the dose to the lung
- i.n. MAD (1ml per nostril) is efficient in lung delivery although more localized and variable – 70%

How to measure efficacy against influenza infection and transmission: direct challenge model

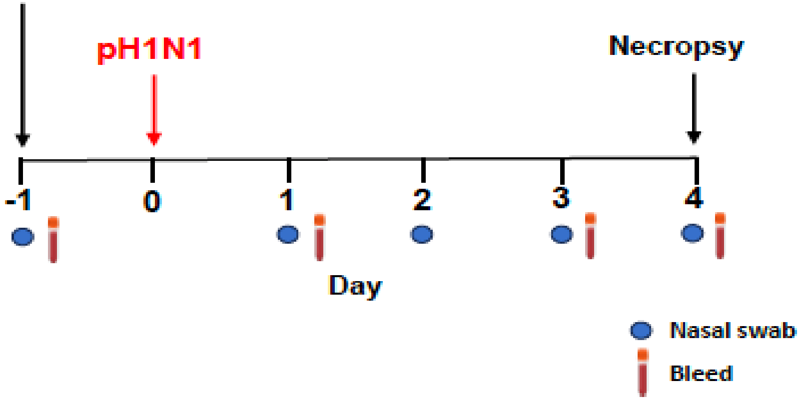


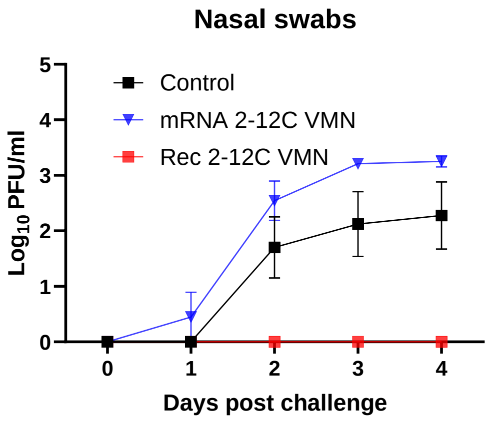
2-12C – human IgG1

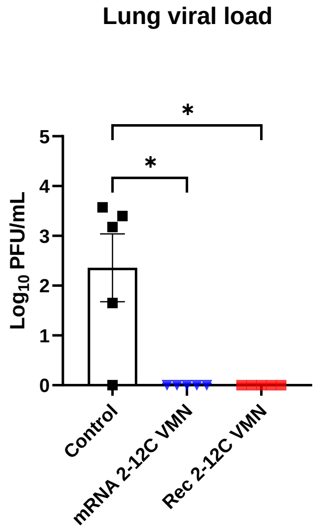
McNee et al J Immunology 2020
Holzer et al PLoS Pathogens 2021
Paudyal et al Frontiers Immunol 2021

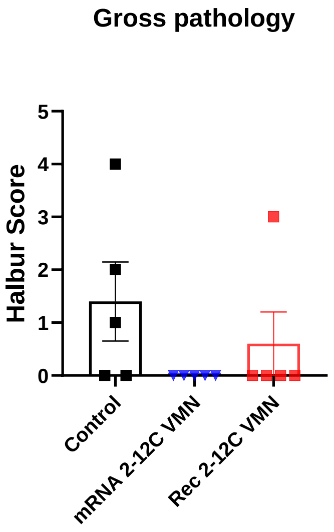
Evaluation of mucosal delivery of 2-1C in direct influenza challenge model

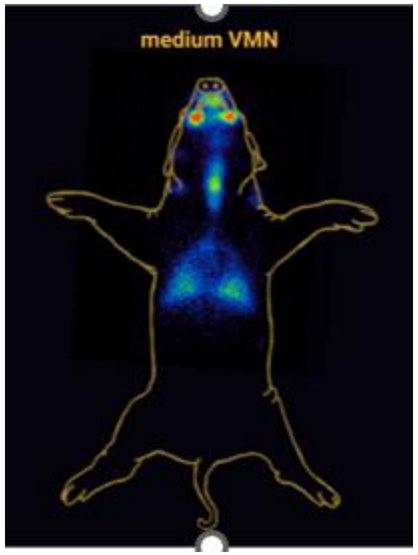
1. Untreated control
2. mRNA 2-12C VMN
3. rec 2-12C VMN (25 mg/ml)





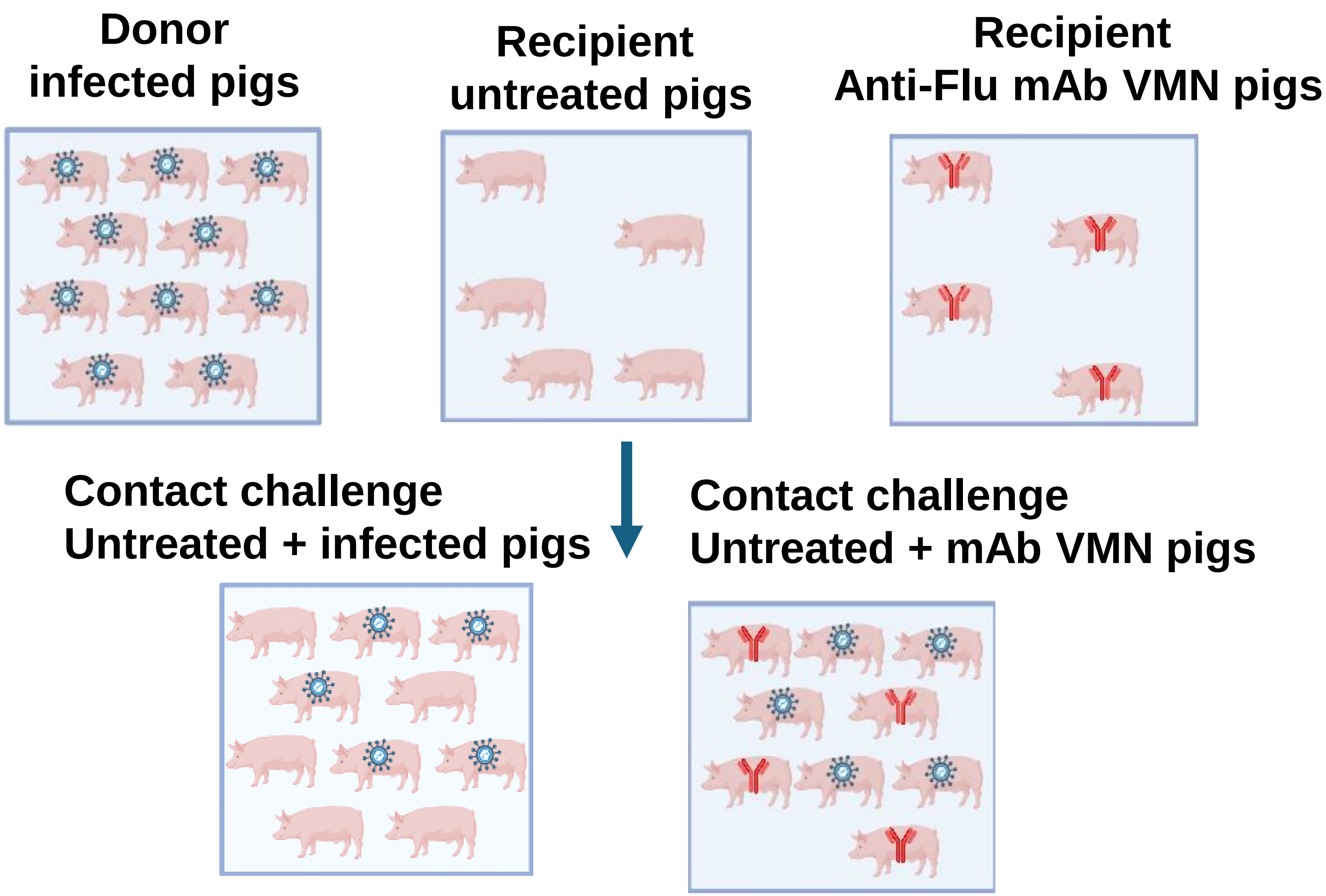


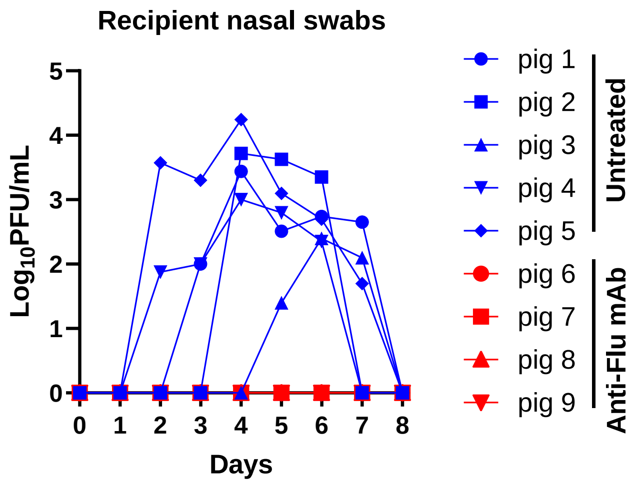




- mRNA 2-12C abolishes lung viral load and pathology but no effect on shedding
- rec 12-C VMN prevents infection

Influenza contact challenge model





- Contact challenge best mimics natural infection
- 2-12C VMN can prevent infection and transmission

Hatton *et al* NPJ Vaccines in press

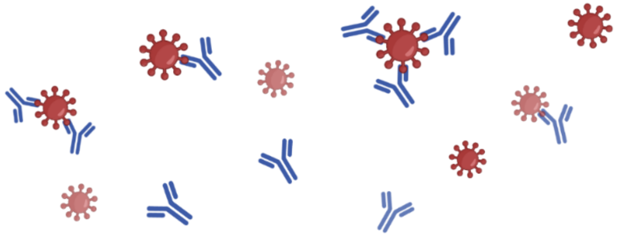
Summary

- Robust positive control 2-12C and pb27 against which to benchmark candidate transmission blockers
- Established direct and contact influenza challenge models to evaluate efficacy of mAb delivery platforms

How best to induce broad protection against different influenza strains?

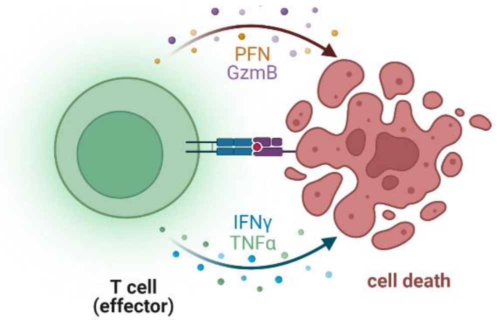
Antibodies can prevent infection

- present vaccines induce antibodies with narrow specificity against the hemagglutinin (HA)



T cells can reduce severity of disease

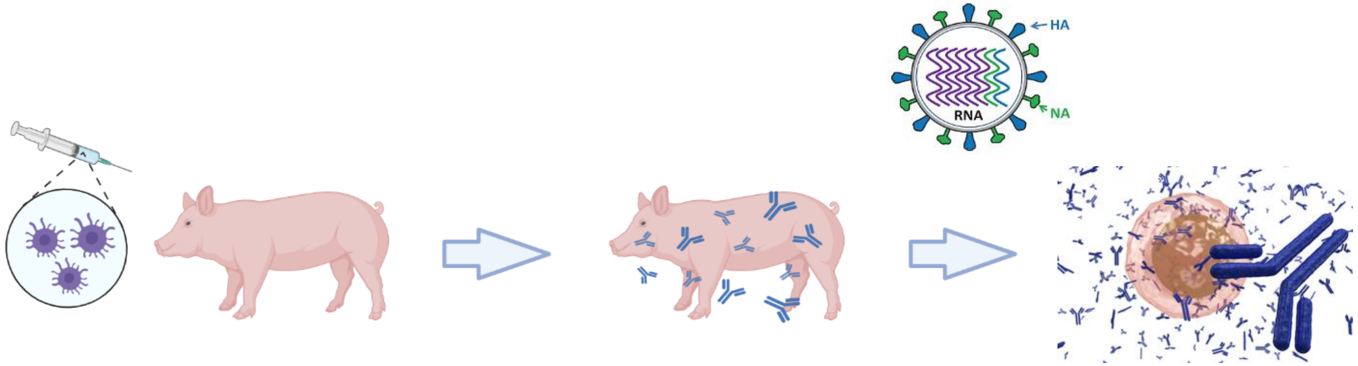
- T cells against conserved internal influenza proteins can provide broad protection
- T cells at the local respiratory sites are crucial for protection
- However present vaccines do not induce strong respiratory T cell immunity



What is the best way of inducing broadly protective antibody and T cell responses?

Current swine influenza vaccines: Whole Inactivated Vaccines (WIV)

Identify the current strain – grow in eggs - inactivated– purified



- **Long production times**
- **Infrequently updated**
- **Do not provide broad protection**
- **VAERD**
- **Interference with MDA**

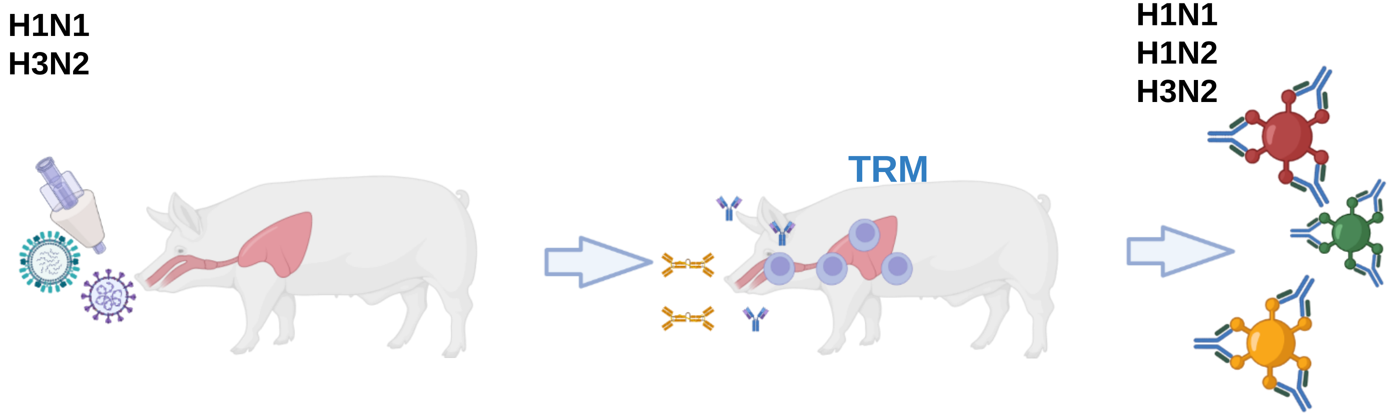
Current swine influenza vaccines: Live Attenuated Influenza Vaccines

Humans - Flumist/Fluenza

- Intranasally – induce mucosal immunity and broader protection
- Attenuated – limited replication in the upper respiratory tract

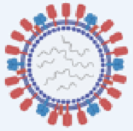
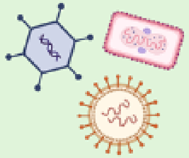
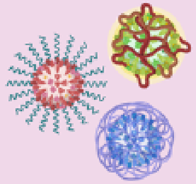
Pigs – US: 2017 NS1D126 LAIV

- Truncation of NS1 – modulates host type I interferon
- Contained 2 strains H1N1 and H3N2 strains
- Piglets 2 days of age



- Reassortment between LAIV and circulating endemic H1 and H3 filed strains
- Removed from commercial use in 2020
- Need for continued surveillance

Novel vaccine strategies

Vaccine	Type	Humoral Immunity	Cellular Immunity	MDA Interference	VAERD Induction	Protection	References
Live attenuated influenza virus (LAIV) 	Elastase-dependent	++/-	++	Not tested	Not tested	Heterologous	Masic et al., 2010; Babiuk et al., 2011; Masic et al., 2009; Landreth et al., 2021; Aubrey et al., 2022
	NS1 truncated and elastase-dependent	+	++	Not tested	Not tested	Homologous and heterologous	Mamerow et al., 2010
	NS1 truncated and bat flu vectored	+	++	Not tested	Resistant	Heterologous	Lee et al., 2021
DNA 	Plasmid encoded	++	+	Not tested	Not tested	Homologous	Larsen et al., 2001; Gorres et al. 2011; Bragstad et al., 2013; Borggren et al., 2019; Karlsson et al. 2018
Viral Vectored 	Pichinde Virus (PICV)	+	Not tested	Not tested	Not tested	Homologous	Kumari et al., 2022
	Orf Virus (ORFV)	+++	++	Not tested	Not tested	Homologous	Joshi et al., 2021
	Adenovirus (AdV)	+++	++	Resistant	Resistant	Heterologous	Wesley et al., 2004; Wesley and Lager, 2006; Braucher et al., 2012; Petro-Turnquist et al., 2023
Computationally Designed 	PigMatrix	-	+++	Not tested	Not tested	Homologous	Gutierrez et al., 2015; Gutierrez et al., 2016; Hewitt et al., 2019
	Epigraph	+++	+++	Not tested	Not tested	Heterologous	Bullard et al., 2022
	Consensus (H1 and H3)	H1:+ H3: ++	H1:++ H3: ++	Not tested	Not tested	Heterologous	do Nascimento et al., 2023; Sun et al., 2019
Nanovaccine 	Polyanhydride	+ (+ CpG agonist)	+++	Not tested	Resistant	Heterologous	Dhakal et al., 2017a; Dhakal et al., 2019
	PLGA	+	+++	Not tested	Resistant	Heterologous	Hiremath et al., 2016; Dhakal et al., 2017b
	Chitosan	+++	+++	Resistant (+mannose)	Resistant	Heterologous	Dhakal et al., 2018; Renu et al., 2020; Renu et al., 2021

Turnquist et al 2024

How best to induce broad protection against different influenza strains?

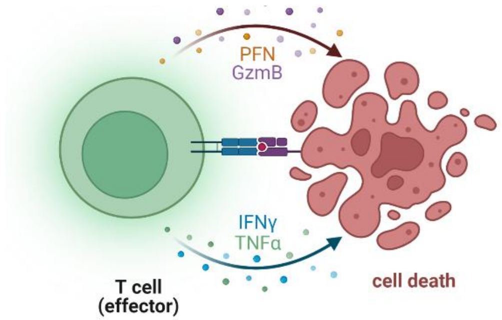
Antibodies can prevent infection

- present vaccines induce antibodies with narrow specificity against the hemagglutinin (HA)

- Antibodies against the NA

T cells can reduce severity of disease

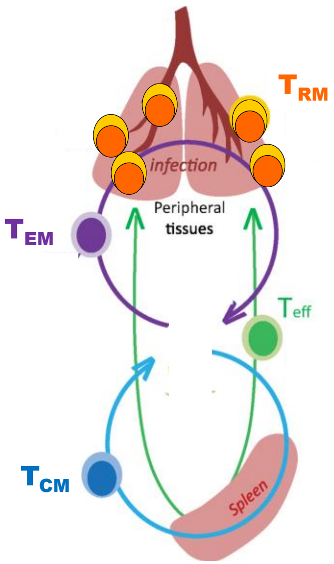
- Lung T cells against conserved internal influenza proteins can provide broad protection



What is the best way of inducing broadly protective antibody and T cell responses?

What is the role of T cell immunity in heterotypic protection?

- reduce viral load in lung
- mild lung pathology
- decreased mortality



- Heterotypic protection Schulman and Kilbourne 1965 - cross protection in the absence of cross neutralizing antibodies

What is the role of T cell immunity in heterotypic protection?

Matthias Tenbusch, University of Erlangen, Germany

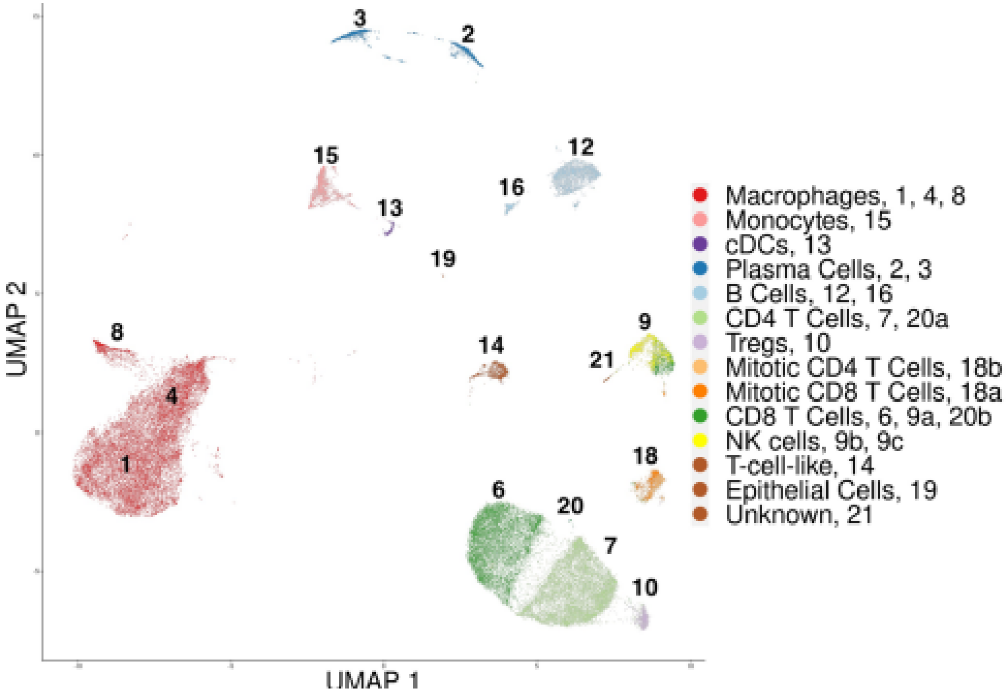
1. Ad HA1/NP
2. Ad HA1/NP +Ad IL-1b
3. H1N1
4. untreated control

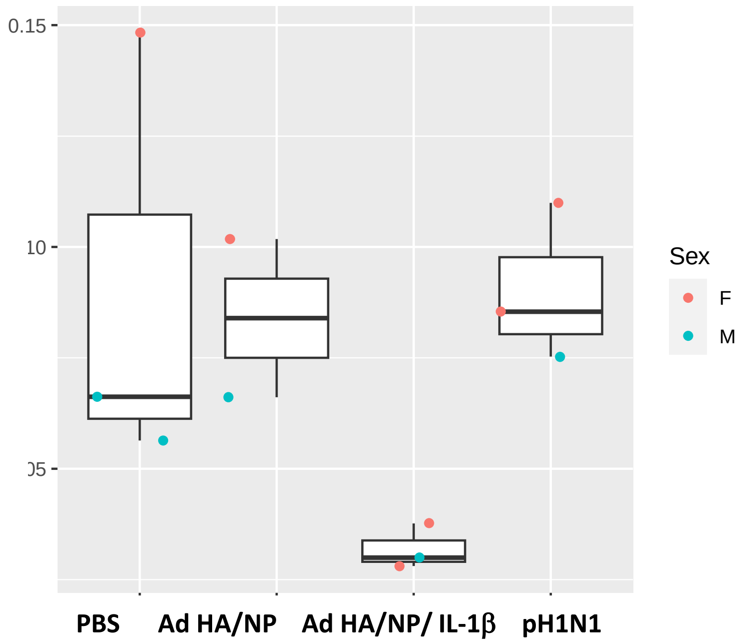
H1N1
pH1N1
H3N2
H7N7

- Ad IL-1b enhanced T cell and Ab responses
- protection against homologous and heterologous challenge

Lapuente et al Mucosal Immunology 2018

Reduced number of T regs in IL-1β group





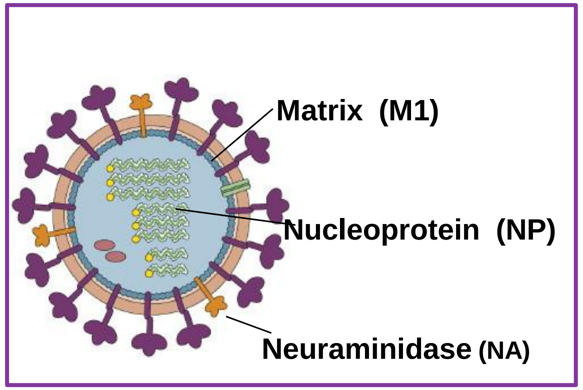
Muir et al PLoS Pathogens2024

How best to induce broad protection against different influenza strains?

1. Viral vaccine vectors

- ChAdOx2
- MVA

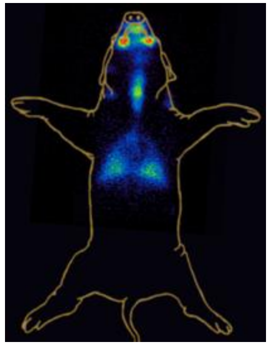
- M1
- NP
- NA



2. Route of delivery

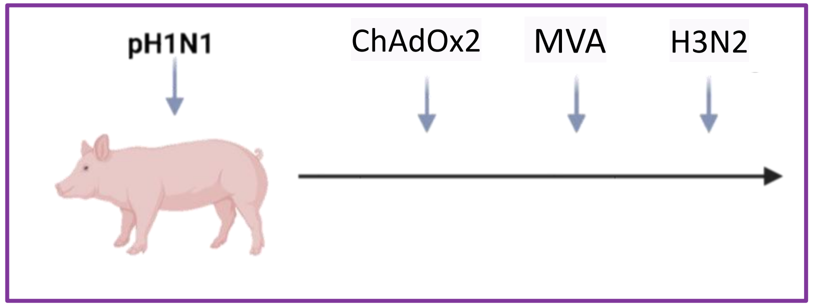
- Intramuscular (I.M)
- Intranasal
- Aerosol (AE)

I.N. – upper respiratory tract >80 µm



AE - whole respiratory tract < 2-5 µm

3. Influenza pre-exposed pigs



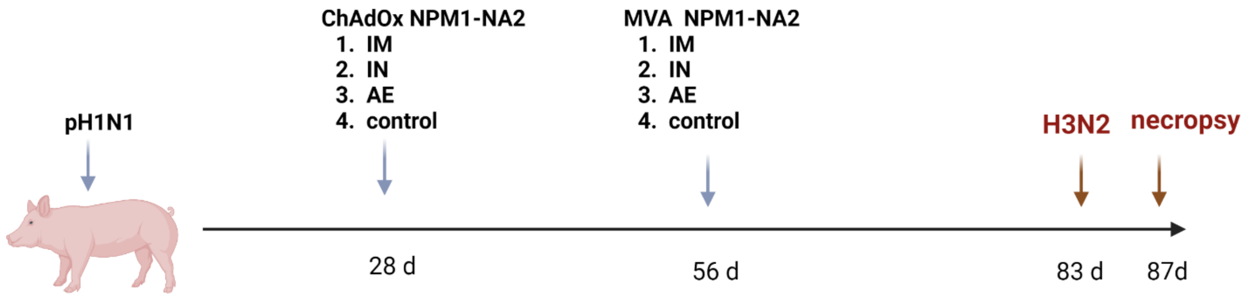
Vatzia *et al* Front Immunology 2020
Vatzia *et al* NPJ *Vaccines 2023*
Vatzia, Paudyal *et al* NPJ *Vaccines 2024*
Gubbins *et al* Front Immunol 2024

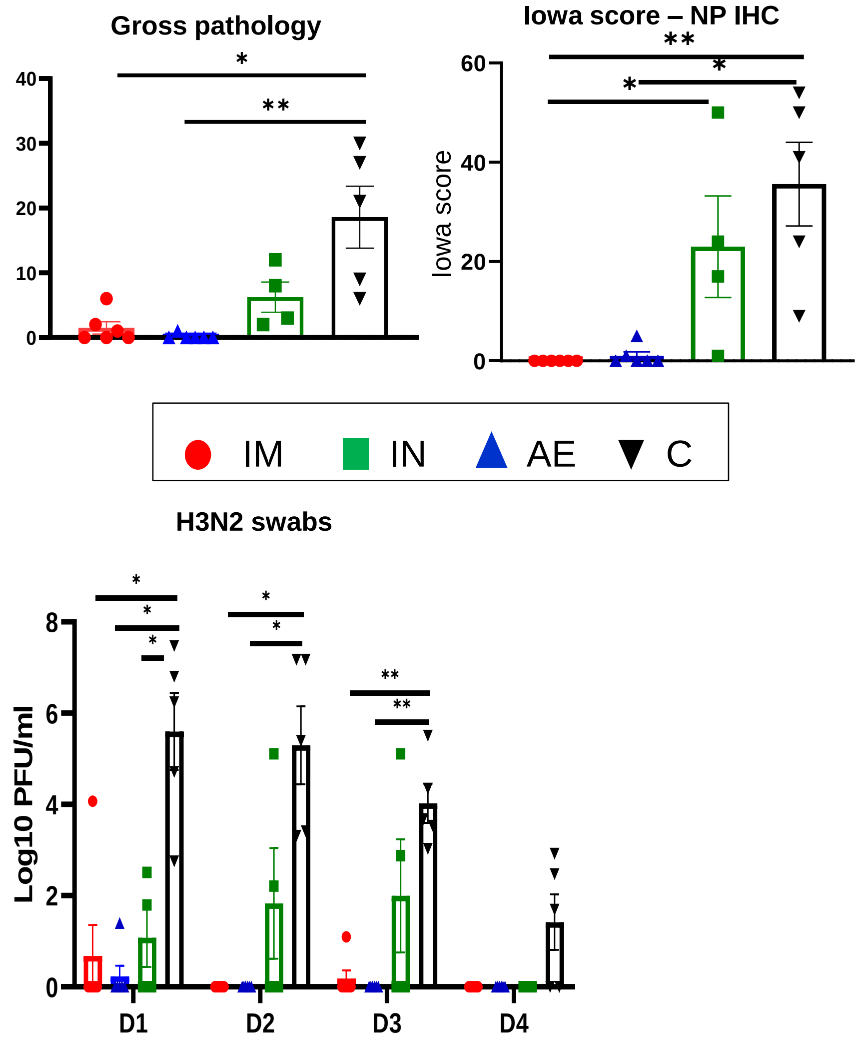
Questions?

1. What is the optimal route of vaccine delivery?

2. What is the contribution of individual antigens in protection – NP, M1 and NA?

Protection against H3N2: NP, M1 and NA2

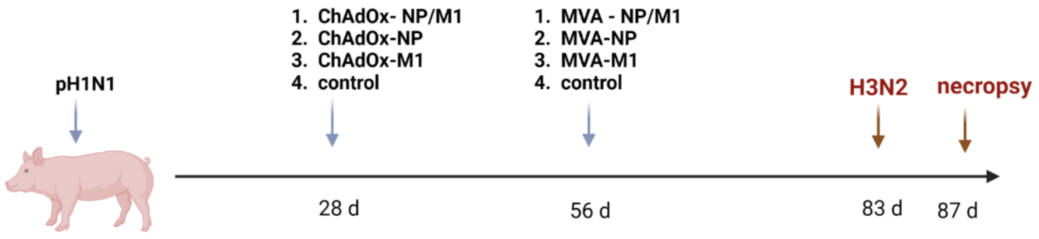


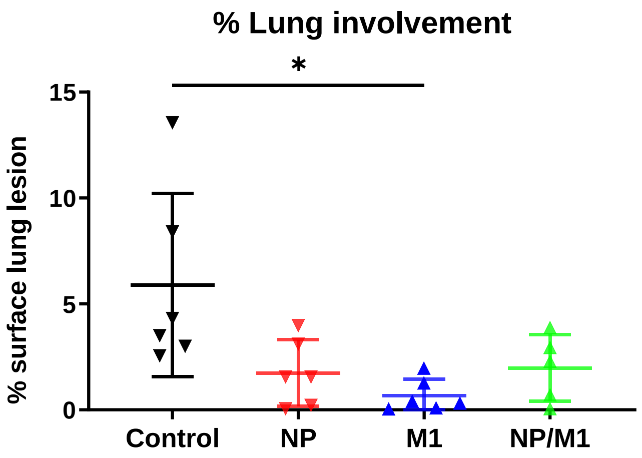


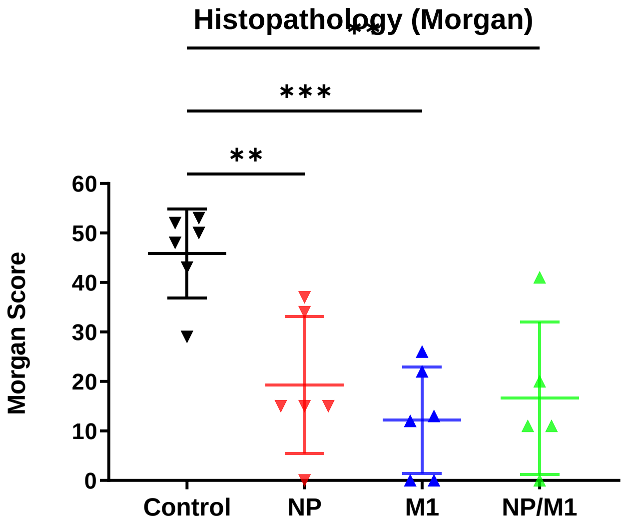
Both IM and AE reduce lung pathology and viral load
However, NA2 in vaccine homologous to H3N2

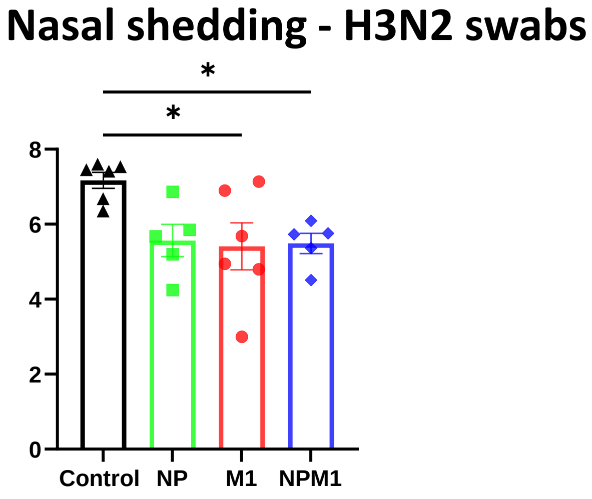
Vatzia *et al* NPJ *Vaccine 2023*

What is the contribution of the internal proteins (NP and M1) in protection?





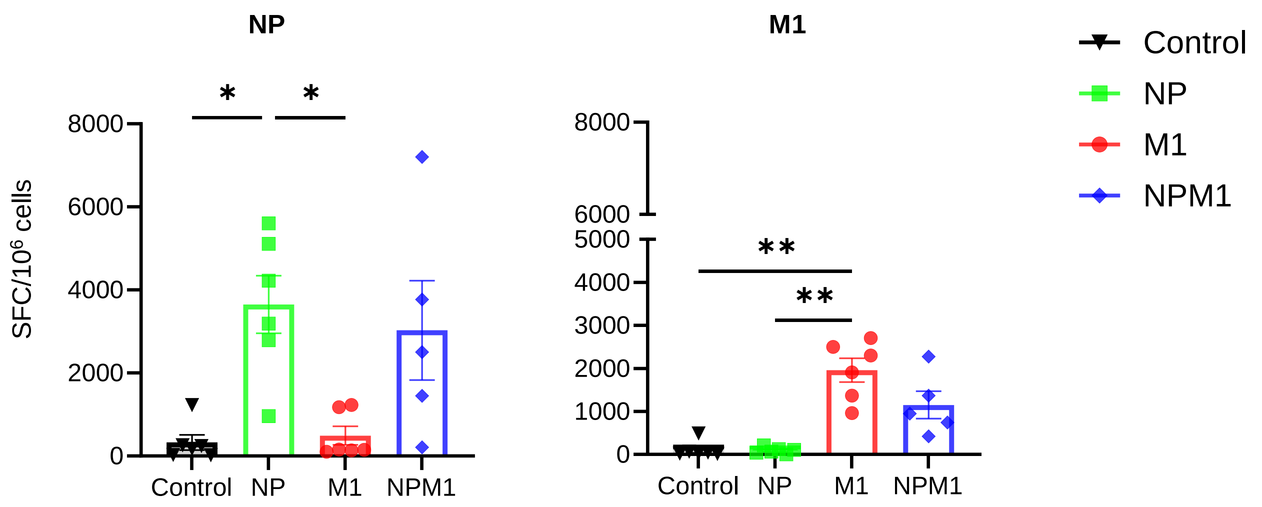


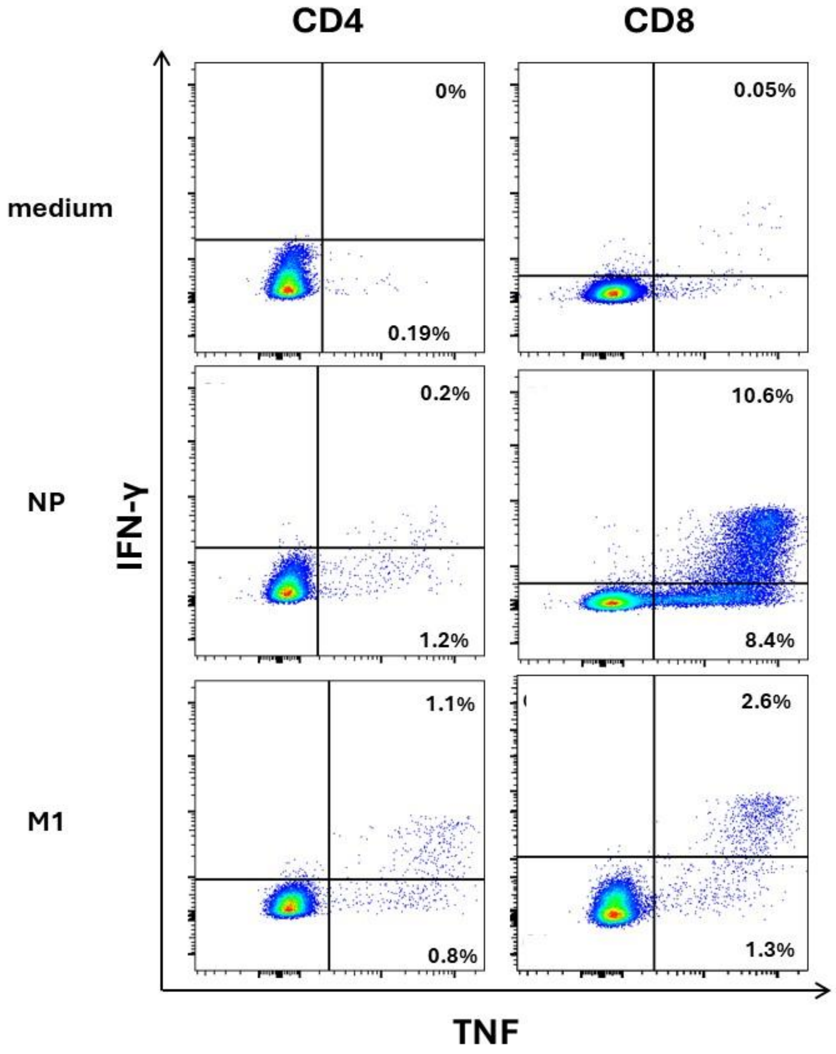


- M1 alone offers the best protection

Vatzia, Paudyal *et al* NPJ *Vaccine 2024*

T cell responses





- **NP induced very strong CD8, while M1 induced more balanced CD4 and CD8 responses**

Summary

- AE immunisation induces greater local lung response, while IM induces stronger systemic response
- NA2 greatly improves vaccine efficacy against homologous H3N2 challenge compared to M1 alone
- M1 alone reduces viral load in lungs and reduces nasal shedding only after AE delivery

Conclusions

- Mice differ from pigs – caution when extrapolating data from single animal model to humans
- Established robust direct and contact influenza challenge models, and positive control 2-12C, to evaluate transmission blocking therapeutics
- Harnessing local respiratory T cell and antibody responses can induce broad protection against disease
- Difficult to prevent transmission in the pig model
- It is important to study immunity to influenza in pigs to develop better immunisation strategies for both pigs and human - One Health approach

Even if therapeutics or vaccines do not prevent shedding, they can still prevent disease and could be life saving

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Barbara Dema Jimenez
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