Site-specific peptide vaccines for immunotherapy and immunization against chronic diseases, cancer, infectious diseases, and for veterinary applications

Chang Yi Wang*, Alan M Walfield
United Biomedical, Inc., 25 Davids Drive, Hauppauge, NY 11788, USA
Available online 26 January 2005

Abstract

United Biomedical, Inc. (UBI) has developed a set of core technologies for the discovery and production of synthetic peptide-based immunotherapeutics and vaccines. These core technologies have led to products that stimulate functional site-directed antibody responses for therapeutic effects. UBI active immunotherapies can be used to modulate physiological processes effective for the control of cell entry by HIV virions, for control of prostate cancer and allergy, and for immunocastration in livestock leading to boar taint elimination and growth promotion in swine. The UBI technologies are also useful to stimulate site-directed antibodies against pathogenic agents such as foot-and-mouth disease virus. UBITh® Immunotherapeutic peptides were developed as antigens to direct antibody responses against targeted epitopes on self-proteins and viral pathogens that are responsible for biological functions and pathogenicity. A collection of promiscuous UBITh® T helper cell epitopes was used to impart these functionally antigenic peptides with immunogenicity. The T cell helper epitopes were covalently linked to the functional antigenic target sites by peptide synthesis, creating well-defined synthetic immunogens. Finally, vaccine formulations were selected appropriate for the delivery of peptide immunogens. Controlled production processes and the means to characterize the final product provide a framework for the GMP-compliant manufacture of UBITh® immunotherapeutics and vaccines.

© 2005 Elsevier Ltd. All rights reserved.

Keywords: Immunotherapy; Active; Peptide; T help

1. Introduction

A set of core technologies for the discovery and production of synthetic peptide-based immunotherapeutics and vaccines has been developed by United Biomedical, Inc. (UBI). These core technologies are being used to produce commercially feasible products for the prevention and treatment of prostate cancer, allergic diseases, HIV, and foot-and-mouth disease (FMD) in swine and cattle [1–4]. These immunotherapeutic products are designed to mobilize the patient’s own immune system through active immunization.

Discovery for an immunotherapeutic vaccine begins with selection of the target self molecule, such as luteinizing hormone-releasing hormone (LHRH) for treatment of prostate cancer, IgE for allergy, and CD4 for HIV. For vaccines to prevent infectious disease, a molecule on the foreign pathogen is targeted, such as the VP1 protein of foot-and-mouth disease virus (FMDV). Then, a target epitope must be selected from the amino acid sequence of the targeted molecule by epitope mapping for functional antigenicity. Functional antigenicity assays show that a candidate target site induces antibodies that neutralize the biological function of the targeted molecule. The target site is then reproduced as an effective site-specific immunogen through optimization of the sequence to stimulate the production of antibodies with high affinity for the natural target including the introduction of conformational constraint if necessary, and fusion to one of our potent UBITh® T helper cell epitopes. Target site sequences may be modified for cyclic constraint based on predictions of surface-exposed loops. Such peptides are designed with introduced cysteines to mimic predicted loop structures by disulphide bonds and naturally occurring cysteines are substituted with serines to prevent the
formation of loop conformations not favored by molecular models.

Our potent foreign UBITh® sites are added to the target peptides to provide extrinsic T cell help that overcomes either the absence of Th sites intrinsic to the target site or the poor immunogenicity of the Th sites found on target sites taken from self proteins. The immunostimulatory UBITh® epitopes and a linker are added to the functional antigenic target sites by continuous peptide synthesis, creating well-defined synthetic immunogens. Carrier proteins and linkages by coupling reactions are not used. Thus, each of our site-specific immunogens is a homogeneous peptide construct produced by a controlled process of solid-phase peptide synthesis. They can be reproducibly synthesized, readily characterized, and readily adapted to large scale manufacturing.

More recently, we have developed a vaccine formulation system customized for the delivery of UBITh® peptide immunogens. This proprietary vaccine delivery system uses a controlled electrostatic interaction that results in a stabilized immunostimulatory complex of peptide immunogens that are easily characterized[5]. The comprehensive collection of core technologies for peptide-based immunotherapeutics and vaccines enables entry into clinical trial.

2. Materials and methods

2.1. Peptide synthesis

Peptide immunogens for vaccines and peptide antigens for ELISAs were synthesized using automated solid-phase synthesis with F-moc chemistry using terminus and side chain-protected amino acids, cleaved from the resin with TFA and deblocked. Peptides were purified (>90%) by reverse phase HPLC and characterized by MALDI-ToF mass spectrometry and reverse phase HPLC. Immunogens with combinatorial UBITh® were characterized by size exclusion chromatography and N-terminal amino acid analysis [4].

2.2. Vaccine formulations

Free peptide immunogens were prepared as water-in-oil emulsions or mineral salt suspensions as specified for each in Section 3. Vaccines having peptide immunogen mixtures were equinolar compositions. Water-in-oil emulsions were prepared in either Montanide® ISA51, ISA 50, or Montanide® ISA720. For mineral salt suspensions, peptides were adsorbed to Alhydrogel 85 (EM Sergeant Pulp and Chemical Co., Clifton NJ, USA) [1–4].

2.3. Assays

Peptide-based indirect ELISAs used to analyze serially diluted sera for anti-target peptide antibody responses are done with microtitre wells coated with 5 µg/ml of a specified target peptide antigen (without the UBITh® site) and sera antibody titers are determined as described [1,4]. Functional assays are described for each target within Section 3.

3. Results

3.1. The UBITh® collection for extrinsic T cell help

The UBITh® T helper cell sites are a collection of promiscuous Th epitopes that either were directly derived from the highly antigenic proteins of pathogens such as measles virus fusion protein (MVF), hepatitis B virus surface antigen (HBsAg), tetanus toxin (TT), and pertussis toxin (PT) [1] or were adapted from these pathogens and designed to hold idealized Th motifs [6,7]. Idealized sites include combinatorial UBITh® sites having both invariable positions and variable positions into which an amino acid was randomly selected for insertion from a choice of two or more amino acids. This accommodates a Th site to a wide range of MHC haplotypes, for broad responsiveness in genetically diverse populations [7]. The best extrinsic Th epitopes for particular target functions sites were selected from among the UBITh® collection by empirical experimentation. Examples of pathogen-derived, idealized and idealized combinatorial UBITh® epitopes are shown in Table 1.

A further modification to some of the UBITh® LHRH peptide immunogens is the further addition to the N-terminus of a domain from Yersinia invasin protein (Inv 718–732). It was shown to contribute adjuvanting activity to the short decameric LHRH target sequence [1].

Table 1  Representative UBITh® epitopes

<table>
<thead>
<tr>
<th>UBITh® code</th>
<th>Description</th>
<th>Sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>UBITh®1</td>
<td>Idealized from MVF288–302</td>
<td>ISITEKGVIVHRLEGV</td>
</tr>
<tr>
<td>UBITh®1a</td>
<td>Idealized from MVF288–302 plus KKK</td>
<td>KKKISITEKGVIVHRLEGV</td>
</tr>
<tr>
<td>UBITh®1b-a</td>
<td>Combinatorial idealized from MVF288–302</td>
<td>KKKITITRIITIITTID</td>
</tr>
<tr>
<td>UBITh®2</td>
<td>Idealized from HBsAg19–33</td>
<td>KKKITITRIITIITTID</td>
</tr>
<tr>
<td>UBITh®4</td>
<td>HBsAg19–33 Th</td>
<td>FFLITRETIPQSLD</td>
</tr>
<tr>
<td>UBITh®5</td>
<td>MVF288–302 Th</td>
<td>KKQYKANSKFOTOES</td>
</tr>
<tr>
<td>UBITh®6</td>
<td>TT118–144 Th</td>
<td>KQNYKANSKFOTOES</td>
</tr>
<tr>
<td>UBITh®7</td>
<td>PT19–41 Th</td>
<td>GAYAPNGTRALVSAEGLNASE</td>
</tr>
</tbody>
</table>
apy for efficacy by showing the effect of the UBITh®-LHRH R3327-H rat tumor model was used to test the immunotherapeutic vaccine. The Dunning tumor vaccine on the growth of this androgen-dependent prostate tumor. Copenhagen male rats (eight per group) were implanted subcutaneously with Dunning tumor pieces (1 mm³) and the tumors were permitted to grow until they reached a volume of approximately 0.4 mm³ at which time the treated group was immunized with the alhydrogel suspension having 100 µg of the peptide mixture. The vaccine was administered at 26, 29, 32, 58, and 82 weeks post-tumor implantation. An untreated control group was given alhydrogel placebo (Fig. 1). The rats were monitored for anti-LHRH and testosterone serum levels, and for tumor size. The tumors in the treated group remained approximately 0.4 mm³ while the tumors in the control group continued to grow. Peak anti-LHRH titers were attained in response to the three priming doses, declined and then rose in response to the booster doses. Testosterone levels declined to baseline and rebounded in concert with anti-LHRH levels (data not shown). At the end of the study, testosterone levels were permitted to rebound and the androgen-sensitive Dunning H tumors started to grow.

In preparation for entry into clinical trial, the UBITh®-LHRH immunotherapeutic vaccine was tested in sexually mature male baboons. A water-in-oil formulation was tested six adult male baboons at peptide dose levels of 25, 100, and 400 µg (each dose level was given to two baboons). The baboons were immunized at weeks 0, 4, and 34 and monitored for anti-LHRH serum testosterone, testes involution and regrowth. After the two priming doses the level of anti-LHRH was at least 0.5 nmol/L in all six baboons at 6 weeks, castrate levels of testosterone were reached and testes involution was observed in all animals. Testosterone rebound at weeks 22–24 and testes regrowth at weeks 26–28 was observed in four of the baboons. Castrate status was restored 2 weeks following the boost at week 34. Two baboons showed testosterone rebound and testes regrowth at 95 weeks (end of study).

The UBITh®-LHRH vaccine may also be useful as a humane and reversible means of contraception for pets. All eight dogs given a water-in-oil vaccine were immunocastrated. It has shown similar activity in livestock where such a vaccine can be a safe and simple means to castrate swine and cattle. It is effective on bulls and on boars. In boars, the vaccine serves to induce immunocastration, eliminate boar taint, and promote growth over that of conventionally castrated animals. Results for individual boars are shown Fig. 2 where two groups of 12 were given 40 or 400 µg doses of the UBITh®-LHRH vaccine in emulsion on weeks 0 and 8. Steady immunocastration levels of serum testosterone were attained in all the animals of both groups following the 8 week dose, with immunocastration correlated to anti-LHRH antibody levels. This vaccine has been effective in thousands of boars in field trials and is being tested as a product for the swine markets in Taiwan and China to eliminate boar taint and as a growth promoter.

3.3. Anti-host cell approach to immunotherapeutic vaccine for HIV

There is an urgent need for effective immunotherapeutic treatments to expand the present therapeutic treatments for HIV infection. The available anti-retroviral drug treatments become less effective over time as the highly mutable virus acquires resistances to the drugs and as the anti-retroviral drugs become increasingly toxic to the patient.

Our approach to HIV immunotherapy has been to inhibit HIV entry by targeting the CD4 receptor/coreceptor complex for HIV on the host cell, rather than by targeting a site on the virus. The anti-host cell strategy circumvents the variable sensitivities of primary HIV isolates to neutralization by antibodies [3,10]. Monoclonal antibodies directed against the CD4 receptor/coreceptor complex for HIV on the host cell have been shown to neutralize the infectivity of primary HIV isolates with high potency, to provide protection from
HIV infection in animal models, and to reduce viral load in HIV-infected patients. Furthermore, such site-specific antibodies have acted on CD4 to prevent virus infection while not impairing the activities of CD4+ T cells sufficiently to cause adverse immunosuppression [10,11].

We have developed a passive immunotherapy treatment based on UBI monoclonal antibody mAb B4, with a specificity for a discontinuous conformational epitope on the cell membrane-associated CD4/coreceptor complex [10].

We have extended our host cell-directed approach to HIV immunotherapy from passive to active immunization by UBI-based immunogens that mimic a vulnerable segment on the CD4-associated receptor of susceptible T cells. The desired specificity was obtained by an exhaustive epitope mapping for functional antigenicity. More than 1000 peptide constructs were designed from the CD4 and co-receptor regions, and selected for immunological cross-reactivity to the mAb B4 binding site and for their ability to elicit neutralizing antibodies. A sequence from the CDR2-like domain of CD4, at positions 39–66, was found to be the most effective target antigenic site for the synthetic immunogen. This site was predicted to produce steric hindrance of the discontinuous recognition site of mAb B4.

The prototype peptide immunogen is represented by the formula: “gp41 772–787 Th-GG-UBITh® 1 comb-GG-cysCD4 39–66 cys” in which the idealized combinatorial UBITh® 1 (Table 1) and an HIV Th epitope were selected as Th epitopes. (The HIV Th epitope should be helpful for restimulation in individuals upon HIV exposure or re-emergence.) The domains are separated by glycine–glycine spacers and the CD4 target site is cyclized through disulphide bonds between the cysteines at the N- and C-termini of the site so as to mimic the loop structure of the CDR2-like domain of CD4. Antibody responses in guinea pigs and swine to this prototype immunogen, in a water-in-oil vaccine, attained concentrations and affinities sufficient to neutralize a broad array of HIV-1 primary isolates. A swine was immunized by multiple injections to provide a large volume of site-specific neutralizing antibodies, with the final dose given at week 46. Swine sera from weeks 46 and 49 were analyzed for neutralizing activity against primary isolates of three clades with PHA-stimulated PBMC indicator cells (Table 2). The swine sera had broadly neutralizing antibodies against HIV-1 isolates of clades A, B, and E at 50 and 90% endpoints.

The immunogenicity of this water-in-oil vaccine was characterized by evoking neutralizing antibody responses in baboons. Neutralizing antibodies against HIV-1 patient isolate VL135, albeit with lower titers than seen in guinea pigs and swine, were consistently observed in baboons upon multiple immunizations. Baboon no. 5805 received the prototype water-in-oil emulsion vaccine only. The neutralizing antibodies of this animal were effective against primary isolate VL135 while having little activity against T cell line-adapted...
HIV-1 MN. In contrast, baboon no. 1988 was given only an MN V3 peptide immunogen and developed strongly neutralizing antibodies exclusively against MN. Baboon no. 1997 was co-immunized with both peptide immunogens and developed neutralizing antibodies effective against both the primary and the T cell line-adapted isolate. That animal showed no suppression of the anti-MN V3 neutralizing response to the second peptide immunogen despite the persistent presence of anti-CD4 neutralizing antibodies. Similar anti-MN and anti-VL3 neutralizing titers coexisted in three other baboons (nos. 1096, 1196, and 1697) that received p2249f, the MN V3 peptide, and other immunogens. The distributions of CD4, CD8, CD3 and CD20 positive B and T cells remained within normal range in the immunized baboons after persistent exposure to the site-specific anti-CD4 neutralizing antibodies [3].

This proposed immunotherapeutic vaccine for AIDS has elicited safe and effective neutralizing antibodies in small animals, swine, and in a non-human primate. We believe that like the antibody for passive immunization it will reduce viral load in HIV-infected individuals without the toxic side-effects of the anti-retroviral drugs, and can be a valuableduce viral load in HIV-infected individuals without the toxic side-effects of the anti-retroviral drugs, and can be a valuable

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Neutralization of HIV-1 primary isolates by swine anti-peptide immune sera, by PHA-stimulated PBMC assay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swine anti-p2249f</td>
<td>DI-25B (Clade A)</td>
</tr>
<tr>
<td>46 wpi</td>
<td>50% neat</td>
</tr>
<tr>
<td>90% neat</td>
<td>160</td>
</tr>
<tr>
<td>49 wpi</td>
<td>50% neat</td>
</tr>
<tr>
<td>90% neat</td>
<td>100</td>
</tr>
</tbody>
</table>

From ref. [3].

3.4. Anti-IgE vaccine for immunotherapy of allergy

The UBITh® technology has been applied to developing immunogens effective for eliciting specific anti-IgE antibodies, as therapy for asthma, anaphylactic reactions to bee sting or peanuts, and other allergic diseases. The vaccine-induced antibodies blocked the binding of IgE to mast cells and basophils as shown by in vitro assays for functional antigenicity. This action prevents the IgE-mediated triggering of histamine release by any allergen. The development of allergic reactions is stopped, independently of the specific allergenic stimulus.

Thirty-five potential effector sites within the Cε2, Cε3, and Cε4 domains of human IgE were selected for synthesis as peptides based on structural models for IgE [2]. Disulphide-bonded loops were incorporated into the designs of candidate peptides corresponding to predicted loop sites in native IgE. Each candidate site was tested for functional antigenicity by generating hyperimmune serum in guinea pigs and evaluating for cross-reactivity to human IgE and for the ability to block histamine release by human basophils. A cyclized target site peptide modified from the 413–435 positions of the Cε3 domain of human IgE by cysteines added to the N- and C-termini and by the substitution of serine at position 18, was selected as the most active site. The target sequence was CGETYQSRTHPHLPRALMRSTTKC [2].

A peptide immunogen having the modified Cε3 site was designed by the addition of an e-lysine linker and the combinatorial UBITh® 1 epitope to the N-terminus. This immunogen was tested in swine and mice as water-in-oil vaccine formulations. Inhibition of IgE binding to human basophils by the swine serum was evaluated by monitoring for sensitization by histamine release assay, and directly by cytofluorometric measurement (Fig. 3). By either method the swine serum yielded equivalent results for inhibition of IgE binding. The resulting swine antibodies were shown by the in vitro assays to block the binding of IgE to human basophils, thereby preventing sensitization. The site-specific mouse anti-IgE antibodies were shown by in vivo assay to suppress the passive cutaneous anaphylaxis reaction of rat mast cells.

Non-atopic beagles were immunized with an homologous combinatorial UBITh® 1-canine IgE peptide immunogen in ISA 720 water-in-oil emulsion. The dogs were divided into five groups, four dogs per group, and four groups were immunized with 2000, 400, 100 or 25 μg of the canine IgE vaccine at weeks 0 and 3. The fifth group was immunized with an irrelevant peptide. All groups were boosted at 7 weeks post-initial immunization with 100 μg doses. Dog sera was collected at weeks 0, 3, 5, and 9 and analyzed for anti-IgE antibody responses by anti-dog IgE ELISA. All four dogs given the 100 μg doses on weeks 0, 3, and 7 achieved peak responses that were sustained through week 9. Three out of the four dogs of the 400 and 2000 μg dose groups were responsive though less so than the 100 μg group, while the dogs of the 25 μg group were only minimally responsive above the control group (data not shown).

The sera collected from two responsive dogs of each responsive group and a dog from control group 5 were assayed for total IgE content including free IgE and IgE within anti-IgE/IgE immune complexes, by quantitative assay on heated sera [13]. Serum IgE for responsive dogs from the 2000 μg group (nos. 27 and 28), the 400 μg group (nos. 30 and 31), the
Inhibition of human basophil IgE-mediated sensitization with vaccine-elicited anti-IgE in swine serum. In the left panel, semi-purified human basophils were sensitized by IgE in the presence of the indicated swine serum and the binding of IgE was assessed by flow cytometry. Swine antibodies were at a concentration of 2 mg/ml. The right panel shows the effect of swine serum on basophils treated with IgE and subsequently stimulating the basophils to release histamine with specific antigen for the IgE. Swine sera was used at a 1:4 dilution. (Adapted from ref. [2].)

100 μg group (nos. 32 and 33) and control dog no. 01 from group 5 are shown in Fig. 4 for weeks 0, 5 and 9. The range of initial IgE levels varied among these normal dogs, but the relative levels of total IgE in circulation declined substantially during the course of the trial immunizations. Dog no. 31, with the lowest anti-IgE (reciprocal titre log_{10} 1.8) and highest IgE at 9 weeks of the group 1–3 dogs tested, had total IgE reduced by close to 10-fold from week 0. However, the water-in-oil IgE vaccines caused localized reactogenicity. A new study in baboons is underway, of UBITh®-human IgE vaccines formulated with non-reactogenic stabilized immunostimulatory complexes.

3.5. Effective UBITh® peptide vaccine for foot-and-mouth disease

Highly contagious foot-and-mouth disease virus (FMDV) is responsible for devastating outbreaks of the disease among cloven-hoofed animals. Foot-and-mouth disease (FMD) can be controlled by slaughter of infected and exposed herds, or by vaccination. Current vaccines consist of semi-purified chemically inactivated virus preparations and elicit antibodies primarily against structural proteins. A synthetic subunit vaccine for FMDV has long been sought as an antigenic marker vaccine and for the safety advantages of a product

Fig. 4. Determinations of total IgE content in heated dog sera. Total IgE content was determined at weeks 0, 5, and 9 post-initial immunization with the UBITh®-canine IgE immunotherapeutic. Dog nos. 27 and 28 were given initial doses of 2000 μg; nos. 30 and 31 were given 400 μg; nos. 32 and 33 received 100 μg priming doses, and no. 01 received placebo. (From ref. [2].)
that does not use biohazardous virus in its manufacturing process [14].

The prominent G-H loop of the VP1 capsid protein of FMDV, spanning residues 134–158, has been identified as the major immunogenic site for neutralizing antibodies. The successful protection of susceptible hoofed species by administration of G-H loop synthetic peptides has not been achieved due to the limited immunogenicity of the peptides. The hypervariability of the immunodominant G-H loop domain has been another major drawback for VP1-based immunogens. We have designed a novel synthetic peptide vaccine with T and B cell sites optimized for both immunogenicity and antigenic cross-reactivities. This peptide immunogen spans the entire G-H loop domain and extensive flanking sequences (129–169), has a unique consensus sequence to confront the hypervariability of serotype O viruses, and includes the promiscuous combinatorial UBITh® 1 T helper site [4].

The UBITh®-VP1 immunogen was formulated into water-in-oil vaccines with ISA51 at the doses of 12.5–100 μg in 0.5 ml. The synthetic vaccines were given by intramuscular injection to groups of three pigs on days 0 and 28. The vaccines caused no local adverse reactions. A positive control group receiving a commercial FMDV O Taiwan vaccine and a non-immunised control group given only adjuvant were inoculated on the same schedule. The pigs were challenged on day 56.

No neutralizing antibodies [15] above background were found in the sera of any of the animals at day 0, indicating a lack of previous exposure. By day 40, almost all the animals immunized with the synthetic peptide had attained significant levels of neutralizing antibodies. All animals given experimental vaccines or a commercial FMDV O1 Taiwan vaccine seroconverted to VP1 reactivity following immunization. The control pigs of the non-immunized group seroconverted to VP1 reactivity within 1 week after challenge due to their infected status. The control pigs with the most apparent signs of FMD seroconverted to NS reactivity, a differential serologic marker for infection [16], by week 2 following challenge, while the other animals remained non-reactive to the 3B NS peptide.

Pigs were observed daily for clinical signs of FMD after the challenge. Of the 21 pigs receiving synthetic vaccine formulations, all but one remained free of clinical signs at all times following exposure. That animal, of the group given the 50 μg dose of peptide vaccine, displayed lameness in one leg on day 2 followed by the appearance of small coronary vesicles on the affected leg on day 4 as signs of limited infection. The three animals of the non-immunized control group developed signs of FMD between days 2 and 4. One animal of the positive control group given commercial killed virus vaccine had a delayed appearance of mild signs by day 11 post-challenge. The results of 13 immunization/challenge trials in pigs of this first UBITh® FMD vaccine are summarized in Table 3.

This prototype FMD vaccine for swine required two doses for effective protection. However, commercial swine operations and government regulatory agencies prefer a one-dose vaccine. A one-dose vaccine is needed for emergency application in the event of an outbreak. The prototype vaccine has been re-formulated and the vaccine has been shown to be an effective one-dose vaccine. All eighteen pigs immunized by a single dose and challenged with infectious virus in accordance with international standards [15] showed no signs of infection (Sia, et al., in preparation). A UBITh®-VP1 FMD vaccine for swine has been approved by the Ministry of Agriculture of PRC, pending in Taiwan. A new formulation also is being developed for cattle.

4. Discussion

The UBI core technologies for the discovery and production of site-specific immunotherapies and vaccines have led to the development of a pipeline of therapeutic and protective vaccines for chronic and infectious diseases, and prostate cancer. The UBITh® peptide immunogens are chemically defined entities produced by controlled processes. Clear physical chemical descriptions of the immunogens can be developed for each vaccine. Controlled production processes and the means to characterize the final products provide a framework for the GMP-compliant manufacture of UBITh® immunotherapeutics and vaccines, and for expedited entry into clinical trial. UBI has applied for INDs for the LHRH therapeutic vaccine for Alzheimer’s disease. The UBITh® amyloid β peptide vaccine has site-specificity for the N-terminus of the amyloid β peptide. It evokes antibody responses in baboons, a non-human primate species, having cross-reactivity to amyloid plaques in brains from human patients and functional activity that neutralizes the neurotoxicity of amyloid β peptide [17]. The veterinary vaccines can be more quickly brought to market. A UBITh® vaccine for FMD has been approved for sale in China, and approval is imminent in Taiwan. An LHRH vaccine to eliminate boar taint in swine is pending approvals in Taiwan and China.

Table 3

<table>
<thead>
<tr>
<th>Placebo Negative Controls</th>
<th>UBITh® FMD vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Protected (no. protected/total)</td>
<td>1.2% (1/84)</td>
</tr>
</tbody>
</table>

References


