Innate-adaptive immunity duo as a regimen for conferring rapid-sustained-broad protection against pathogens

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September 29, 2015

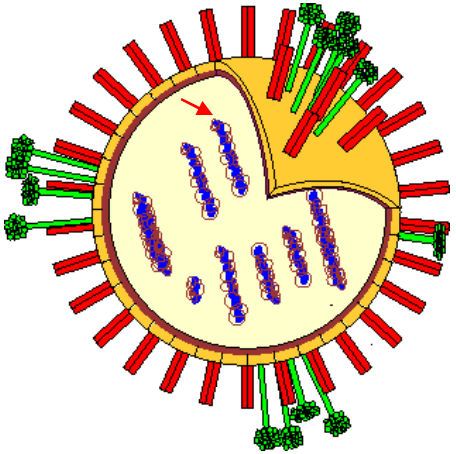
A litany of demands for better vaccines

Problem: Current vaccines confer protection in a slow motion.
Solution: Develop a drug-vaccine duo (DVD) by activating a protective innate-adaptive immunity duo.

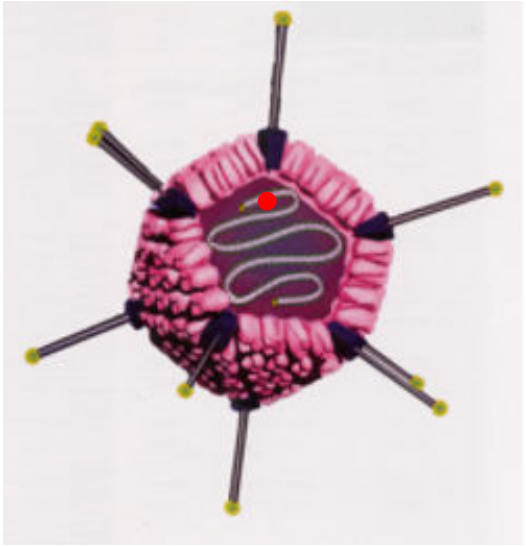
Problem: Current vaccines do not confer broad protection.
Solution: Develop a universal vaccine component within a DVD context.

Problem: Current injectable vaccines are associated with pain; fear; medical license; syringe needle disposal; and systemic inflammation.
Solution: Develop noninvasive vaccines by delivering vaccines to the interface between the body and environment (e.g., oral vaccine; nasal vaccine; skin-patch vaccine).

Ad5-vectored influenza vaccine



Clone HA



Influenza virus

- Growth varies from strain to strain
- Some strains are lethal
- Prone to reassortment/mutation events
- Low-titer production in eggs

Ad5 vector encoding influenza HA

More consistent growth rates

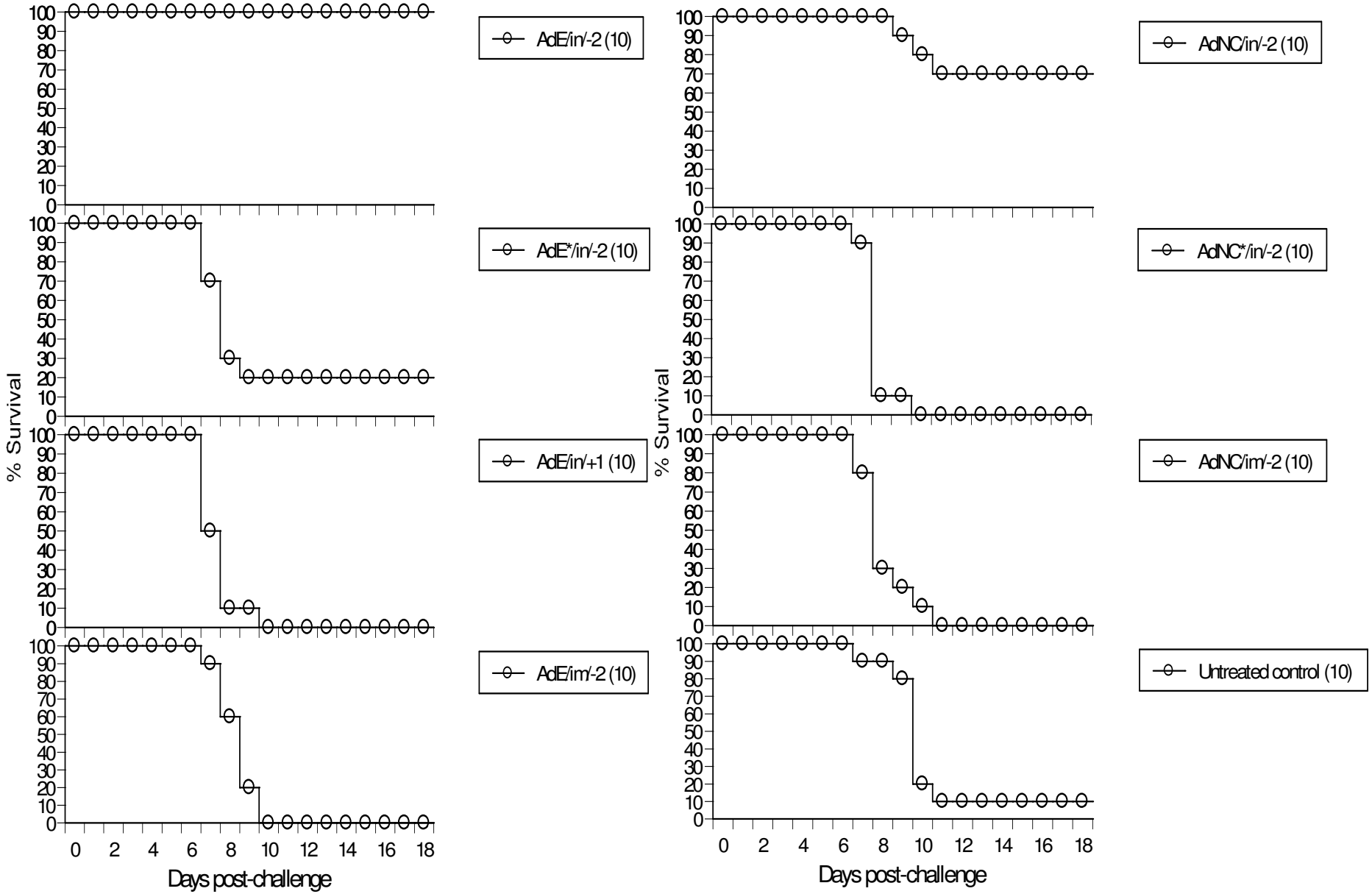
Benign vectors

No reassortment events

High-titer production in cultured cells

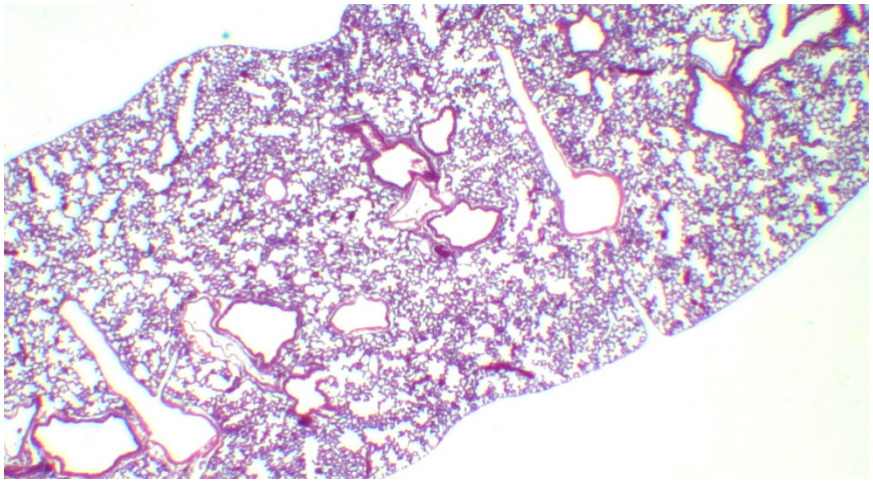
A new RCA-free Ad5 can be generated by the AdHigh system within one month

Prophylactic influenza therapy by Ad5-vectored drug-vaccine duo

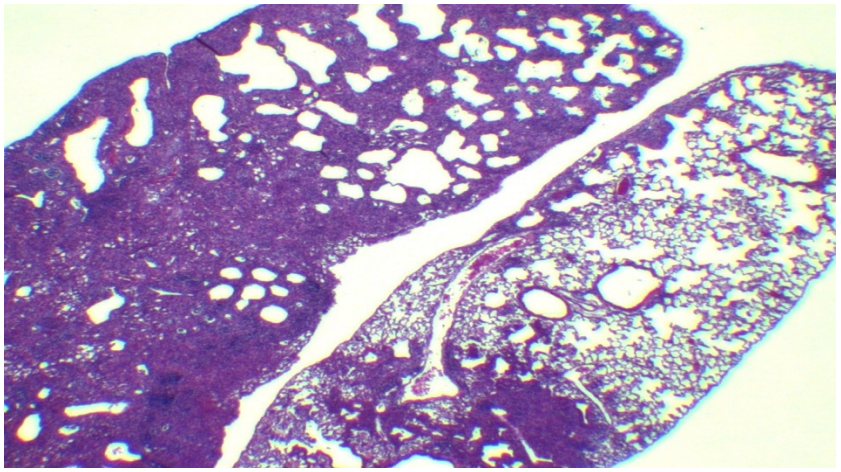


-Zhang J *et al. PLoS ONE* 6: e22605, 2011

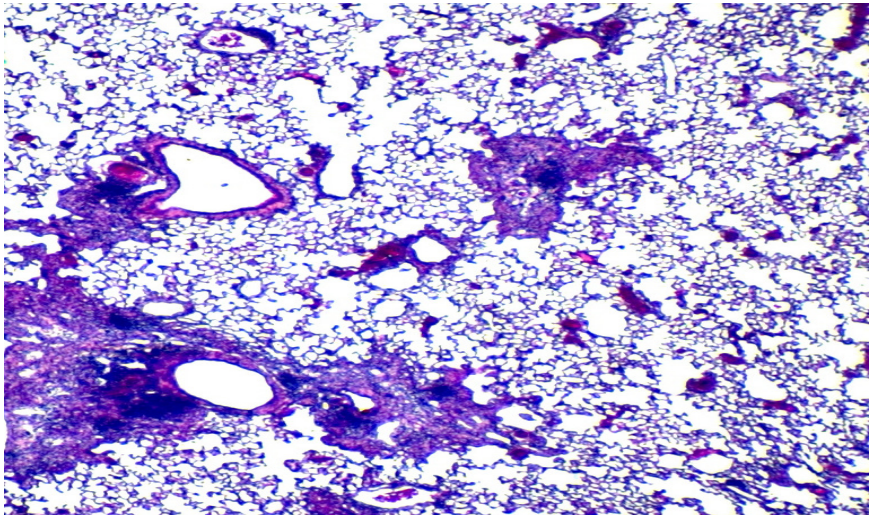
Lung histopathology 19 days post-influenza virus infection (2X)



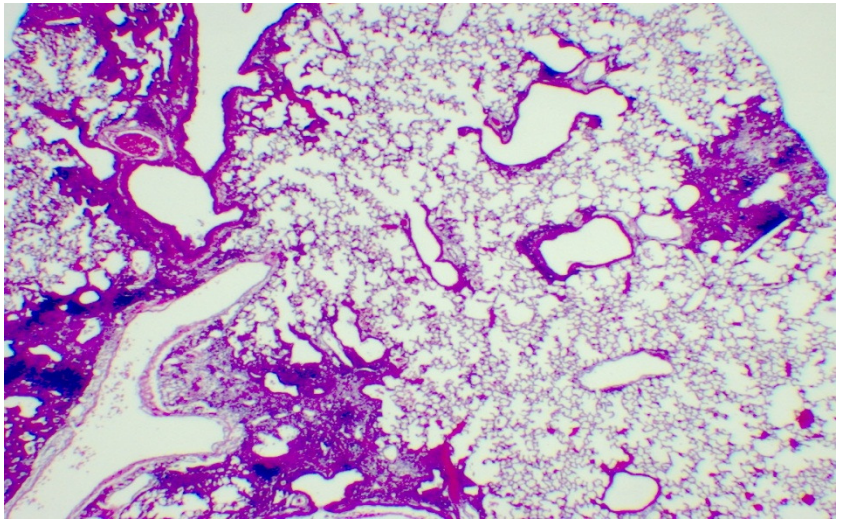
Normal; no PR8



No Ad5 pre-exposure; PR8 challenge



Pre-exposure to AdE; PR8 challenge



Pre-exposure to AdNC.H1.1; PR8 challenge

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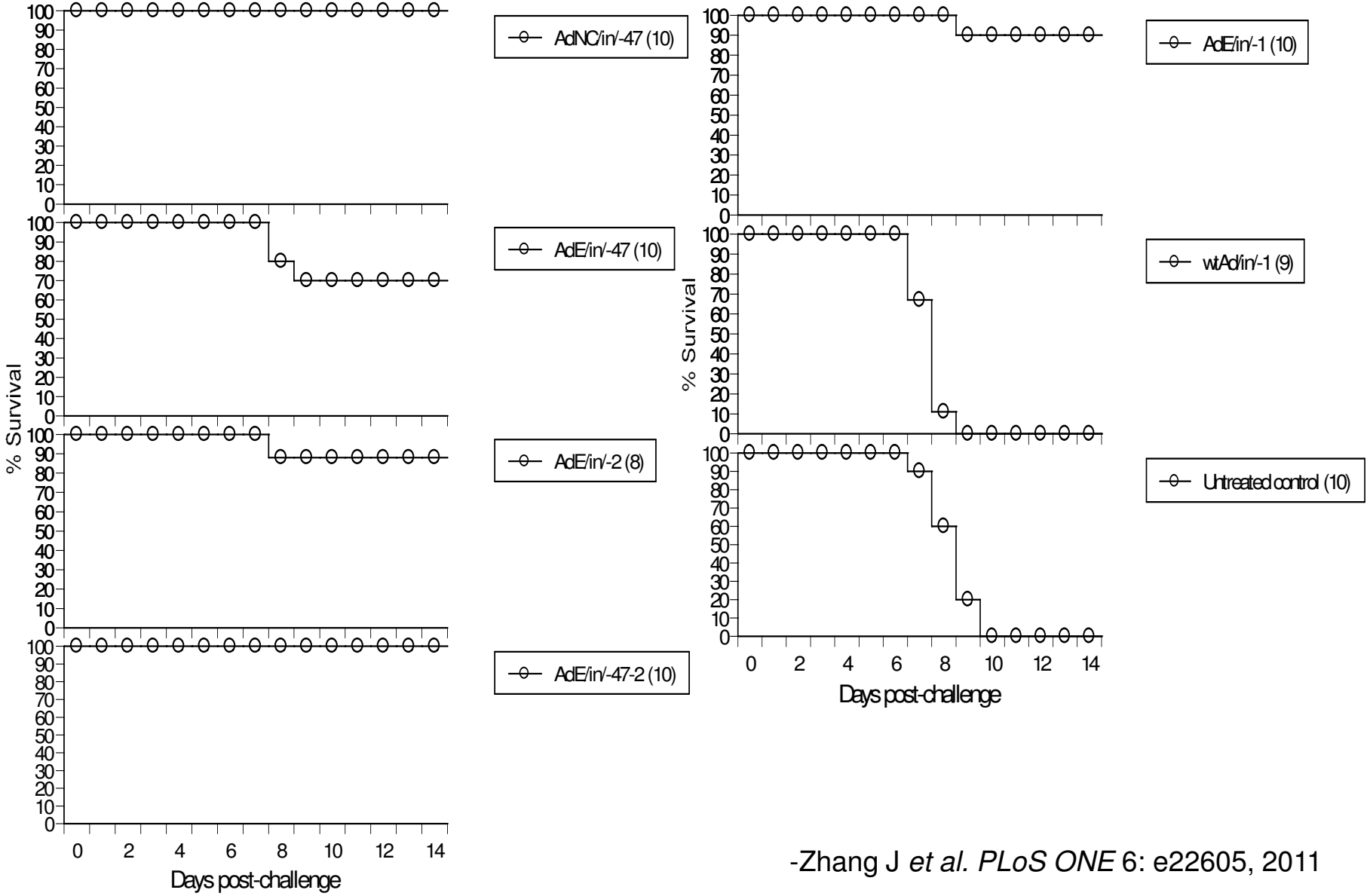
Ad5-vectored drug-vaccine duo induces rapid-sustained protection against influenza – a vaccine more than just a vaccine



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Influenza drugs

Class I: M2 ion channel blockers – impaired by drug resistance

- Amantadine
- Rimantadine

Class II: Neuraminidase inhibitors – impaired or to be impaired by drug resistance

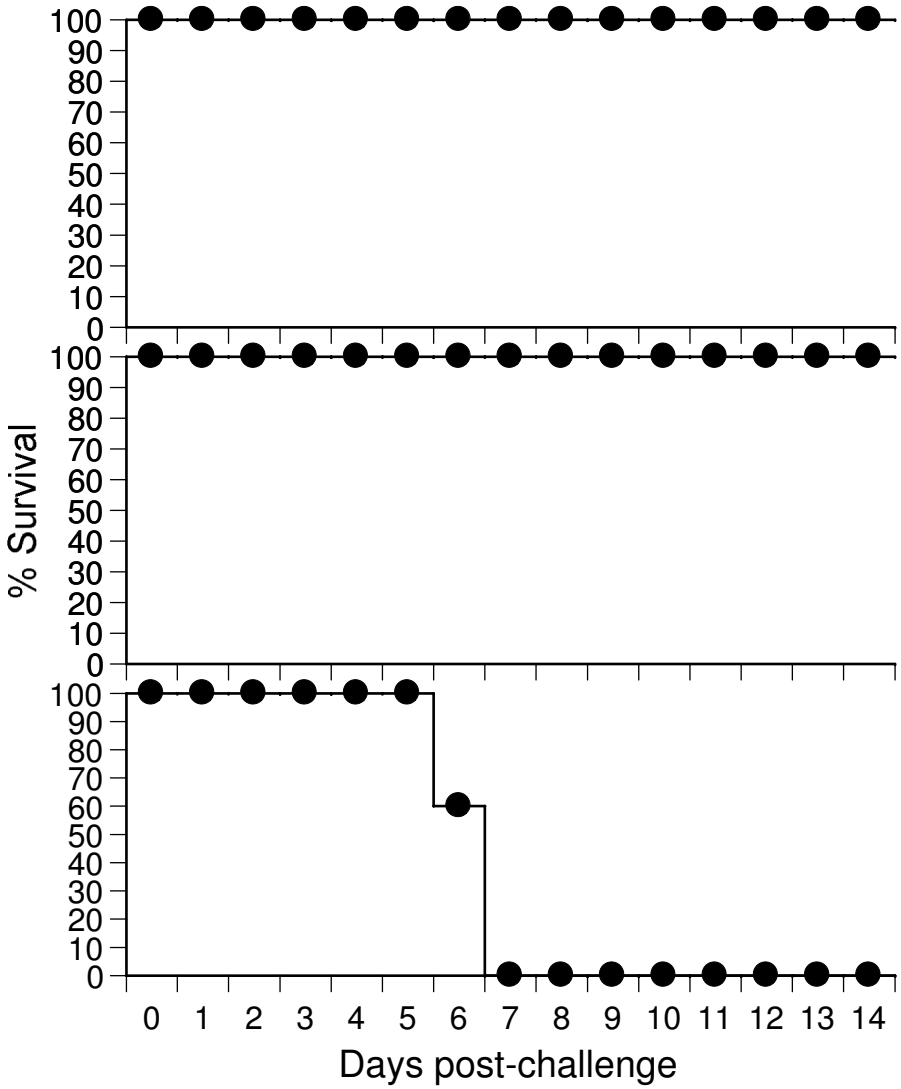
- Oseltamivir (Tamiflu)
- Zanamivir (Relenza)
- Peramivir

To bypass drug resistance: Taking the way a licensed drug as we know how it works, then doing the exact opposite.

Class III: Induction of an anti-influenza state – may not induce drug resistance

- Adenovirus-vectored drug-vaccine duo (DVD)

Ad5-vectored nasal influenza vaccine protected ferrets against the A/VN/1203/04 (H5N1) avian influenza virus



HAE10 HI=22 (5)

HA1E10 HI=5 (5)

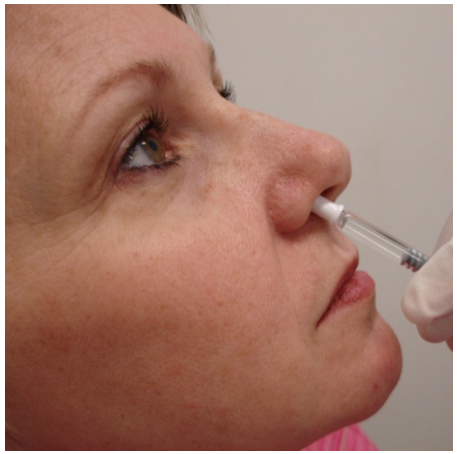
Control HI=5 (5)

Ferrets were immunized i.n. on Day 0; and challenged with A/VN/1203/04 at a dose of 10 FLD_{50} (10^2 EID_{50}) at SRI on Day 56. HA, Ad encoding HA1+HA2; HA1, Ad encoding HA1; E10, 10^{10} vp; HI, GMT of serum HI titers on Day 51.

Human Phase I clinical trial of an Ad5-vectored nasal avian influenza vaccine

Study design

- Ad_hVN1203/04.H5 vector encodes HA1+HA2 of the A/VN/1203/04 (H5N1) avian influenza virus
- Randomized, double-blind, placebo-controlled, single-site study
- Three cohorts at an escalating dose of 10^8, 10^9, and 10^{10} vp
- Administered by nasal spray
- Two doses on Days 0 and 28
- Total of 48 healthy volunteers, aged 19 – 49
- Sixteen human subjects per dose cohort, including 4 placebo controls per cohort
- RCA free, cell culture based manufacturing in PER.C6 suspension cells in serum-free medium at SAFC
- Human clinical trial was performed by Dr. Scott Parker at UAB



Rationale to develop an Ad5-vectored nasal influenza vaccine

	Licensed TIV	Licensed LAIV (FluMist)	Ad5-vectored nasal influenza vaccine
IFV required	Yes	Yes	**No**
Egg required	Yes	Yes	**No**
Mode of administration	Intramuscular injection	**Nasal spray**	**Nasal spray**
Replication postvaccination	**No**	Yes	**No**
Reassortment	**No**	Yes	**No**
Antiviral co-administration	**Yes**	No	**Yes**
Nearly-immediate protection	No	**Yes (animal model)**	**Yes (animal model)**
Systemic inflammation	Yes	**No**	**No (conceivably)**

Inflammation induced by noninvasive vaccination tends to be benign

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