Potent, Rapid and Cost-Effective

Influenza Vaccines

Made in E. Coli

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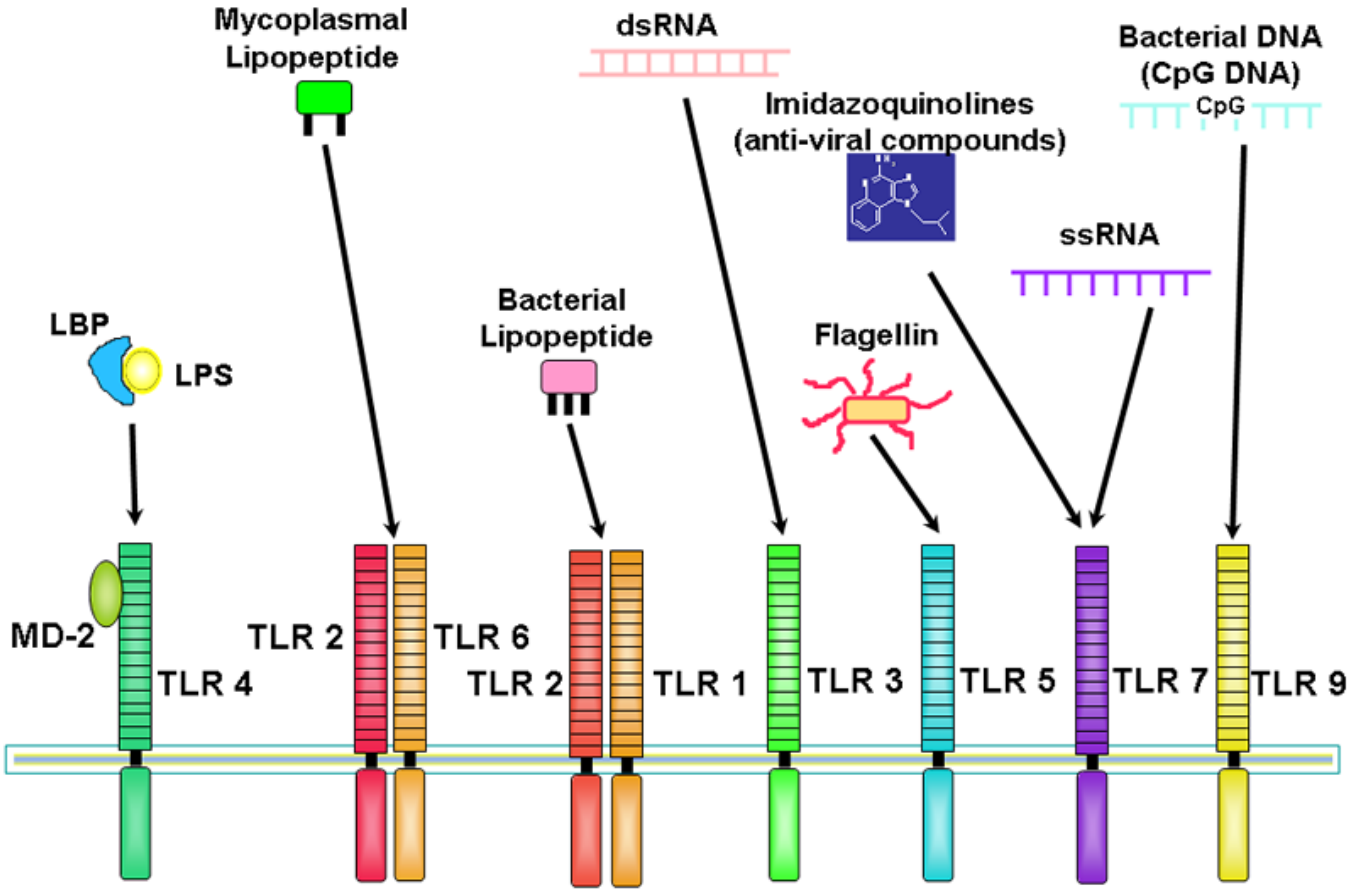
VAXINNATE

Key Topics

- VaxInnate's proprietary technology
  - activates innate and adaptive immune system
  - provides highly immunogenic and well tolerated vaccines
  - allows fast, low cost manufacturing in E. coli at unlimited capacity

Innate Immune Responses are Mediated by Toll-like Receptors Expressed on the Surface of Immune Cells

Toll Like Receptors Recognize Pathogen Associated Patterns (PAMPs)



VaxInnate's Current Influenza Vaccines Incorporate Flagellin, a TLR5 Ligand, the Only Well Studied Protein Agonist that can be Expressed in E. coli.

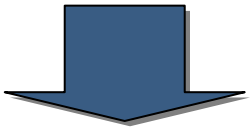
VaxInnate's Platform

Advantages of Flagellin Fusions

Physically linking TLR ligands to antigens is more efficient and specific than simply co-administering them

- In normal responses to natural infection, TLR signaling and antigen presentation are tightly linked since TLR ligand and antigen are contained in a single pathogen
- VaxInnate's technology mimics natural infection by ensuring that TLR agonist and antigen are presented simultaneously at the same antigen-presenting cell
- Ordinary (unlinked) adjuvants must find their way to the same APC by chance, and therefore require high doses

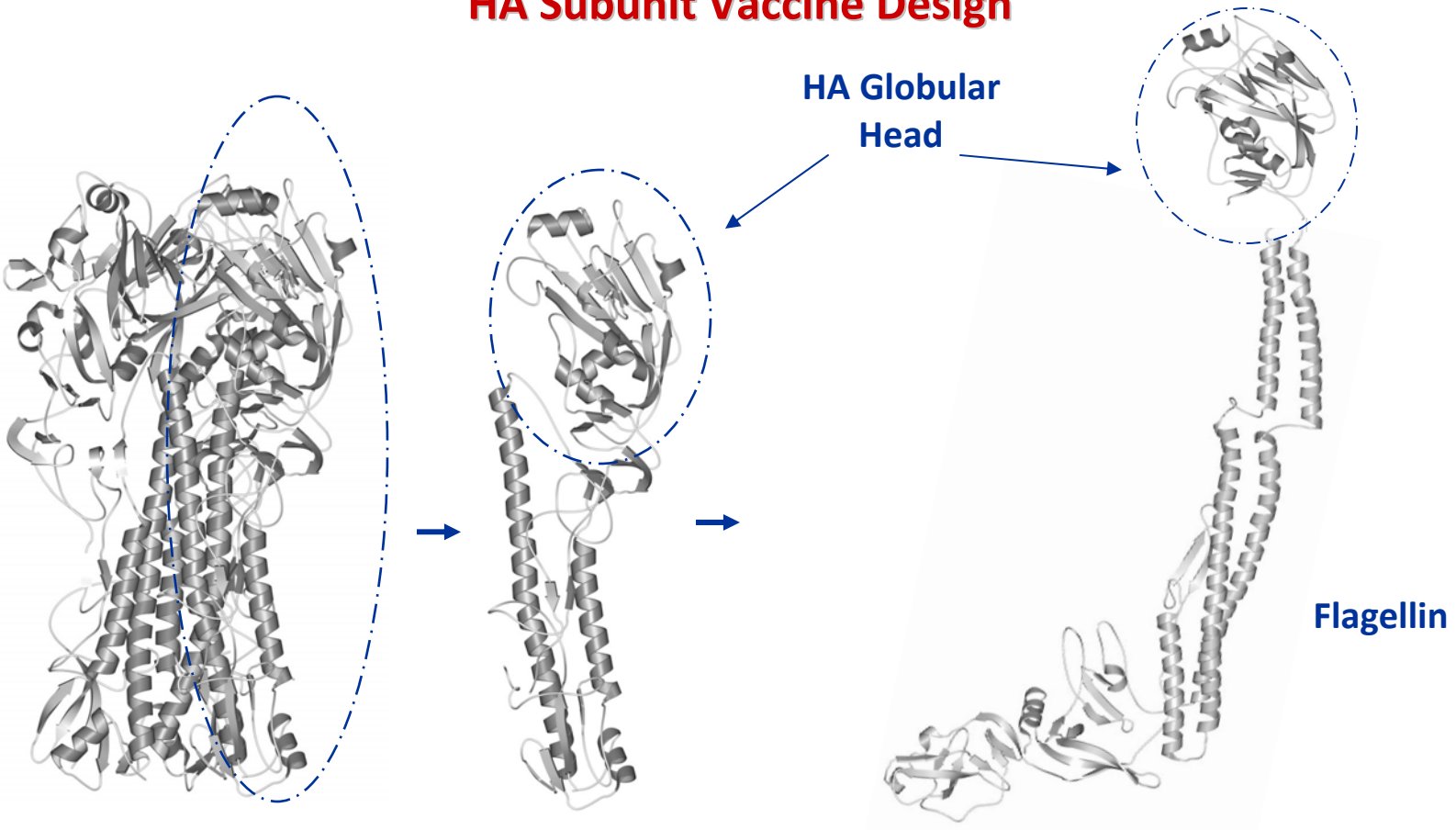
TLR Agonist	Antigen
• Targets to APC • Leads to internalization • Induces co-stimulation • Breaks tolerance • Activates B cells	• T-cell and B-cell epitopes • Confers protective immunity • Specific memory



✓ Signal 1 (antigen) and Signal 2 (co-stimulation) in the same APC
✓ Fusion proteins expressed in *E. coli* are flexibly and inexpensively produced

Influenza Vaccine

HA Subunit Vaccine Design

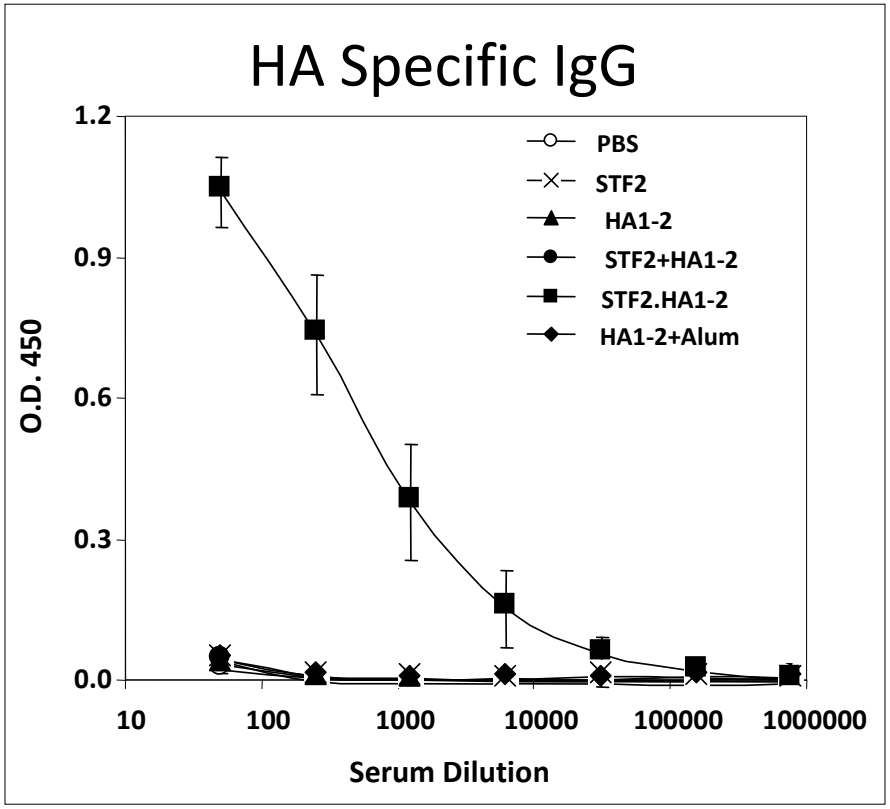


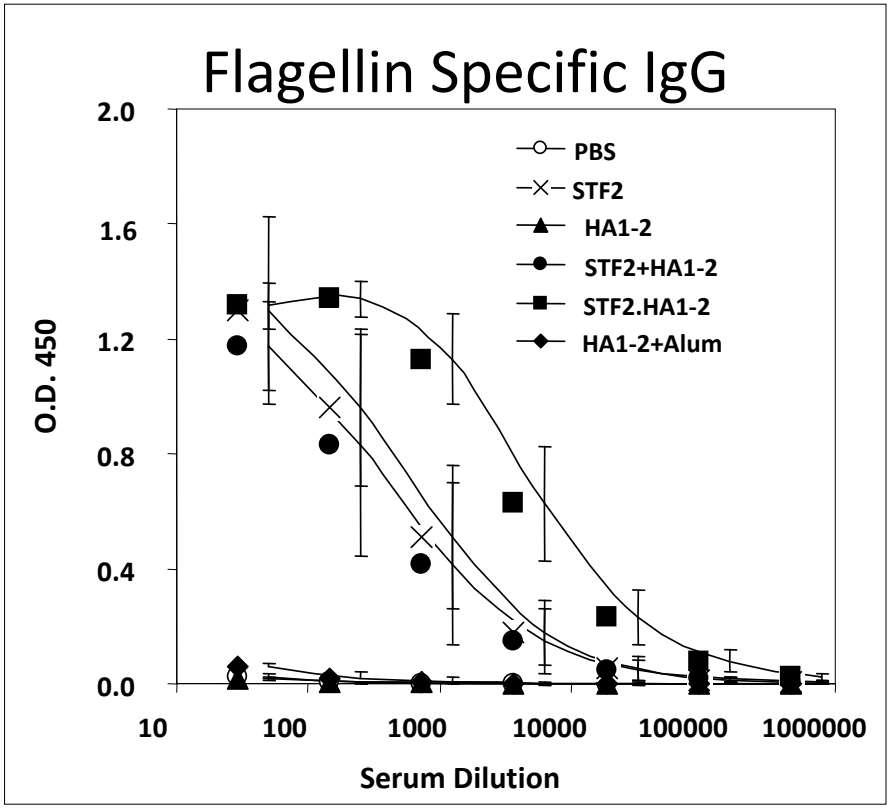
Fusion of HA globular head (HA1-2) and *S. typhimurium* flagellin type 2 (STF2) [a TLR5 ligand] to form STF2.HA1-2

VaxInnate's HA Subunit Vaccines can be Produced in E.coli.

Influenza HA Vaccines

Importance of Fusion to Flagellin

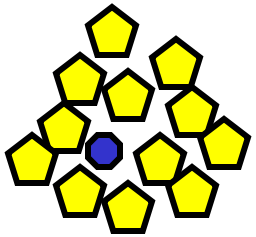




The Potency of VaxInnate's Vaccines are Dependent on the Fusion.

Influenza HA Vaccines

Importance of Fusion to Flagellin



Conventional Adjuvants

Ag-specific immune response
Excessive inflammatory response
Non-specific immune response
Autoimmune response

VaxInnate's vaccines

Ag-specific immune response
Minimal inflammatory response

 = antigen

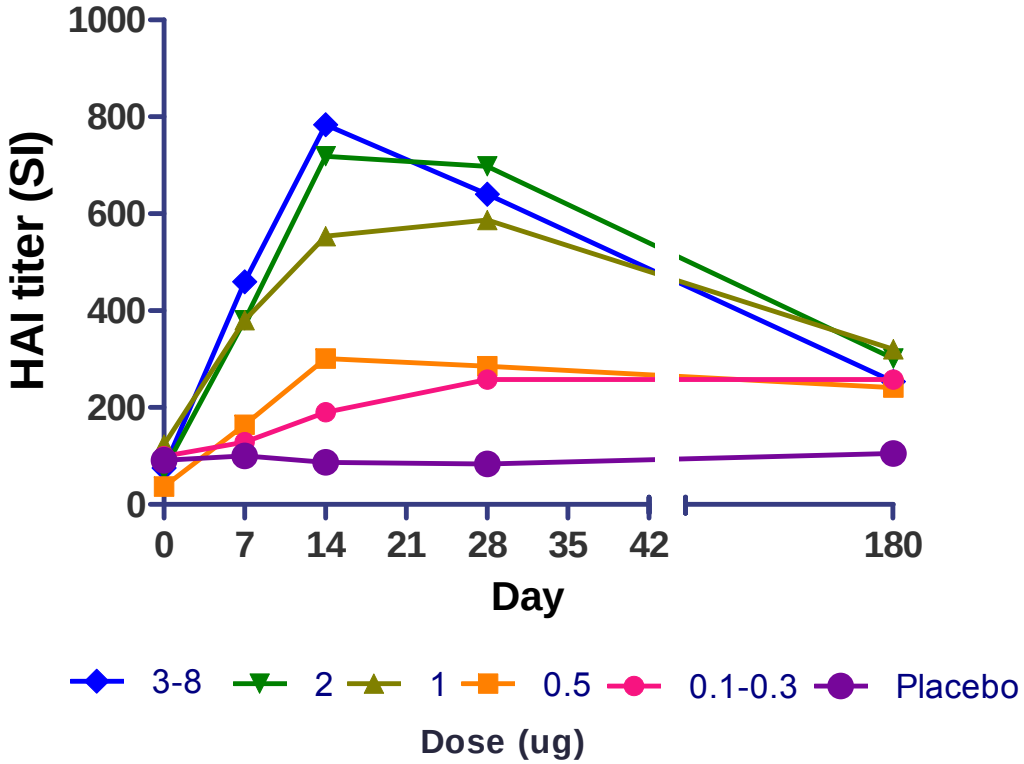
Genetic Fusions of the Vaccine Antigen and TLR Ligand Efficiently Stimulate both the Innate and Adaptive Immune Systems and Mimic Natural Infection.

Seasonal Vaccines

VAX125: A Seasonal Vaccine Based on A/SI/3/2006

Phase I Clinical Evaluation

Geometric mean HAI antibody titers to HA Solomon Islands by dose for healthy adult subjects 18-45 years old



Immunogenicity for Doses of 1 µg or Above is Excellent.

Clinical Evaluation of VAX125 Phase I

Summary of HAI GMTs, Seroprotection and Seroconversion Rates

	Dose	Control	VAX125 dose range (ug)		
			0.1-0.3	1-3	5-8
		n=16	n=16	n=56	n=16
GMT	Day 0	91	99	102	50
	Day14	87	190	672	698
	Day 28	84	258	640	640
GMT fold increase	at day 14	1.0	1.9	6.6	14.1
	at day 28	0.9	2.6	6.2	12.9
	SR*	0	5 (31%)	33 (59%)	12 (75%)
	SP**	0 of 2	4 of 4	12 of 13 (92%)	5 of 6 (83%)

* **Seroresponse:** increase in HAI antibody titer of at least fourfold with a min. post vaccination titer of 40

**Seroprotection: achievement of a minimum post vaccination HAI titer of 40 among subjects with pre vaccination titers of <40

High Seroconversion and Seroprotective Rates are Observed for Low Microgram Doses of VAX125 in the Clinic.

Efficacious Flu Vaccine is Needed

Retrospective Analyses of Vaccine Efficacy

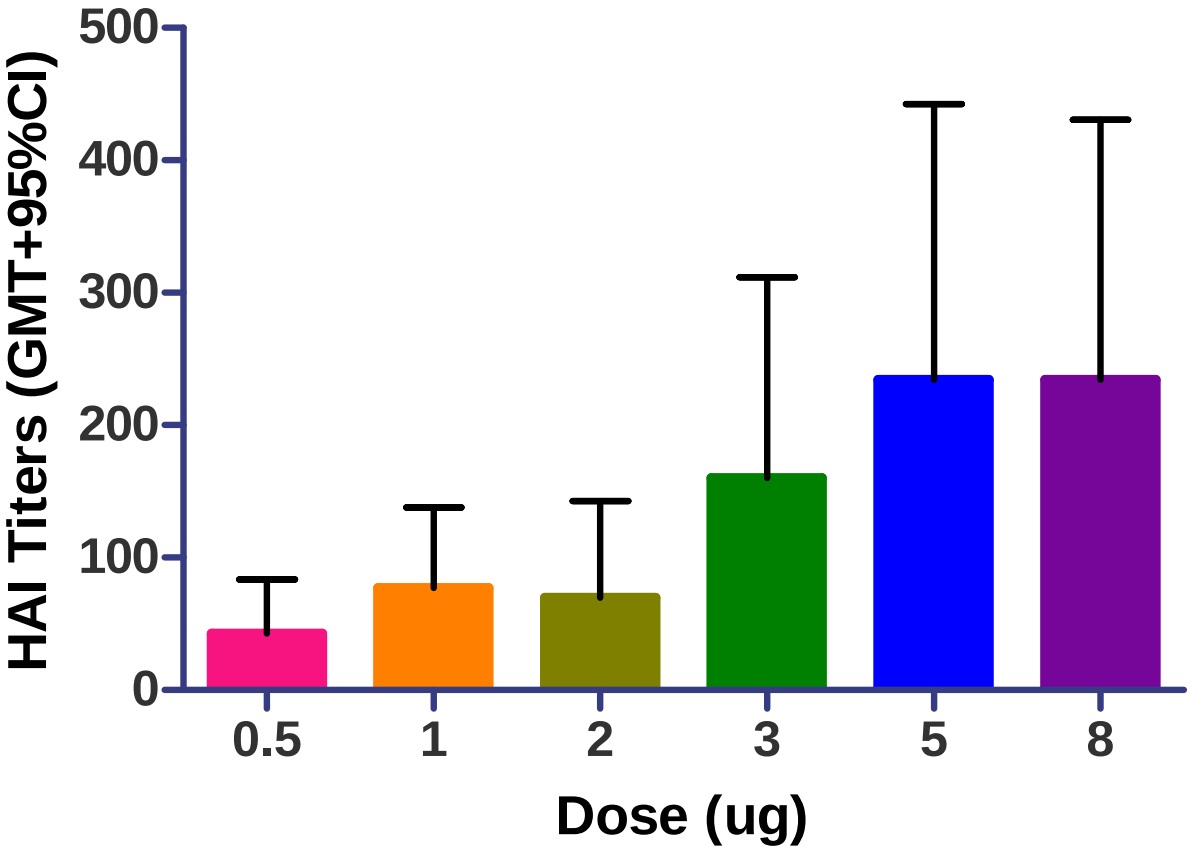
Age (years)	1-5	6-64	**65+**
Trivalent Inactivated Vaccine serology MMWR 2004 53:743	44-49%	70-90%	**30-40%**
31 vaccine antibody response studies '86-'02 Vaccine Vol 24 issue 8, Feb 2006 pg 1159-1169		70-90%	**17-53%**

"…We conclude that the antibody response in the elderly is considerably lower than in younger adults. This highlights the need for more immunogenic vaccine formulations for the elderly."

Vaccine Vol 24 issue 8, Feb 2006 pg 1159-1169

HAI Seroresponse Against H1N1 Solomon Islands

in adults ≥ 65 years old with VAX125 at doses ranging from 0.5 to 8 µg



5 µg and 8 µg Doses Showed a Marked Increase in Immunogenicity.

Comparative Seroresponse

against H1N1 antigens in adults over 65 for VAX125 and Fluzone® standard dose and high dose

	VAX125 dose (ug)		Fluzone® dose (ug)	
	3	**5**	**15**	**60**
Number of subjects	20	20	1252	2543
GMT (A/H1N1)				
Pre-vaccination	51	19	29	29
Post-vaccination	160	234	67	116
Fold increase	3.1	12.6	2.3	4.1
Seroconversion (%)	40	80	23	49
Seroprotection (%)	95	95	77	90

A/H1N1 Solomon Islands for VAX125 and H1N1 New Caledonia for Fluzone®. Fluzone® (Sanofi) SD standard dose 15 ug, HD high dose 60ug each antigen. From Falsey et al. JID 2009;200:172-80

VAX125 Surpasses High Dose Fluzone® in the Elderly.

Clinical Evaluation of VAX125 - Phase I

Local and Systemic Reactogenicity

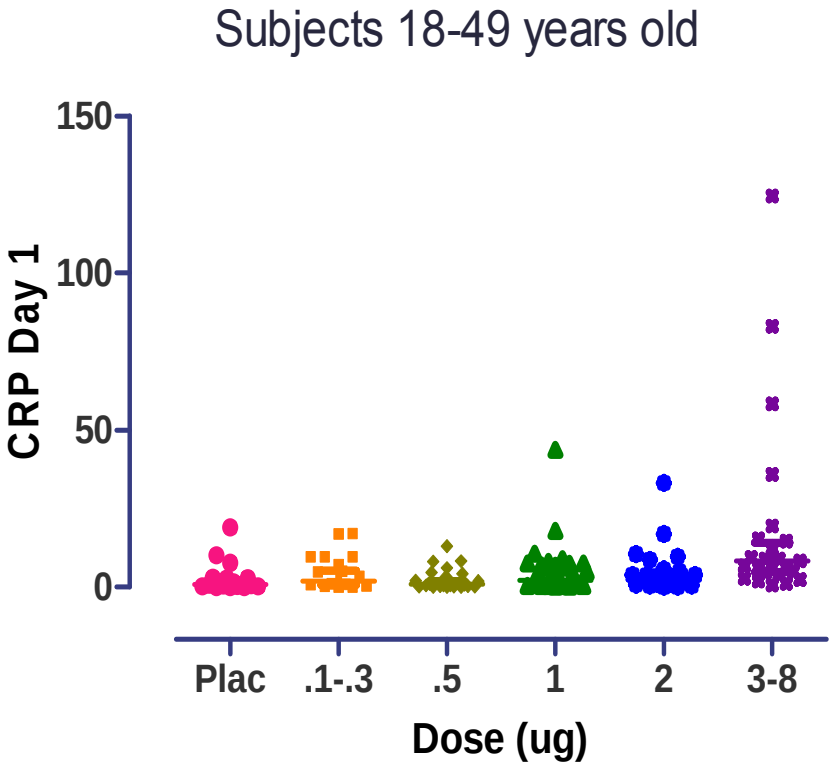
Dose (ug)	No. of subjects	Any local event			Any systemic event			Fever >100°F
		Mild	Mod	Severe	Mild	Mod	Severe	
P	16	1 (6)	2 (13)	0	5 (31)	1 (6)	0	
0.1	8	2 (25)	2 (25)	0	3 (31)	1 (13)	0	
0.3	8	7 (88)	0	0	0	1 (13)	2 (25)	
0.5	24	11 (46)	4 (17)	0	5 (21)	3 (13)	0	
1	24	13 (54)	4 (17)	0	4 (17)	4 (17)	1 (4)	1 (4)
2	24	14 (58)	5 (21)	0	5 (21)	0	2 (8)	
3	8	6 (75)	0	0	2 (25)	1 (13)	0	1 (13)
5	8	0	8 (100)	0	3 (38)	1 (13)	0	
8	8	2 (25)	4 (50)	0	0	2 (25)	0	

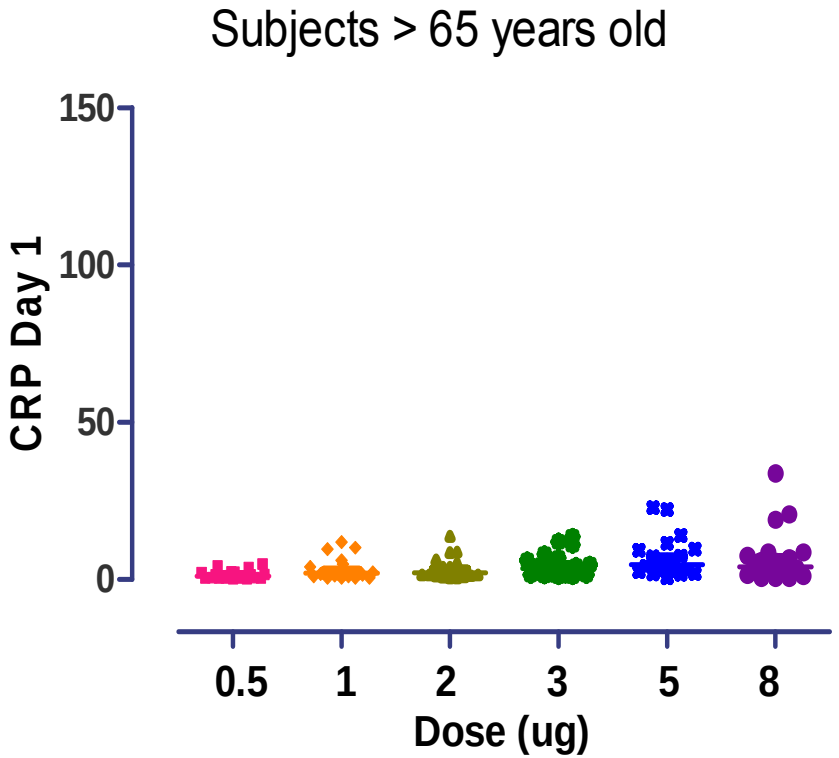
Numbers of subjects (%) experiencing any local or systemic event reported by dose group
Subjects from all trial stages are combined
Local events include: injection site pain, redness, bruising or induration within 7 days of vaccination
Systemic events include: headache, fatigue, joint pain, muscle aches, chills and sweats within 7 days of vaccination

Reactogenicity is Similar to Other Flu Vaccines- No Serious Side Effects Observed.

Comparison of CRP responses

measured one day after immunization with VAX125

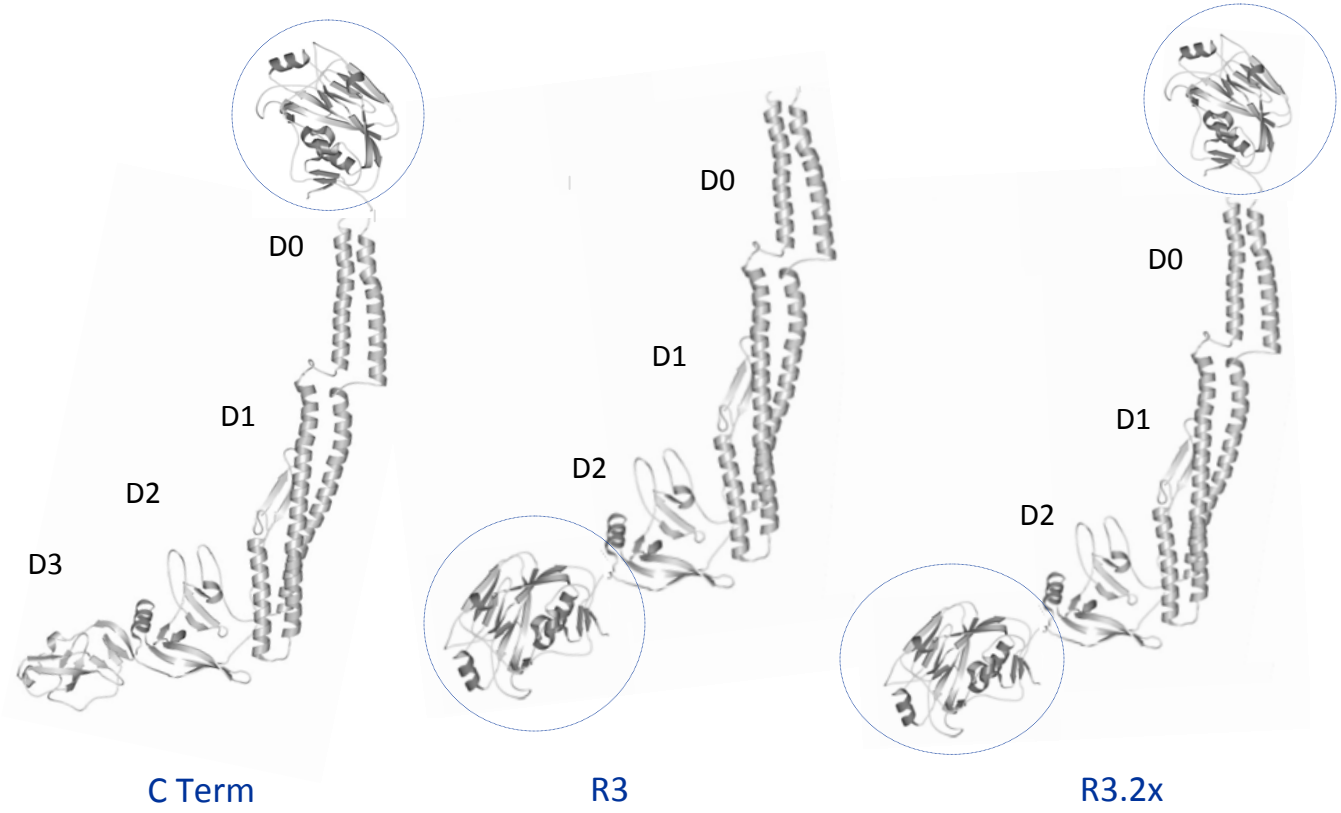




CRP Values Were Less in the Elderly - Particularly in the Higher Dose Groups.

Pandemic Vaccines - HA Subunit Vaccine Design

Overview of Constructs



Three Construct Formats are Under Evaluation for Novel-H1 Vaccines.

Pandemic Vaccines
Novel H1 Flu Vaccine Development

Efficacy in Mice Against Lethal CA04 Challenge

Dose	Type of construct	Immune Response to Vaccination			Response to challenge	
		GMT	HAI > 5 n (%)	HAI ≥ 40 n (%)	Max. Wt loss (%)	Survival (%)
3.0 ug	R3_2x	211	14 (93)	14 (93)	-2	100
	R3	139	14 (93)	14 (93)	-2	100
	CT	116	15 (100)	14 (93)	0	100
0.3 ug	R3_2x	88	15 (100)	14 (93)	+1	100
	R3	30	12 (80)	9 (60)	-1	100
	CT	17	10 (67)	5 (33)	-1	100
0.03 ug	R3_2x	11	6 (40)	3 (20)	-15	90
	R3	6	3 (20)	0	-28	60
	CT	5	0	0	-33	20
F147	Placebo	5	0	0	-33	0

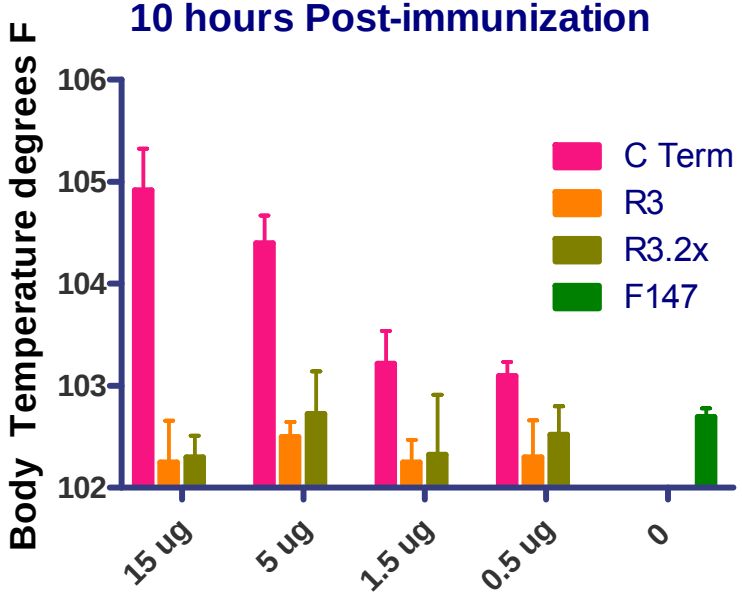
N=15 mice per group. Mice were immunized twice with the indicated doses. Weight loss is expressed as a percent of initial body weight 7 days after challenge.

R3 and R3.2x are at Least as Protective as C.

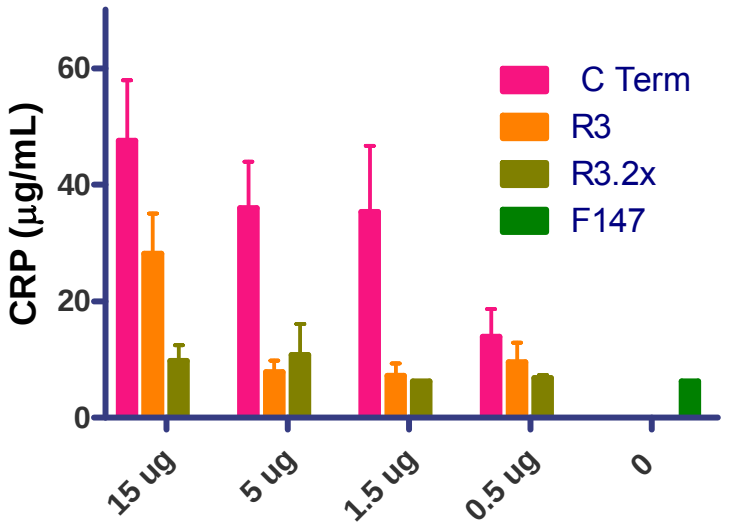
Pandemic Vaccines
Novel H1 Flu Vaccine Development

Reactogenicity in Rabbits

Body Temperature:
10 hours Post-immunization



Serum CRP:
Day +1



R3 and R3.2x CA07 Constructs Have a Lower Reactogenicity Profile than C Term. Doses up to 15 mg are Well Tolerated.

VaxInnate's *E. Coli* Based Manufacturing

High Efficiency & Large Capacity

Manufacturing Influenza Vaccine for the US

Substrate	Cost of Recently Built Facilities *(without validation)*	Time to build and Validate New Facility	Annual Capacity (TIV)
Eggs	$150 million	≥ 3 years	100 million
Cell Culture	$680 million	≥ 3 years	50 Million
Baculovirus	$40 million	≥ 2 years	100 Million
E. coli/VaxInnate	**$0 (CMO)**	**0 years**	**100-400 million***

**VaxInnate's capacity is based on performing a single 1,000 liter run for each antigen included in the vaccine. Yields differ by antigen and construct.*

Manufacturing Efficiency & Speed

- **VaxInnate's recombinant expression in E.coli**
  - M2e: ~0.2 g purified vaccine antigen per liter: **1,000L = 200 million doses**
  - SI HA: ~0.4 g purified vaccine antigen per liter: **1,000L = 400 million doses**
  - Fermentation and purification process takes ~10 working days
- **Total cycle time comparison:**
  - Eggs = 6 months (time to first dose)
  - Cell Culture = 3 months (time to first dose)
  - Baculovirus = 3 months (time to first dose)
  - *E.coli* = 3 months (time to first and last dose)
- **Allows for complete and inexpensive demand satisfaction of several products in a multi-product manufacturing facility**
  - No single product committed facilities required
  - Transient use of contract manufacturers can easily fill need

In Summary

- **VaxInnate has developed an innovative technology that is unsurpassed in terms of:**
  - *Speed to generate a potent vaccine against a novel antigen (pandemic situations)*
  - *Low cost and unlimited capacity of manufacturing (rush capacity, emerging markets)*
  - *Portability and low capital investment requirements (emerging markets)*
  - *Excellent efficacy and safety*

- **Our Technology platform can be enabling for new and established vaccines by:**
  - *Transferring IP protection to public antigens*
  - *Overcoming poor immunogenicity*
  - *Solving cost and capacity constraints*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