

Vaxfectin®

Adjuvant Licensing Opportunity



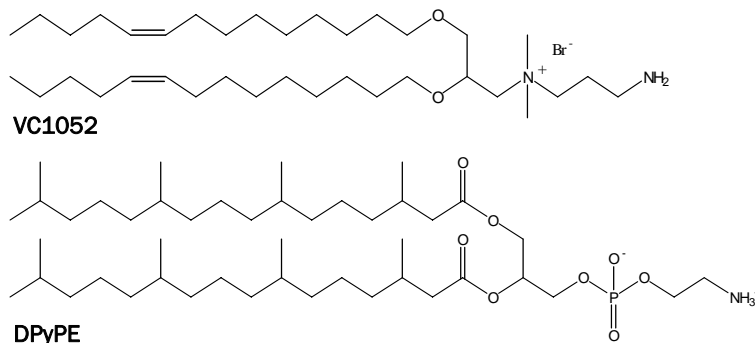
Vaxfectin® is part of Vical's portfolio of proprietary adjuvants and has been shown to enhance the immunogenicity of DNA, peptide and protein vaccines

- ◆ Synthetic
- ◆ Well-characterized
- ◆ cGMP manufacturing
- ◆ Simple to formulate
- ◆ IP extends beyond 2020

Vical

- ◆ Vaxfectin® is a novel synthetic adjuvant identified through *in vivo* screening of Vical's cationic lipid library
- ◆ Vaxfectin®-formulated pandemic influenza (H5N1) DNA vaccine stimulated strong immune responses in Vical's recent Phase 1 trials
 - ◇ 50-67% hemagglutination inhibition (HI) antibody response rate in same range as reported response rates obtained with protein vaccines
 - ◇ Mild to moderate local reactogenicity, no serious systemic reactions
- ◆ Vaxfectin®-formulated DNA vaccines have demonstrated increased antibody and T-cell responses in multiple animal models, including nonhuman primates
- ◆ Vaxfectin®-formulated DNA vaccines have provided protection from disease in animal challenge models of anthrax, influenza, dengue, and measles
- ◆ Vaxfectin®-formulated commercial seasonal influenza protein vaccine has demonstrated greater than 10-fold dose sparing effect
- ◆ Vaxfectin®-formulated cancer peptides increased T-cell responses and exhibited antitumor activity in an animal model
- ◆ Vaxfectin® was named one of 100 Great Investigational Drugs in the Eighth Annual Ranking by the editors of R&D Directions
- ◆ Vical is currently seeking partnership opportunities for Vaxfectin® as an adjuvant for vaccines and immunotherapeutics
- ◆ Vical can provide
 - ◇ Detailed application know-how
 - ◇ cGMP manufacturing
 - ◇ Formulation expertise
 - ◇ Development support and collaboration

Vaxfectin® is a mixture of a cationic lipid, VC1052, and neutral co-lipid, DPyPE



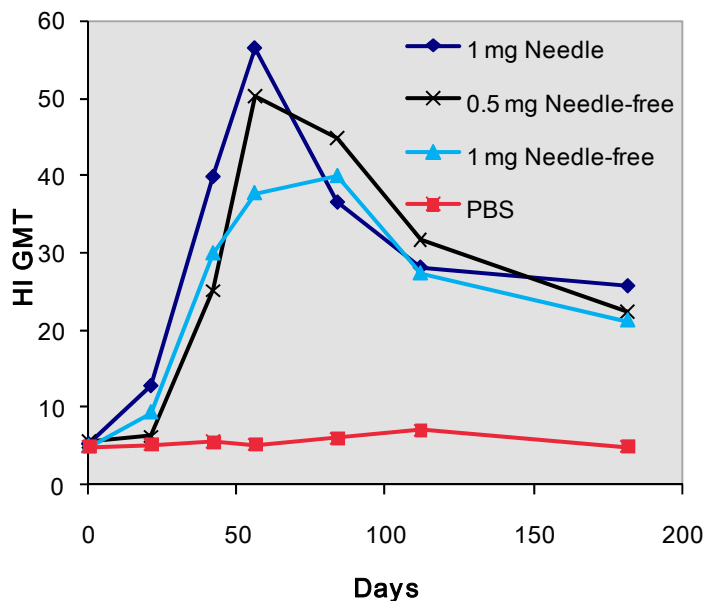
DNA Vaccine: Pandemic H5N1 Influenza

Phase 1 trials to evaluate the safety and immunogenicity of a **Vaxfectin[®]**-formulated DNA vaccine encoding HA from A/Vietnam/1203/04 were performed in healthy subjects.

Subjects received two doses of vaccine, formulated at a 4:1 molar ratio of DNA:cationic lipid, or placebo on Days 0 and 21, using either needle or needle-free delivery.

No vaccine-related serious adverse events or dose-limiting reactions were observed. The most common reactions were injection site pain and reactions, headache, malaise and myalgia. All events typically resolved within a few days.

Strong HI Titers Induced by Vaxfectin[®] in Humans



Cohort	% Achieving HI Titer ≥ 40 by Day 56	GMT (Geometric Mean Titer)
1 mg Dose Needle	5/8 (63%)	57
0.5 mg Dose Needle-free	4/6 (67%)	50
1 mg Dose Needle-free	6/12 (50%)	38
PBS	0/18 (0%)	5

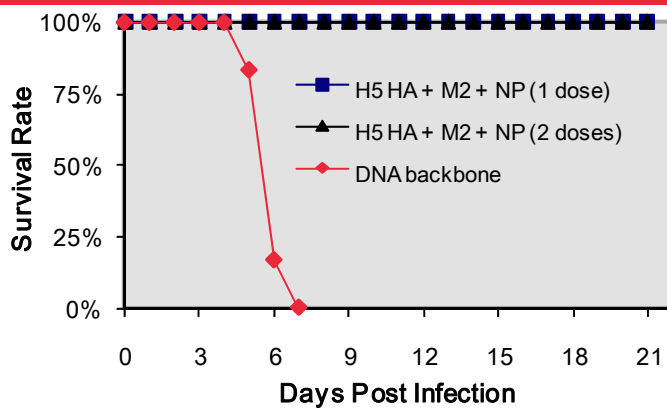
- ◆ 25% of responders exhibited HI titers ≥ 40 after a single dose
- ◆ Sustained HI titers (≥ 40) for at least 6 months in 33-50% of subjects
- ◆ Good correlation between HI and microneutralization (MN) titers
- ◆ HI titers are in the range of those reported for most protein vaccines
- ◆ Current U.S. licensed H5N1 influenza vaccine induces HI titers of ≥ 40 in 44% of subjects
- ◆ Cross-clade HI antibodies against A/Hong Kong/156/97 (7/14 subjects) and A/turkey/Turkey/1/05 (5/14 subjects)
- ◆ T-cell responses to HA in 75-100% of subjects, sustained for at least 6 months

- ◆ **Vaxfectin[®]**-formulated vaccines were well tolerated with no vaccine-related serious adverse events occurring in two Phase 1 trials
- ◆ **Vaxfectin[®]**-formulated DNA vaccine induced strong HI titers, in same range as protein vaccines
- ◆ Broad T-cell responses and strong cross-clade HI titers were achieved

DNA Vaccines: Infectious Diseases

Vaxfectin[®]-formulated DNA vaccines encoding a variety of immunogens have been tested in multiple animal models, ranging from mice to nonhuman primates. The animal models have consistently shown enhanced responses compared with unadjuvanted vaccines and have protected the animals against microbial challenges.

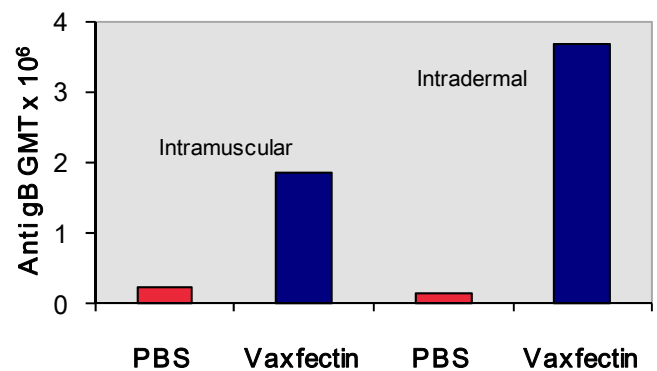
H5N1 Ferret Challenge Model



Ferrets injected with **Vaxfectin**[®]-formulated DNA (0.3 mg each DNA).

Challenge with H5N1 influenza virus A/Vietnam/1203/04 (100 x LD₅₀) showed complete protection after one immunization. (Lalor et al., *J. Inf. Dis.* 2008)

CMV Rabbit Immunogenicity Model



Vaxfectin[®]-formulated CMV gB DNA vaccine (0.1 mg) was delivered using a needle-free device on Days 0 and 21.

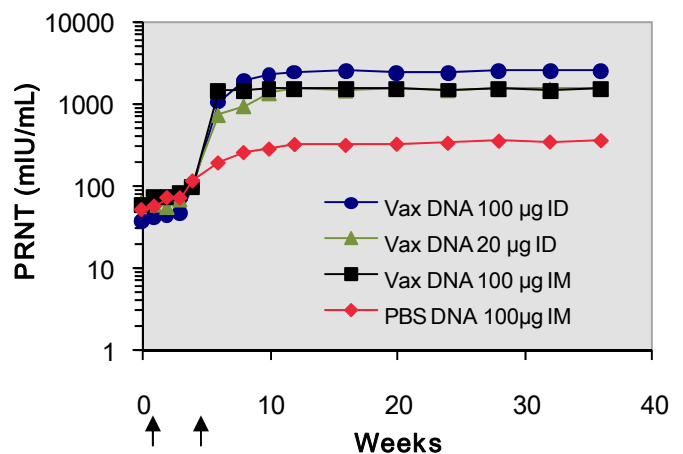
Anti-gB titers increased 8-fold vs unadjuvanted DNA when delivered IM, and 16-fold with ID delivery.

Measles Nonhuman Primate Challenge Model

Vaxfectin[®]-formulated DNA delivered IM resulted in 5- to 7-fold higher neutralizing titers than unadjuvanted vaccine and exhibited similar responses when delivered ID.

In a separate study, **Vaxfectin**[®]-formulated DNA induced persistent neutralizing titers and T-cell responses against measles in juvenile and infant macaques.

Macaques survived challenge with 10⁴ TCID₅₀ of Bilthoven wild type measles virus and showed no signs of disease or viremia. (Pan et al., *Clin. Vaccine Immun.* 2008)



- ◆ **Vaxfectin**[®]-formulated DNA vaccines increase antibody responses and elicit strong T-cell responses in several animal models, including mice, ferrets, rabbits and nonhuman primates
- ◆ **Vaxfectin**[®]-formulated DNA vaccines can protect against lethal viral challenge

Protein Vaccine: Seasonal Influenza

Commercially available licensed trivalent inactivated split influenza vaccine (TIV; Fluzone®; sanofi pasteur) containing HA from 3 influenza virus strains (H1N1, H3N2, influenza B) was formulated with **Vaxfectin®** and immunogenicity of the formulations evaluated in a mouse model.

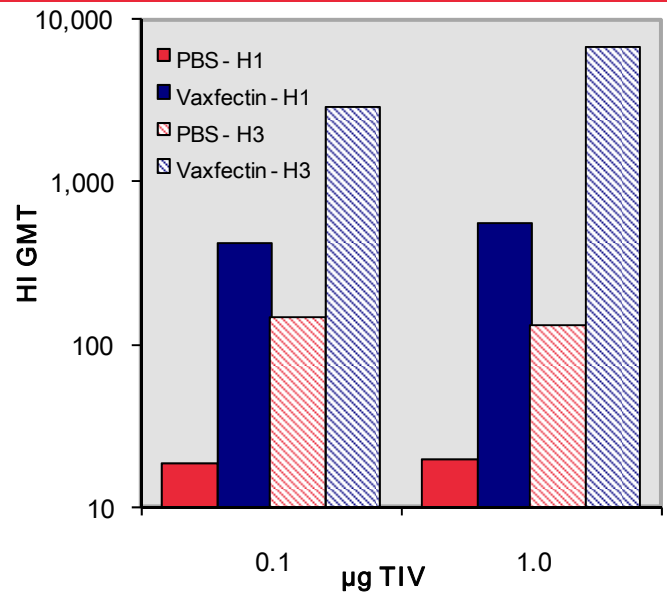
Humoral Immune Responses to TIV

Mice were immunized IM with 0.1 or 1.0 µg of unadjuvanted TIV or TIV formulated with 900 µg Vaxfectin®.

Vaxfectin® increased H1 and H3 HI titers 20-50-fold and provided a more balanced IgG isotype distribution.

A dose response study indicated that increasing doses of Vaxfectin® resulted in progressively stronger antibody responses.

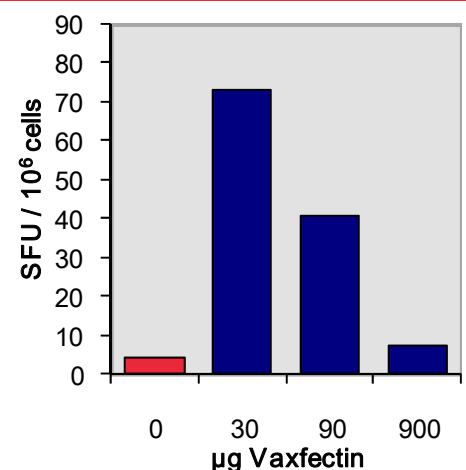
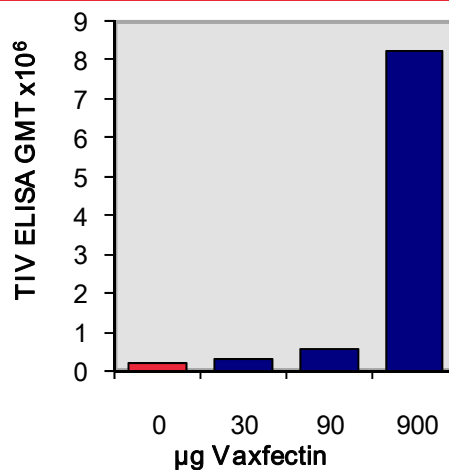
TIV ELISA Titers for IgG Isotypes		
	TIV	+Vaxfectin
IgG1	259,921	4,457,219
IgG2a	10,000	2,743,740
IgG1 / IgG2a	26	1.6



Formulation Modification Preferentially Induces Antibody vs T-cell Responses

Mice were immunized with TIV formulated with different amounts of Vaxfectin®.

ELISA and ELISPOT assays indicated that increased antibody responses are obtained by high Vaxfectin®:antigen ratio, whereas lower ratios result in enhanced cellular responses.

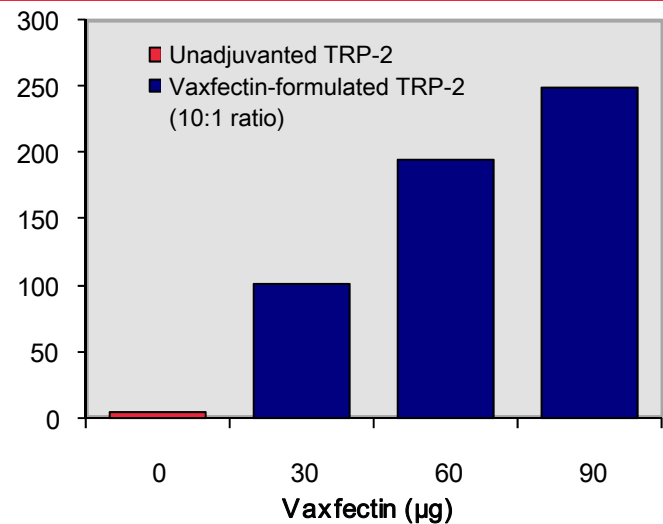
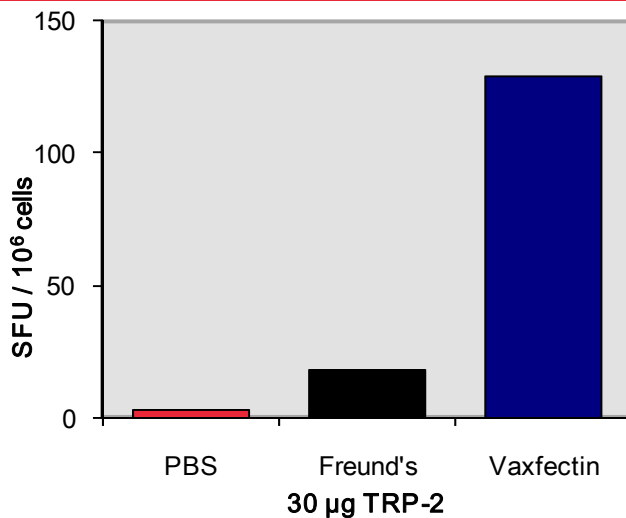


- ◆ **Vaxfectin®**-formulated seasonal influenza vaccine resulted in
 - ◇ Markedly increased antibody responses with a more balanced IgG isotype distribution
 - ◇ ≥10-fold dose-sparing
 - ◇ Significantly increased IFN-γ secreting T-cells, indicating enhanced Th1 responses
- ◆ Ability to direct humoral or cellular responses based on **Vaxfectin®**:antigen ratio

Peptide Vaccine: Cancer

The effect of **Vaxfectin**[®] on a murine tumor model was evaluated using a Class I-restricted peptide of a tumor antigen tyrosinase-related protein 2 (TRP-2₁₈₀₋₁₈₈). First, the immunogenicity of the Vaxfectin[®]-formulated TRP-2 was evaluated by subcutaneous injections in normal mice; TRP-2 formulated with Vaxfectin[®] resulted in significantly higher T-cell responses than those obtained with TRP-2 formulated with PBS or Freund's adjuvant, as measured by ELISPOT assay. Separately, a dose response was observed with increasing vaccine dose at a 10:1 Vaxfectin[®]:TRP-2 mass ratio.

Cellular Responses to TRP-2 in Mice

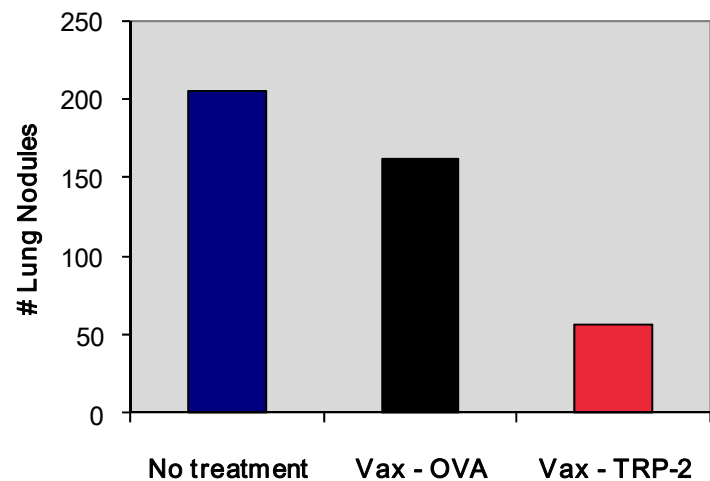


Anti-tumor Responses in Mice

Anti-tumor responses in mice vaccinated with Vaxfectin[®]-formulated TRP-2 were evaluated in a therapeutic B16F10 melanoma model.

Mice were vaccinated subcutaneously 3 days after intravenous injection of 1 x 10⁵ B16 tumor cells, and boosted 12 days later. Vaxfectin[®]-formulated TRP-2 significantly decreased the number of pulmonary tumor nodules in euthanized mice on Day 25, compared to the untreated control and a control peptide, OVA.

Furthermore, survival of the mice was significantly increased relative to the untreated controls.



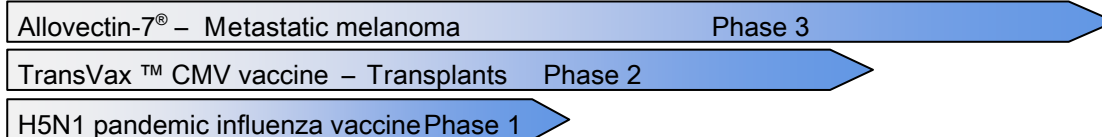
- ◆ Formulating Class I restricted peptide with **Vaxfectin**[®] resulted in up to a 70-fold increase in T-cell responses compared to nonadjuvanted peptide and 7-fold higher than Freund's adjuvant
- ◆ **Vaxfectin**[®]-formulated TRP-2 exhibited an anti-tumor effect against pulmonary melanoma tumors

About Vical

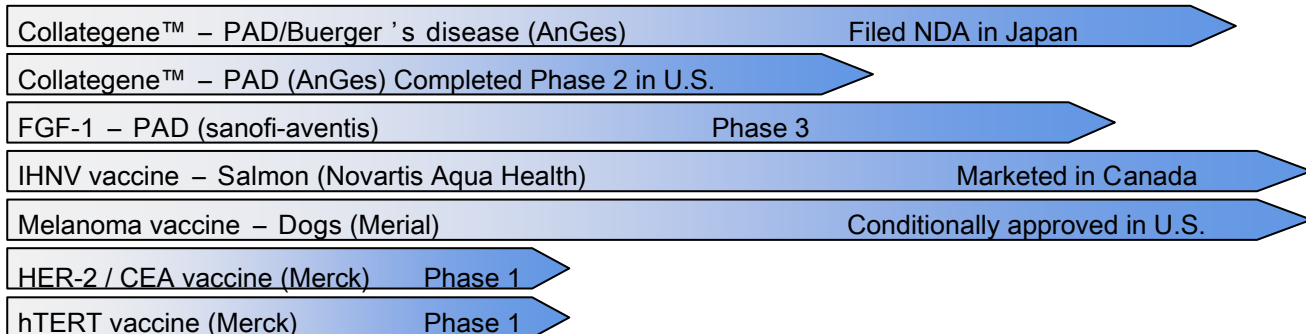
- ◆ Vical is developing plasmid DNA-based vaccines and immunotherapeutics
- ◆ Vical is currently conducting clinical trials in the area of oncology and infectious diseases:
 - ◇ Ongoing Phase 3 trial evaluating the safety and efficacy of Allovectin-7[®] for stage 3 or 4 metastatic melanoma patients
 - ◇ Ongoing Phase 2 trial evaluating the safety, immunogenicity and clinical benefit of a therapeutic cytomegalovirus (CMV) vaccine, TransVax[™] to prevent reactivation of the virus in CMV-seropositive recipients undergoing hematopoietic stem cell transplant (HCT)
 - ◇ Recently completed Phase 1 trial evaluating the safety, tolerability, and immunogenicity of an H5N1 pandemic influenza DNA vaccine formulated with Vical's proprietary adjuvant, **Vaxfectin[®]**
- ◆ Vical has developed strategic partnerships with companies such as Anges, Merck, sanofi-aventis, Merial, Novartis and others to develop products for other diseases
 - ◇ Vical's partner, Anges, has filed an NDA in Japan for their angiogenesis DNA product, Collatogene[™]
 - ◇ Sanofi-aventis is evaluating a DNA vaccine encoding an angiogenic growth factor in a Phase 3 trial
- ◆ Vical has a strong intellectual property position with issued patents on core DNA delivery technology, lipid technologies, DNA therapeutics, and DNA process technology
- ◆ Vical has a 68,400 sq. ft cGMP facility and manufactures its own products as well as products for other clients, including the Vaccine Research Center (NIH), International Aids Vaccine Initiative (IAVI), and the US Navy

CLINICAL-STAGE PRODUCT PIPELINE

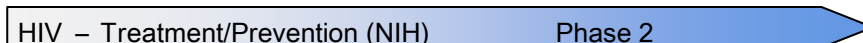
Independent Programs



Corporate Collaborations



Government Collaborations



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