

Efficacy and broadly reactive immunity directed against seasonal and pandemic strains of influenza using Variosite™ technology

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Abstract

Background:

Trivalent seasonal influenza vaccines have a number of disadvantages including limited breadth of vaccine-induced immunity and relatively poor efficacy in at-risk populations such as the elderly. We have used a novel technology to develop a synthetic seasonal influenza vaccine designed to provide multi-season protection and address these disadvantages.

Methods:

We used crystallographic structural data while designing discontinuous B cell epitopes and also considered the location of human T cell epitopes. Our SFV2 vaccine contains 5 immunogens, as either single peptides or cocktails of peptides (Variosite formulations) that contain 16 peptide variants (a total of 35 distinct peptides). These peptide variants account for the antigenic variability present at these epitopes, accounting for past and future antigenic variation of the influenza virus in hemagglutinin (HA) and nucleoprotein (NP). These peptides were entrapped within a liposomal delivery vehicle that was then adsorbed to aluminum hydroxide (NAM1 adjuvant system). We immunized ferrets intramuscularly on days 0 and 28 with SFV2/NAM1, the NAM1 vehicle lacking the SFV2 antigens, or with commercial influenza vaccine, and 14 days after the final vaccination, animals were challenged with influenza A/Solomon.

Results:

Peak (day 2) viral load was 1-log lower in animals vaccinated with our SFV2/NAM1 vaccine formulation, and the magnitude and duration of fever was reduced. Efficacy correlated with very high titers of virus-specific serum IgG titers, as well as induction of hemagglutination inhibition (HI) titers. This reactivity extended across many drifted subtypes of influenza, including the recently emerged pandemic H1N1/California "swine" isolate.

Conclusions:

This vaccine and underlying technology represent a novel means of inducing broadly reactive immunity needed to protect against infection with variable pathogens.

Figure 2: HPLC analysis of the antigenic components of the SFV2 vaccine formulation

Antigen Type	Common Name	Peptides/Variosite formulations	# of Variants	Length	GMP Peptides
Flu A					
Hemagglutinin H3/H1	H3-V1	1 Variosite formulation	16	22 aa	✓
Flu A					
Hemagglutinin H1	H1-S1	1 single sequence peptide	1	88 aa	✓
Flu A					
Nucleoprotein NP	NP-V1	1 Variosite formulation	16	17 aa	✓
Flu B					
Hemagglutinin	HB-S1, HB-S2	2 Flu B peptides	2	~50aa	✓
TOTAL PEPTIDES/VARIOSITES (APIs):			5		
TOTAL VARIANTS:			35		

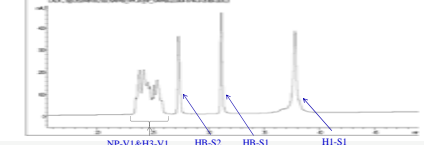
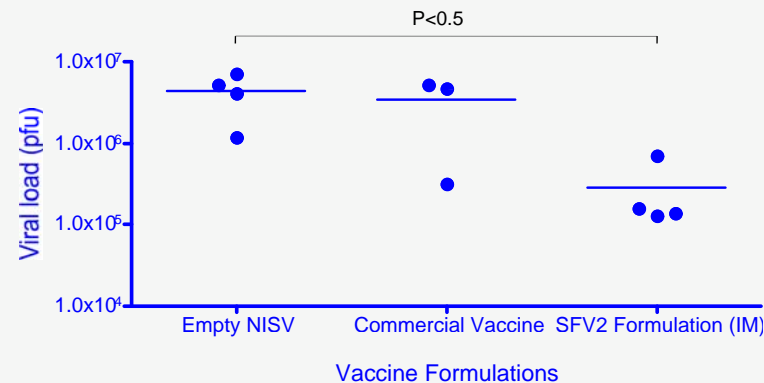


Figure 3: Intramuscular vaccination with SFV2/NAM1 reduces peak (day 2) viral load associated with H1N1/Solomon (2006) challenge



Note: The commercial vaccine (Vaxigrip (2008/2009)) was mismatched against the challenge strain of virus, and these data emphasize the requirement to reformulate existing vaccines, but not SFV2, each year.

Figure 1: The NP Variosite™ formulation in SFV2 detects endogenous T cell responses in individuals recently infected with pandemic H1N1 influenza

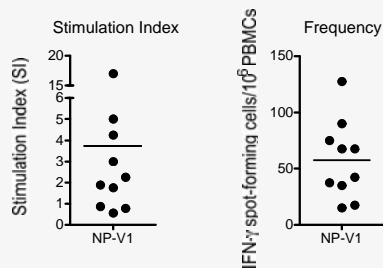


Figure 4: Intramuscular vaccination with SFV2 shortens and ameliorates fever associated with H1N1/Solomon challenge

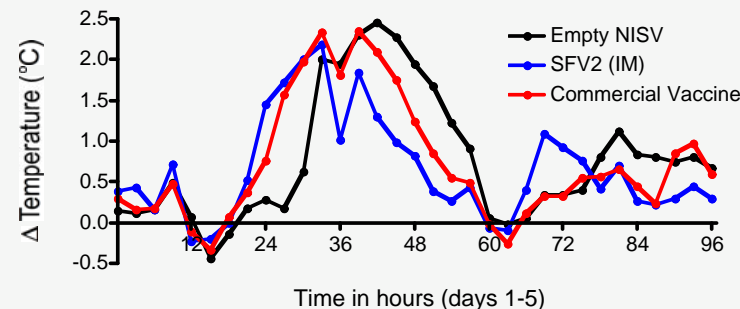
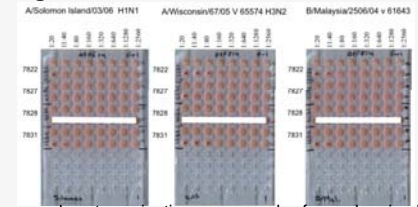
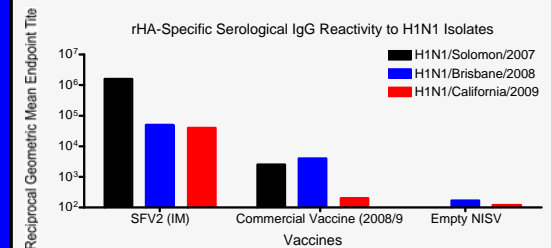


Figure 5: SFV2/NAM1-induced HI titers



Note: pre- and post-vaccination sera samples for each animal appear on top and bottom rows, respectively.

Figure 6: Intramuscular vaccination with SFV2/NAM1 induces broadly reactive immunity, including the pandemic H1N1 strain of influenza



Key Points

1. A fully synthetic vaccine, SFV2/NAM1, has been manufactured using GMP quality components.
2. The vaccine is stored in lyophilized form, and is expected to be stable at room temperature.
3. The SFV2/NAM1 vaccine induces protection against challenge in the ferret model.
4. The vaccine induces broadly reactive humoral and cellular immunity.
5. Use of Variosite™ technology enabled vaccine design that anticipated the emergence of the pandemic strain of H1N1 influenza.