



Vaccines Based Upon LAMP Technology

A Novel Immuno- Potentiator Mitigates Allergic Rhinitis via DNA Vaccines in a Multi-Allergen Format for Allergy Immunotherapy

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Executive Summary

Immunomic Therapeutics (“ITI or The Company”) is commercializing a differentiated vaccine platform that **directly accesses** the pathway in the immune system responsible for induction of active humoral immunity *and simultaneously* directs a cell mediated response against a targeted biological agent (e.g., an allergen, infectious agent or cancer protein). ITI’s vaccines are based on the pioneering research of Dr. Thomas August (Johns Hopkins School of Medicine, “JHU”) known as **LAMP Technology**. The Company holds the exclusive rights to the patent estate from JHU for all applications worldwide.

Introduction

Immunomic Therapeutics is currently focused on developing novel allergy immunotherapies based on LAMP Technology to treat pollen allergies. The approach creates DNA vaccines that link allergens (e.g., cedar, birch, oak, ragweed) to Lysosomal Associated Membrane Protein (LAMP). Following immunization, the expressed LAMP-allergen fusion protein is localized in the MHC-II compartment in antigen presenting cells, resulting in a strong Th1-mediated response producing antigen specific IgG to therapeutic levels whereas vaccines without LAMP induce low IgG and high IgE titers.

ITI’s first planned vaccine product is JRC-LAMP-vax to treat cedar pollenosis endemic in Southeastern U.S. (North Carolina and East Texas), and the ~40% allergic population in Japan. The product represents the first of ITI’s allergy vaccines that we expect to broadly impact the treatment and prevention of many allergies. The economic impact of allergy is significant: since 1995, the number of Americans suffering from allergies has doubled leading to a 338% rise in medical expenses with Americans spending \$5.4 billion on allergy drugs in 2009, and it is estimated that ~30% of the western world population is allergic (source: Fortune, 2010).

LAMP-vax allergy vaccines will be the only formulation **that treats allergy without introducing free allergen into the patient systemically**. This important safety element makes this platform an ideal procedure to desensitize allergic patients, where allergy desensitization can result in anaphalaxis such as with food allergies to peanut and shellfish. Currently, only allergen immunotherapy actually attempts to treat the disease, but requires monthly injections over many years and has certain risks. ITI initiated cGMP production and preclinical safety studies for an IND submission in the 3rd Quarter of 2011 for JRC-LAMP-vax. To date, five clinical studies have been performed using LAMP vaccine constructs, including Geron’s GRNVAC1 cancer vaccine study in AML patients that showed safety in individuals receiving up to 30 doses, long term boost-able IgG titers and increased patient survival.

About LAMP Technology

Lysosomal Associated Membrane Protein (“LAMP”) localizes to the Major Histocompatibility Complex Type II (MHC-II) compartment in antigen presenting cells (APC). Work in the laboratory of Dr. J. Thomas August at Johns Hopkins (supported by multiple NIH grants) showed that when LAMP is combined with the sequence of an antigen, the LAMP intracellular targeting sequence directs the antigen to the lysosome resulting in MHC-II presentation to the immune system. This induces a significantly enhanced immune response, particularly an IgG antibody response. ITI’s LAMP-vax vaccine formulations utilize this intracellular trafficking function to access the MHC-II pathway and in the case of allergy vaccines, convert the immune system response from a Th2/ IgE allergen response to a Th1/ IgG antigen response with the concomitant elimination of allergy symptoms. This supports one of the mechanisms of action attributed to efficacious allergy vaccination, namely a re-orientation in TH1 and TH2 cell activity. Thus, the ITI approach allergy vaccines involves attacking the problem using a

traditional method – converting the immune response from an IgE mediated response to allergen to an IgG mediated response.

LAMP vaccines are currently in multiple human clinical trials for applications in cancer. GRNVAC1 (under license to Geron) has shown both safety and immunoreactivity in treated cancer patients. In addition, work by Chua with dust mite allergen has shown LAMP vaccines capable of converting IgE allergy response to an IgG antigen response in a mouse model and to form protective antibodies. Both areas of study suggest a successful outcome for LAMP-vax allergy vaccines in terms of safety, efficacy and potency.

Current Status of Development

ITI has an immuno-potentiating nucleotide sequence (Lysosomal Associated Membrane Protein- LAMP) for DNA vaccines to enhance antibody responses through the TH1 and MHCII pathways for therapeutic vaccines to meet unmet medical needs. ITI’s pre-IND meeting with FDA, March 10, 2009, provided FDA responses to its draft pre-clinical and clinical protocols confirming multivalent vaccines are treated as a single product. This guidance will allow ITI to develop allergy vaccines that contain multiple allergens, such as tree, grass, weed, animal dander rather than individual allergen vaccines for these major allergen families. In Apr. 9, 2008 FDA met with ITI on a multivalent HIV vaccine receiving the same guidance.

ITI retained a cGMP manufacturer to provide JRC-LAMP-vax (CryJ2) vaccine for pre-clinical and clinical studies. Additionally, ITI retained BioReliance to perform 85 Day General Toxicity and the Biodistribution safety studies in rabbits. The preliminary data from this study has been received and the final report is due on/about August 1, 2011. In Q3 2011, ITI plans to submit an investigational new drug (IND) filing for Phase 1a safety study in Japanese Red Cedar CryJ2 allergen allergic patients, then a 6-9 months follow-up to assess long-term safety and IgG and IgE anti-CryJ2 antibody levels (Phase 1b). ITI is negotiating with a clinical study site and finalizing Phase 1a/1b protocols assessing vaccine doses/dosing regimen versus safety, IgG & IgE anti-CryJ2 titers, Treg cell titers. ITI will file Phase 2 protocol 1st quarter 2012 assessing therapeutic effects of the JRC-LAMP-vax vaccine in 48 sensitive patients that LAMP-vax vaccines induce sufficient antibodies to be therapeutically beneficial using Allergen Exposure Chambers and/or “park” (environmental) studies of vaccinated sensitive patients to CryJ2. ITI may file an IND in Fall 2011 to validate Allergen Exposure Chambers to be used in Phase 1a/1b and 2 using CryJ2 sensitive patients exposed to pollen.

TASK	2010				2011				2012			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Pre-Clinical Validation												
cGMP Mfg												
Biodistribution												
Toxicology												
Milestone: IND Filed								◆				
Phase I Study												
Phase II Study												

Projected Timeline to Complete Phase I/II

Management Team & Resources

Immunomic Therapeutics has assembled an experienced management and scientific team to execute this project: Dr. William Hearl, CEO has over 25 years bench and executive experience in immunology and vaccine development and holds multiple patents in gene immunization; Dr. Bruce Mackler, VP Regulatory Affairs also an immunologist is a regulatory affairs expert having processed over 130 IND

applications with the FDA; and Medical Director Dr. Lawrence Weiner is a practicing allergist with a large and respected practice in North Carolina. The Company maintains two laboratories: one in Rockville, Maryland and one at Franklin & Marshall College (Lancaster, PA) under the direction of Dr. Teri Jones-Heiland, a molecular biologist with over 20 years experience and supported by Dr. Thomas August, distinguished professor at Johns Hopkins.

ITI has raised private equity in 2009/2010 to support the clinical trials with follow on commitment from these same investors. The Company continues to raise capital from the private equity markets and is also evaluating venture proposals. ITI believes it has sufficient capital pledged to meet the JRC-LAMP-vax project requirements through 2011.

Corporate Alliance Opportunities

Immunomic Therapeutics is seeking a corporate partner(s) to license full rights to its Lysosomal Associated Membrane Protein LAMP-based allergy vaccines for planned clinical and commercial development, primarily focused on the US, EU and Japanese allergy markets. ITI has designed and validated its LAMP-based allergy vaccines for Japanese red cedar and initiated animal studies. The company has also designed a unique clinical development program (outlined in the enclosed Information Memorandum) to move these products through the regulatory process in two years. An efficient process for manufacturing its vaccine formulations for commercial sale has also been developed.

The Company seeks a collaboration that will be structured as: upfront-fee based upon defined product/technology/market rights desired, R&D payments against development milestones, and transfer pricing or royalties based upon manufacturer, and ITI will also consider separate equity investment by a corporate partner. An initial R&D collaboration for the JRC-LAMP-vax project, with option to expand license and product/market rights will also be considered. Interested parties will be required to sign a CDA with the Company in order to receive associated documents that contain more detailed and confidential information about LAMP-based allergy vaccines.

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OVERVIEW

Immunomic Therapeutics, Inc. (ITI), a private biotechnology and therapeutics company located in Lancaster, PA USA, is focused on the development of DNA-based vaccines using its patented **Lysosomal Associated Membrane Protein (LAMP)** technology for allergy and other disease applications. The Company's **LAMP-vax** vaccine technology directly accesses the pathway in the immune system responsible for induction of active humoral immunity *and* simultaneously direct a cell mediated response against a targeted biological agent. The company's allergy vaccine product development efforts (LAMP-vax allergy vaccines) are currently targeting Japanese red cedar, short ragweed and multivalent pollen allergy formulations.

Allergy is a hypersensitivity disease characterized by the production of **IgE antibodies** against antigens (i.e., allergens) affecting more than 25% of the population. Allergens can enter the body through the respiratory tract, skin contact, ingestion, insect bite or injection of a drug. Thus, allergic patients can exhibit a variety of allergic manifestations including rhino-conjunctivitis, asthma, food allergy, skin reactions, and severe systemic reactions such as anaphylactic shock when they encounter the allergens against which they are sensitized. In contrast to non-allergic individuals who respond to allergens with production of IgG antibodies and a balanced T cell response, allergic patients produce allergen-specific IgE antibodies and show a preferential allergen-specific Th2 response. The class switch to IgE antibody production occurring during primary sensitization in allergic patients is driven by IL-4, which is a product of Th2 cells and other effector cells of the allergic immune response.

Treatment of allergy most often falls into two categories: avoidance and dosing with anti-histamines. A third alternative, **allergy immunotherapy** requires the patient to receive weekly injections small amounts of the offending allergens in order to help the immune system reeducate its response to the allergen. Most currently available approaches for allergy immunotherapy continue to elicit a predominately TH2-inducing T-cell response, producing IgE antibodies. This mechanism requires a lengthy and frequent treatment regimen, oftentimes lasting several years and necessitating 100 or more shots. Consequently, patient compliance is a significant issue. Results from current immunotherapy vary widely and this course of treatment is not an option for those suffering from highly reactive allergies (e.g., peanut, penicillin).

There is increasing recognition of the potential benefit of genetic immunization as a method for both prophylactic and therapeutic treatment of the broad spectrum of protein allergens. The underlying rationale is that allergen protein encoded as a DNA vaccine will preferentially activate allergen-specific T-helper type 1 (Th1) responses with the production of interferons by antigen presenting cells (APC), natural killer cells (NK), and T cells, rather than the characteristic Th2-type responses, such as secretion of interleukin (IL) -4, -5, and -13, and the formation of immunoglobulin E (IgE) by B lymphocytes and the maturation and recruitment of eosinophils in late-phase reactions. It is believed that (a) the cellular trafficking properties of the allergen protein in transfected cells is one of the major determinants of the immune system response to the allergen, and that (b) a design of the allergen-encoded DNA vaccine that will facilitate trafficking into the MHC II processing and presentation pathway of APCs is critical for optimal and precise expression of Th1 immune responses.

Lysosomal Associated Membrane Protein or "LAMP" is a protein that localizes in antigen presenting cells (APC) to the same compartment as the Major Histocompatibility Complex Type II (MHC-II). Work in the laboratory of Dr. J. Thomas August at Johns Hopkins University showed that when LAMP is combined with the sequence of a target antigen, the LAMP intracellular targeting sequence directs the antigen to the lysosome (MHC-II) antigen

processing pathway resulting in a significantly enhanced immune response, particularly an IgG antibody response. ITI's LAMP-*vax* vaccine formulations utilize this intra-cellular trafficking function to access the MHC-II pathway and in the case of allergy vaccines, convert the immune system response from a Th2/ IgE allergen response to a Th1/ IgG antigen response with the concomitant elimination of allergy symptoms. This supports one of the mechanisms of action attributed to efficacious allergy vaccination, namely a re-orientation in TH1 and TH2 cell activity, possibly through induction of T-regulatory cells. (See Figure 3, page 8 below for diagram of immune system pathway). Thus, the ITI approach allergy vaccines involves attacking the problem using a traditional method – converting the immune response from an **IgE** mediated response to allergen to an **IgG** mediated response. LAMP-*vax* allergy vaccines introduce the allergen (antigen) to the immune system exclusively through the MHC-II / Th1 pathway which favors the generation of an IgG response and is accomplished without exposing the patient to free allergen as is required in conventional immunotherapy.

There is no current consensus regarding the mechanism of successful allergy vaccination apart from the view that there is a modulation of the activity of T helper cells. One possibility is that there is a switch, changing cytokine profiles of allergen-specific T cells from a more TH2 like to a more TH1 like profile leading to down-regulation of the late-phase reaction, associated inflammation and reduction in IgE antibodies. Thus, switching to a TH1 response should increase the level of immune IgG, which bind circulating allergens, which is the main therapeutic paradigm for desensitization by allergists.

A further advantage of the LAMP-*vax* DNA vaccine approach using is the ability to develop formulations that target more than one allergen. The FDA has stated that formulations of up to six different plasmids are acceptable and we also have shown that we can successfully create plasmids that express up to four different antigens. This could be very valuable in meeting the needs of patients with multiple allergy indications.

Potential indications for LAMP*vax* allergy vaccine immunotherapy include:

- Patients diagnosed with allergic rhinitis (hay fever), allergic conjunctivitis, urticaria, atopic dermatitis, or allergic bronchial asthma, particularly severe patients who have not responded to conventional desensitization protocols.
- Patients with severe symptoms, who have not responded to other forms of treatment – drugs and allergen avoidance methods
- Patients showing slow or no response to conventional immunotherapy
- Adults and children above age 6 years
- Patients with single or multiple allergen sensitivities.

1.0 Partnering Opportunity

Immunomic Therapeutics (ITI) is seeking a corporate partner(s) to license full rights to its Lysosomal Associated Membrane Protein LAMP-based allergy vaccines for planned clinical and commercial development, primarily focused on the US, EU and Japanese allergy markets. ITI has designed and validated its LAMP-based allergy vaccines for Japanese red cedar and initiated animal studies. The company has also designed a unique clinical development program to move these products through the regulatory process in two years. An efficient process for manufacturing its vaccine formulations for commercial sale has also been developed with OEM partners. Interested parties will be required to sign a CDA with the Company in order to receive associated documents that contain more detailed and confidential information about LAMP-based allergy vaccines.

2. 0 Company Introduction

2.1 Company History

Immunomic Therapeutics, Inc. (ITI), which is privately held, was formed to commercialize LAMP Vaccine Technology. LAMP (Lysosome-Associated Membrane Protein) facilitates the presentation of antigens in nucleic vaccine formulations, resulting in an enhanced and effective immune response in humans. LAMP Technology was invented and patented by Dr. J. Thomas August, M.D., Distinguished Professor at Johns Hopkins University; the LAMP patent estate was exclusively licensed (worldwide, all applications) by ITI from Johns Hopkins University in 2006. LAMP-based vaccines have been developed for a wide array of diseases and have been successfully applied in human clinical trials for prostate cancer and acute myeloid leukemia. This research has been supported by over \$20 million in government research grants and has been the subject of over 70 research papers in the life science literature. Recent publications have shown that LAMP vaccines can provide protection against rabies virus in dogs, against yellow fever in mice and prevent & cure dust mite allergies in mice.

Immunomic Therapeutics has completed multiple transactions including sub-licenses to the Geron Corporation (telomerase in hyper-proliferative disease) and Nature Pharmaceuticals (research sale of vectors containing LAMP) for the commercial development of LAMP-based vaccines and has active collaborations with several laboratories. ITI has an experienced management team in place, expansion resources identified, and strong opportunities for multiple licenses to pharmaceutical and biotechnology companies active in vaccine development.

2.2 Location and Organization

Immunomic Therapeutics maintains its corporate offices in Lancaster, PA and primary laboratories at 9620 Medical Center Drive in Rockville, MD.

ITI's management is led by Dr. William Hearl, an experienced biotech CEO and entrepreneur. Dr. Bruce F. Mackler (Ph.D. J.D.), who was a Professor of Immunology with over 100 publications and then an attorney representing biotech and drug companies before FDA for 27 years, is the Vice President of Regulatory Affairs and Development and is directing the Company's strategy and interactions with the FDA. ITI has already had its first successful pre-IND meeting for a DNA vaccine and intends to file for the pre-IND meeting for allergy later this year. Dr. Teri Jones Heiland leads the Company's research program as its VP of R&D; in addition to her extensive professional experience at the NIH and within the industry, Dr. Heiland is a visiting scientist at Johns Hopkins University. Mr. Barry McDonald, a member of the Board of Directors, heads the Company's business

development activities drawing on over 30 years of industry experience. In addition, Ms. Lisa Salley and Dr. Tama Copeman provide organizational and business leadership as strategic advisors to ITI.

2.3 Intellectual Property

ITI has exclusively licensed the LAMP technology from Johns Hopkins University and has a strong patent portfolio, which covers the allergy area. In preparing specific DNA vaccines, ITI would either use allergy nucleotide sequences in the public domain or license the use of proprietary allergens. Additionally, ITI has sublicensed the LAMP technology to Geron for use in two telomerase anti-cancer DNA based vaccines; the first such vaccine has shown good safety and efficacy in AML cancer patients.

3.0 LAMP Technology Overview

3.1 DNA Vaccines: Advantages and limitations

An alternative to conventional vaccines is DNA vaccines, an expanding area of vaccine development with a growing portfolio of candidates entering clinical trials. With DNA vaccines the individual is not injected with the viral antigen, but with DNA sequence encoding the antigen. DNA vaccines are injected into patients either as “naked” DNA or DNA carried by a non-pathogenic virus vector. In either case, the DNA gains access to cells where the antigen protein is synthesized by normal cell mechanisms and presented to the immune system to stimulate the immune response to it. Because DNA can be synthesized to encode many different elements, there are many alternative ways to build a DNA vaccine.

As illustrated in the diagram below, nucleic acid is delivered to the cells either as DNA, RNA or as part of a specially modified virus that acts only as a carrier of the target DNA. It does not cause an infection because the DNA is selectively made to encode only the antigen(s) of the pathogen which evoke protective immune responses.

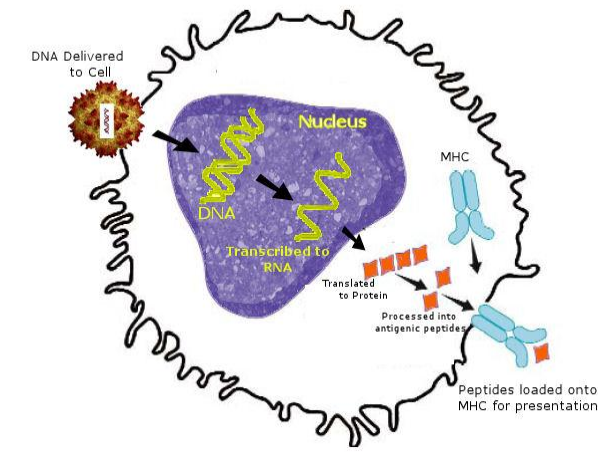


Figure 1: DNA Vaccines

Once the nucleic acid is inside the cell, it uses the cell’s own biochemistry to make the antigenic protein(s) coded in the vaccine nucleic acid (the “red diamonds” inside the cell in step 2). The cell, then processes this antigenic protein, as it does all proteins, by digesting it into small pieces. A certain number of these pieces attach to specialized MHC proteins, and move to the outside of the cell. (In the diagram, the grossly exaggerated piece of

the protein is represented in orange.) The protein is now free to interact with the outside world, and in particular the immune system. Depending on the type of cell that received the DNA, the antigenic protein will follow either MHC I or MHC II presentation. Class I MHCs are found in all cells; the MHC-IIs are only found in specialized “antigen presenting cells” (APCs) such as dendritic cells (“DCs”).

DNA vaccines have several distinct advantages: ease of manipulation, use of a genetic technology, simplicity of manufacture, and chemical and biological stability. However, the majority of work to date has been performed using laboratory animals, through which these vaccines have been able to protect against tuberculosis, SARS, smallpox, and other intracellular pathogens. Further, the recent approval of Vical’s melanoma vaccine for dogs validates the commercialization of DNA vaccines for use in large mammals as well as their recent report on the immunization of humans against influenza antigens.

3.2 ITI’s LAMP Technology

LAMP Technology distinguishes itself from other vaccine approaches by specifically delivering antigen directly to the MHC-II compartment in professional antigen presenting cells. This is in contrast to non-LAMP DNA vaccines that process antigen in somatic cells (e.g. muscle cells) and presenting through the generic MHC-I pathway. In this manner, ITI’s LAMP vaccines directly access the immune system via helper T-cells while maintaining its ability to stimulate cellular immunity. This process has been shown in both animal model and human clinical subjects.

As previously noted, LAMP is a protein that localizes in antigen presenting cells (APC) to the same compartment as the Major Histocompatibility Complex Type II (MHC-II) and it has been proven that fusion proteins containing the LAMP targeting sequence will localize in the MHC-II+ lysosome in APC’s. This observation has important implications to the processing of antigens when used in DNA or RNA vaccinations. Shown in the left panel below is the process an APC follows when it encounters a foreign protein as it is delivered in a traditional vaccine. The protein is brought into the cell and processed in the endosome and then delivered to the MHC-II containing lysosome where the peptides bind the MHC-II molecule and are escorted to the surface of the cell for presentation to the immune system. This process activates the CD4+ Helper T-cell pathway leading to cytokine & antibody production as well as immunological memory.

In the center panel, the pathway of a DNA vaccine is shown. Once the DNA enters the cell (most often a muscle cell lacking MHC-II lysosomes), the protein is expressed in the cytoplasm and is directed to the proteasome where it is digested into peptides. These peptides find their way into the ER & Golgi where they bind the MHC-I protein for presentation on the surface of the cell. This process activates CD8+ cells and the cytotoxic T-cell pathway. The CD4+ cells are not directly activated through this pathway and in muscle cells. When LAMP is included in the DNA vaccine construct, the resulting chimeric protein moves to the Golgi upon synthesis and the intracellular targeting sequence directs the antigenic protein to the MHC-II compartment in the cell. This results in a DNA vaccine directly activating the CD4+ pathway while maintaining the CD8+ cytotoxic T-cell response. LAMP nucleic acid vaccines induce both humoral and cellular immune responses; this response has been observed in mice, rats, monkeys and humans.

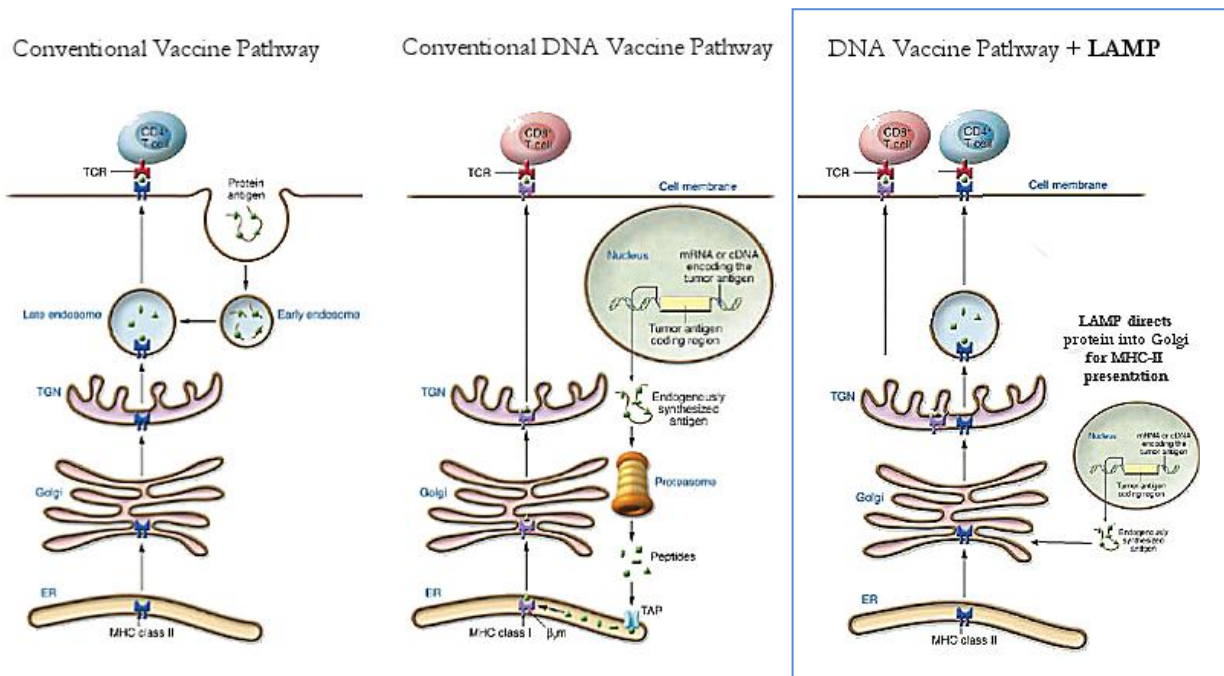


Figure 2. Presentation of Antigens on the surface of Cells

3.3 LAMP-vax DNA Vaccines As Immunotherapy For Allergy

The underlying rationale is that allergen proteins encoded in a LAMP-vax DNA vaccine will preferentially activate allergen-specific T-helper type 1 (Th1) cellular responses with the production of interferons by antigen presenting cells (APC), natural killer cells (NK), and T cells, rather than the characteristic Th2-type responses, such as secretion of interleukin (IL) -4, -5, and -13, and the formation of immunoglobulin E (IgE) by B lymphocytes and the maturation and recruitment of eosinophils in late-phase reactions. It has been demonstrated that LAMP-encoded allergen- DNA vaccine that will facilitate trafficking into the MHC II processing and presentation pathway of APCs is critical for optimal and precise expression of Th1 immune responses.

In the case of allergy, treatment with LAMP-vax vaccines convert the immune system response from an IgE allergen response to an IgG antigen response with the concomitant elimination of allergy symptoms. This conversion of the patient antibody responses from IgE to IgG is the principle therapeutic paradigm that allergist try to achieve with either sublingual exposure or intradermal injections of allergens during desensitization therapy; thus, we are not changing the current allergy therapeutic paradigm.

As shown in the figure below, the ITI approach to allergy immunotherapy involves attacking the problem using a traditional method – converting the immune response from an **IgE** mediated response to allergen to an **IgG** mediated response. LAMP-vax Allergy vaccines introduce the allergen (antigen) to the immune system through the MHC-II / Th1 pathway which favors the generation of an IgG response (see diagram below).

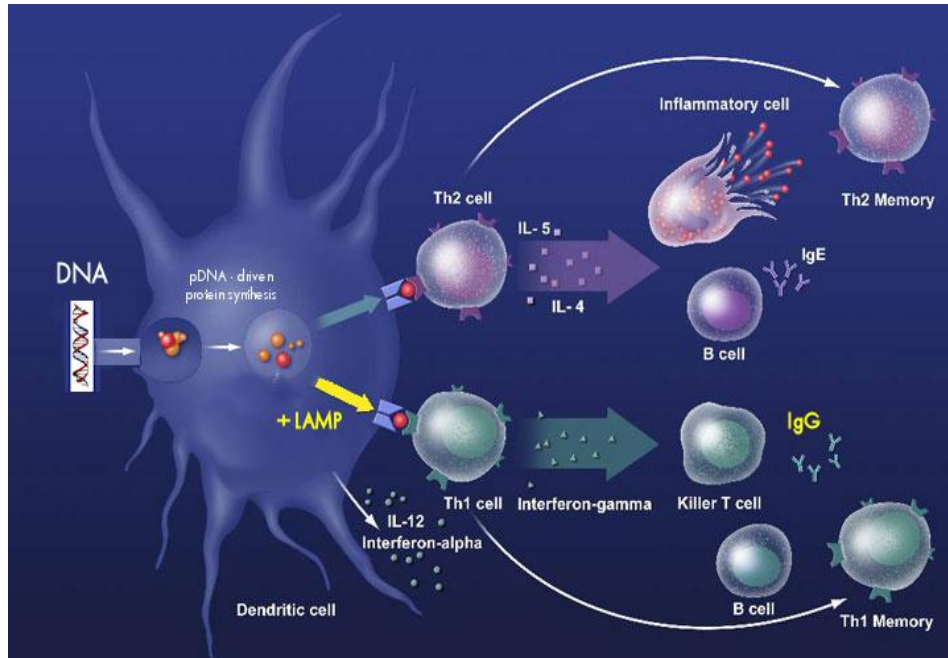


Figure 3. The Allergy Cascade and LAMP DNA Vaccination. DNA vaccines which utilize LAMP intracellular targeting result in immune system presentation that favors Th1 / IgG and Interferon- γ as opposed to Th2 / IgE & IL-4. (figure based on graphic from dynavax.com).

3.4 Competitive Advantages

A Key Safety Advantage – No Free Allergen is Present in the Therapy

The structure of the LAMP-allergen chimera offers a unique safety feature that is not present in any other allergy vaccine formulation: the allergen is isolated in a specific cellular compartment (i.e., the lysosome) and is “encased” in LAMP. The diagram to the right shows the lysosome in a cell expressing allergen. The allergen is anchored in the lysosome with the tail of LAMP and then is linked to the remaining sequence of LAMP. Work with dust mite allergen showed that the LAMP sequence eliminates circulating free allergen; thus, allows patient exposure to allergens without the fear of atopic reactions during sensitization therapy with DNA-based vaccines.

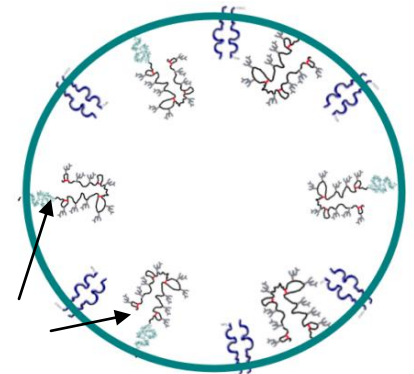


Figure 4. The LAMP Fusion Protein (arrows) is membrane-bound.

“Plug & Play” Vaccine Design for Rapid Product Line Development

The design of the LAMP-vax allergy vaccines utilizes a standard plasmid backbone that includes the LAMP elements. The target allergen is inserted into this plasmid easily at a multi-cloning site and then validated for proper expression characteristics. This process routinely requires about 30 days in design and development and an additional 30 days for validation of the construct. Thus, any given target can be developed into a working vaccine candidate (or component of a multi-vector formulation) within a business quarter and with limited expense. This versatility will enable ITI to not only expand its product line to address all the key allergic targets quickly, it will also make it possible to respond to emerging market demands in an extremely timely manner. It is important to note that the FDA has stated that it accepts safety data on DNA vaccines from earlier clinical studies as well as multi-vector formulations as a single vaccine entity.

Proven Performance & Safety in the Clinic

The LAMP-vax platform has been incorporated into clinical studies: patients at high risk with AML were given the cancer immunotherapy vaccine, GRNVAC1 in a Phase II study sponsored by our licensee, the Geron Corporation. In this study, 15 of 21 patients have been in extended complete remission for up to 30 months (as of May 2010). These patients have shown that not only is the LAMP formulation is safe with some patients receiving up to 30 injections of therapy, but also that LAMP-mediated education of the immune system does occur and does so primarily through helper T-cells. This study supports the earlier Phase I study in prostate cancer patients which also revealed a strong interferon-gamma response and a boost-able memory capability.

Multiplexing Allergens & Multiple Delivery Options Address Market Concerns

LAMP-vax allergy vaccines can be configured to address important market concerns for allergy immunotherapy. One key issue is the ability to include more than one target allergen in a given formulation. We currently know that the FDA is accepting of a vaccine formulation that includes 6 different plasmids configured as a blend. Using this configuration, it is possible to deliver 6 – 12 different allergens in a single treatment. This has strong advantages over the approach using sublingual drops which deliver only 1 antigen at a time. Further, although the current proposed study will initially use an intramuscular injection for our safety studies, we believe the vaccine is well suited for intranasal delivery making home therapy possible (as with sublingual drops).

3.5 LAMP-vax Allergy Vaccines In Development

JRC LAMP-vax is the Company's first allergy vaccine targeting Japanese red cedar which is a highly problematic allergenic pollen in Japan with over 25 million affected. This vaccine has been designed and validated. Animal studies to show immuno-reactivity are currently underway. ITI is seeking a **corporate** partner to develop this vaccine in Japan under favorable terms. In Texas, antigens of Japanese red cedar (Cry J1 / J2) induce occupational allergic asthma in saw mill employees providing a orphan drug populations of patients available for immediate clinical study of allergens that are directly relevant to the patients in Japan. ITI is now preparing to submit a pre-IND meeting request for occupational allergic asthma to conduct a Phase I safety study in workers in Texas saw mills processing cedar trees and to file an Orphan Drug Designation, both of which could be transferred to potential Japanese partner. The cedar allergen found in the saw mills shares allergic epitopes with Japanese red cedar, the target of our vaccine formulation.

Multivalent LAMP-vax is the Company's allergy vaccine targeting conifer/ tree pollens & short ragweed / weed pollens for development as multivalent formulations and is intended for the North American and European markets. These vaccines will be used as a model for the FDA and is intended to develop a second generation of formulations of a single vaccine targeted against grasses, weeds and trees. Such a vaccine (containing multiple plasmids with different allergens) will ultimately address all of the major outdoor allergies in a single therapy regimen.

4.0 Market Opportunity

ITI believes its technology can be a market driver in that a single DNA LAMP-based vaccine can incorporate multiple allergen targets given the FDA's acceptance that DNA vaccines can be composed of up to six plasmids in a single product. This broadens the commercial potential for the technology and the product family. The Company sees the LAMP technology as complementary to ongoing vaccine commercial initiatives.

As evidenced by Pfizer's purchase of PowderMed in 2006, pharmaceutical companies are making a stronger push into field of vaccine development. A confluence of events, including the concern about pandemic flu, the threat of bioterrorism, and worries about seasonal flu, have created an opportunity for those companies that can access new technology to rapidly produce vaccines in large quantities. Partly as a result of the improved understanding of immune-system function, the field is undergoing a renaissance, whereby the development of the prophylactic vaccine is giving way to vaccines that can treat previously untreatable infectious diseases, cancer, allergy, influenza and the like. Internationally, strategic players and financial backers are following this trend. In 2006, Danish allergy vaccine company ALK-Abello introduced a tablet vaccine in Germany for grass pollen allergy. Other Danish companies are focusing on vaccines against smallpox, HIV, breast, prostate and other cancers, and TB.¹

At the same time, investors are betting that biotech startups will foster the next great advances in the field. For example, Kleiner Perkins Caufield & Byers' new pandemic and biodefense fund invested \$6 million in Juvaris BioTherapeutics, targeted to the company's influenza vaccine development. Clarus Ventures led a \$35.7M first round investment in seasonal and pandemic influenza vaccine developer Variation Biotechnologies of Ottawa, Canada. New Leaf Venture Partners led a \$40M third-round financing for Cranbury, New Jersey vaccine manufacturer Vaxinnate.²

Vaccines represent an estimated \$15 billion annual revenues in 2007 (Company reports) and include candidates for infectious diseases, such as measles, mumps, rubella, diphtheria, pertussis, varicella, Haemophilus influenza type b, polio, hepatitis A and B, meningitis and relatively new to the pediatric market, rotavirus and pneumococcal disease. New global health threats such as the bird flu and pandemic flu plus concerns over bioterrorism agents (e.g., anthrax), have brought increased energies, funds, and new players into the vaccine marketplace.

Currently marketed products are prophylactic vaccines designed with antigen-bearing constructs for stimulating the body's immune system to mount a response to a specific antigen. In recent years, new techniques have enabled the industry to create recombinant proteins as specific antigens or couple traditional antigens with novel immunostimulants (adjuvants).

4.1 Allergy Vaccine Market and Competition

Over 150 million individuals are affected by allergic rhinitis in the U.S. and Europe, driving a large pharmaceutical market for anti-histamines and related drugs. However, there is an emerging demand and opportunity to provide a more long term solution to allergy through treatment with vaccines. Approaches to create tolerance (desensitization) to an allergen have traditionally required a lengthy course of therapy, requiring multiple and weekly or bi-weekly shots over a period of one or two years. Successful results are not guaranteed.

World-wide market leader for immunotherapy (desensitizing allergy shots) is Denmark-based AKL-Abello with 2007 revenues of \$320 million. The company's history dates back to 1923 when the first allergen extracts were produced in a pharmacy at the Copenhagen University Hospital. In the early 1990's, AKL-Abello was the first

¹ Breakthrough for Danish vaccine companies, Copenhagen Capacity, June 12, 2006

² Brian Gormley, Vaccine market draws venture capital interest, International Herald Tribune, January 17, 2007

company to launch a sublingual immunotherapy [under-the-tongue drops] in a single dose container. By the end of 2007, the company had over 40 different allergen types and mixes including different strains of pollen and dust mites. This administration allows patients to treat themselves to avoid doctor visits. The company made history in 2006 when it launched the first registered (in ECM) allergy tablet to address grass pollen allergy (GRAZAX™). The GRAZAX tablet is a fast dissolving, once a day immunotherapy for home treatment. The company has an extensive pipeline with products in tablet form for asthma, grass pollen, ragweed hayfever, tree pollen (birch), and dust mites in various phases of clinical trials in the US for both children and adults; and it continues to develop products for subcutaneous administration. The company prides itself as the technical leader in the immunotherapy field with basic research and scientific publications a significant corporate effort. AKL-Abello is publicly traded in Denmark and is profitable (pre-tax EBT \$50 million) (company reports).

Stallergenes was created within the Institute Merieux in 1962, subsequently merged with the allergy division of the Institute Pasteur. Today, it is public and listed on the Eurolist, with annual revenues for 2007 were \$231 million. Although it sells globally, about 50% of its business is in France with most of its remaining business in the ECM. Close behind AKL-Abello in product innovation, Stallergenes launched sublingual allergen administration in 1994 and has a number of clinical studies ongoing for allergy immunotherapy in tablet form for grasses, dust mites and birch pollen (company reports).

Trailing these two market leaders is Allergy Therapeutics (UK), a public UK-based company that had 2007 product revenues of about \$50 million. The company originates from the CL Bencard Foundation, a specialty allergy company, bought by the Beecham Group in 1949. With vaccines for grass pollen and ragweed allergies marketed for the UK and Canadian markets in 1972 and 1975 respectively, the company launched a sublingual allergy desensitizing vaccine in 1994. In 1998, Allergy Therapeutics was created via a management buyout from SmithKline Beecham. In mid-2007, the company's Phase III study for grass was placed on clinical hold by the FDA due to a rare adverse event. This clinical hold has compromised the company's progress for a ragweed allergy product for the US market as well. Allergy Therapeutics is developing a vaccine for Japanese Cedar, the product is in pre-clinical phase. (company reports)

Curologic is a Phase II development company based in Denmark which in-licenses projects for further advancement. In early 2008, the company announced that it will cease its development of oral immunotherapy projects internally. In late December 2007, the company had announced the results of its Phase III ragweed allergy study which showed that the dose tested was not efficacious. And after a thorough assessment of those data and the results of other studies in grass and house dust mite allergies which utilized the same technological approach, the company decided to stop developing the product line. The company's future plans are unclear.

Cytos, based in Switzerland, is commercializing the Immunodrug™ therapeutic vaccine platform, technology based on synthetic immunostimulatory DNA sequences targeting dendritic cells. The company has two allergy products in Phase II studies, vaccines house dust mite and cat allergy. The Immunodrug™ technical approach is not dissimilar from ITI's as the Immunodrug is designed to shift the immune system to produce a non-allergic immune response to an allergen. The company's other immunotherapies include treatment for malignant melanoma, nicotine addiction (now partnered with Novartis), and hypertension. Cytos is publicly traded and has no product revenues.

Cytos Biotechnology's CYT003-QbG10 is an immunotherapeutic product candidate currently in development for the treatment of allergic diseases. This allergy product has previously shown strong efficacy in conjunction with

a specific allergen in patients with house dust mite allergy. The vaccine uses an empty virus filled with DNA and attached to a protein from the dust mite excrement in order to trigger a response from the immune system. This boosts the activity of the immune system which tries to suppress that allergic reaction.

Recent trials have suggested that CYT003-QbG10 might work as a general allergy therapy. The therapy works by distracting the overactive immune system which is thought to be the cause of most allergic reactions. Patients receive a molecular "decoy" which makes their body behave as if it is under attack by a bacterium. Distracted, it stops reacting to otherwise harmless allergens. The company recently announced that 80 volunteers with either house dust mite or cat dander allergy who received a six-shot course of CYT003-QbG10 had experienced a 61 per cent reduction in symptoms, twice that seen in volunteers who received a placebo. Cytos will now start a trial of the mono-therapy in 300 people with dust-mite allergy later this year and another trial in people with hay fever next year. Still, larger studies are needed to determine the long-term effectiveness and safety of the series of shots.

Dynavax Technologies Corporation is a biopharmaceutical company that discovers, develops and focuses on commercializing Toll-like Receptor 9 (TLR9) agonist-based products to treat and prevent infectious diseases, allergies, cancer and chronic inflammatory diseases using approaches that alter immune system responses. Dynavax's TLR9 agonists are based on immuno-stimulatory sequences (ISS), which are short deoxyribonucleic acid (DNA) sequences that enhance the ability of the immune system to fight disease and control chronic inflammation. The Company's product candidates include TOLAMBA, a ragweed allergy therapy and HEPLISAV, a hepatitis B vaccine. Dynavax is also engaged in programs to develop an influenza vaccine.

Recently, TOLAMBA was shown to fail in clinical trials and will no longer be funded. Consistent with the results of earlier trials, TOLAMBA showed a trend toward a reduction of the symptoms of ragweed allergic individuals relative to placebo, although statistical significance was not achieved. The current trial displayed an unexpectedly high degree of variability in the data set possibly due to the subjective nature of symptom scoring used to assess efficacy. A similar effect was observed in previous TOLAMBA clinical trials. It was concluded that this problem may be difficult to overcome in future clinical studies. It is still uncertain as to whether Dynavax will continue with the development of their peanut and cat allergy therapies.

Dynavax's TOLAMBA anti-allergy vaccine is based on immuno-stimulatory DNA sequences linked to the major allergen of ragweed. In this technical approach, the vaccine attempts to inhibit and suppress the immune response responsibility for the inflammation associated with an allergic response. This product failed to achieve its primary clinical endpoint in a 2006 Phase II study; today this product is partnered with Deerfield Management in a second ragweed Phase II study. Data from this current study is expected in mid-2008. This vaccine is positioned to be administered in conjunction with conventional allergy shots or using prescription or OTC medications. The company has peanut and cat allergy vaccine in pre-clinical development. The company is publicly traded (Nasdaq:DVAX) and has development partnerships with Merck and AstraZenca and has no product sales.

5.0 Clinical Strategy & Development

Overview

ITI has developed a DNA-LAMP based vaccine to the major allergens of Japanese Red Cedar CryJ1 (cross reactive with Mountain Cedar, Jun a1), & Cry J2, as a model program to establish in a clinical program immunogenicity, vaccination dose, dosing regimen and anamnestic response characteristics for DNA-LAMP base vaccines. ITI has recently executed a cGMP manufacturing agreement, organized animal safety studies and will file an Investigational new Drug (Biologic) application [IND] by September 2011. The Phase Ia study will assess the safety and immunoglobulin (IgG & IgE) responses to two doses of the DNA vaccine (4-6 immunizations) in 24 -36 adults (16-50 years) with demonstrable allergic rhinoconjunctivitis symptoms by their assessing the allergic reactions of immunized patients in an Allergen Challenge Chamber (ACC) post vaccination.

ITI will recruit Japanese expatriates, who naturally acquired sensitivity to Cry J1/J2 in Japan, where the incidence of allergy to Cry J1/J2 is 50-60%. At the conclusion of the 3-4 month Phase Ia, the patients will be rolled over into a long term follow-up (9-12 months) Phase Ib protocol to assess IgG levels over time, then revaccinated when these levels fall 40-50% from their peak and allergic symptoms to Cry J1/J2 assessed in the ACC chambers. ITI will seeks a Japanese pharmaceutical partner for the subsequent Phase III pivotal studies in Japan and US for FDA licensure of the vaccine for an Orphan Drug indication in adults and children; children will be assessed in a separate subsequent clinical study.

ITI believes that it can demonstrate the clinical utility of DNA-LAMP-allergen vaccines and address FDA's potential regulatory issues using the Cry J1/J2 model. Many of the R & D, manufacturing, preclinical and clinical issues addressed in the Cry J1/J2 model are directly applicable to development of other DNA-LAMP-allergen vaccines. The Development Phase of Cry J1/J2 vaccine as outlined below is now ongoing to generate sufficient research data to support the therapeutic rationale. ITI is now executing Agreements with a contract manufacturing to produce cGMP compliant product and negotiating with several Contract Laboratory Organizations to perform the two animal safety studies requested by FDA/CBER during its prior March 10, 2009 Pre-IND interaction. In the clinical area, ITI has developed a focused Phase Ia & Ib clinical protocol with its Medical Director, Dr. Larry Weiner, an immunologist-allergist with a substantial allergy practice. ITI is exploring the use of the Allergen Challenge Chamber, which is acceptable by FDA and EMEA, to generate supporting data to design a Phase III pivotal study protocol: dose, dosing regimen, anamnestic booster immunizations; the FDA/NIH has held two meetings exploring the utility of using Allergen Challenge Chambers to conduct Phase III pivotal studies:

- a. ITI is now negotiating with several Contract Laboratory Organizations to finalize the animal safety testing protocols that would supported the clinical studies protocol.
- b. ITI anticipates receiving a sufficient quantity of its investigational DNA-LAMP-allergen from its contract manufacturer by mid-June in order to begin dosing animals in July to meet the timetable for the end of year submission of IND. ITI is scheduling the production of the cGMP material from its contract manufacturer to use in clinical studies to be initiated in the 1st Quarter of 2011.

- c. ITI anticipates filing an IND application in the first quarter of 2011 to support patient recruitment and evaluation of the environmental chamber. This study is planned to begin in March 2011. The IND to support testing JRC-LAMP-vax is expected to be filed in July / August 2011 and the study to begin in September / October 2011. (Note: ITI has yet to complete its evaluation of the environmental chamber study approach. The Company may determine this additional expense is unnecessary for a Phase I study).

5.1 Product Rationale

ITI has chosen to use the CryJ2, a polygalacturonase molecule, [*Cryptomeria japonica*], which has a sequence identity with Cha o 2 from Japanese Red Cedar trees and is considered to be the major allergen for its initial safety evaluation. ITI recognizes that the United States market for Japanese Red Cedar vaccine is quite limited and it is likely to be viewed by FDA as an orphan disease [<200,000 patients per year], but there is another population of Japanese expatriates, who were sensitized during their prior life in Japan. The CryJ2 confers cross-allergenicity among Taxodiaceae and Cupressaceae, as well a 40% identity with the polygalacturonase from tomatoes, which may provide ITI with additional clinical intended uses to extend the US market for a FDA licensed CryJ2 or a Cry J1/J2 vaccine. Following Phase I safety studies, Cry J1 allergen, a pectate lyase with cross reactivity to Mountain Cedar allergen Jun a1, will be incorporated into the vaccine formulation in a 1:1 ratio with Cry J2, creating the complete JRC-LAMP-vax formulation. ITI believes that after completion of Phase Ia & Ib, it will be able to license the Cry J1/J2 DNA-LAMP vaccine to a Japanese partner, who will fund further clinical development. ITI intends to retain the intellectual property rights to pursue FDA licensure in the US for the Cry J1/J2 vaccine, using both clinical data from a US site and from Japanese clinical Phase III data; ITI has the CryJ1 DNA-LAMP construct available to include in any licensing deal.

ITI is interested, based on the demonstration of the DNA-LAMP-Cry J1/J2 vaccine response, to develop a multivalent DNA-LAMP vaccine that uses 4-5 plasmid vectors in one product, each containing 1-2 allergens, in partnership with a partner. Greer Laboratories, which has expressed an interest in such a vaccine for Oak, Birch, Cedar/Juniper, Ash & Elm trees. This product rationale is possible because FDA has allowed the use of 4-5 plasmids, containing different antigens, to be testing as a single product, substantially reducing preclinical and clinical testing costs, initiating plasmid development by 4th quarter of 2010 and entering Phase Ia & Ib clinicals within 9-12 months. ITI would develop separate adult and pediatric multivalent conifer vaccine products.

5.2 Clinical Formulations

Japanese Red Cedar (Cry J1/J2) vaccine: a dual DNA plasmid containing a LAMP nucleotide sequence linked to a CryJ1 or Cry J2 nucleotide sequence vaccine to treat sensitive adults and children.

- Adult vaccine BLA licensure – Dec. 2015
- Pediatric BLA licensure – Oct. 2015

Conifer: Oak, Birch, Cedar/Juniper, Ash & Elm vaccine: a mixture of 4-5 plasmids each containing 1-2 allergen nucleotide sequences linked to a LAMP nucleotide sequence to treat sensitive adults and children.

- Adult vaccine BLA licensure – April 2016
- Pediatric vaccine BLA licensure – Dec. 2016

5.3 Project Milestones

Milestone	Completion
<i>Japanese Red Cedar/Mountain Cedar</i>	
Development/validation of plasmid vaccine constructs	completed
Investigational Product Manufacturing under cGMPs	completed
Phase II Manufacture of Cry J1 Plasmid Under cGMP	Production to begin following Phase Ia; Cry J1/J2 formulation to be ready for Phase II
Preclinical Safety Testing 85 day Toxicology & Biodistribution	Testing completed. Final report due in August 2011
Clinical Development Phase Ia *	IND to be submitted Aug/Sep 2011 & clinical study initiated Oct / Nov 2011
Clinical Development Phase Ib	Rollover protocol to be initiated Q2 2012
Regulatory Development Orphan Drug Designation Application for CryJ1/J2 sensitivity	In progress with Orphan Drug Designation to be submitted in 2012 / 2013
Phase 3 pivotal Study to be undertaken with Japanese partner (Japanese & US sites)	January 2013-July 2014
Biological License Application (BLA) Submission	Dec. 2014 targeted
Expected FDA Licensure	Dec. 2015

Milestone	Completion
Multivalent DNA Conifer Vaccine	
Development & Validation of all five (5) plasmid [Stage 1 – R & D)	Initiation Sept. 2011 – completion by Feb. 2012 for Pre-IND Meeting with FDA/CBER
Stage 2 - implementation	
cGMP manufacturing	Mar. 2012 >> July 2012
preclinical safety studies	June 2012 >> Dec. 2012
IND Preparation & Submission	Oct. 2012 >> Jan. 2013
Phase Ia & Ib clinical studies *	Mar. 2013 >> June 2014
Phase 3 pivotal study	Sept. 2014 >> Sept. 2016
Biological License Application (BLA) Submission	Sept. - Dec. 2016
Expected FDA Approval	June – Sept. 2017

** The strategy assumption is that ITI will be able to demonstrate some indication that elevated IgG ant-Cry J1/J2 antibodies have some therapeutic effect during the Phase Ia using the Allergen Challenge Chamber, but realize that the success of the strategy is predicated on validating that pollen challenges of sensitized patients in such chambers is a creditable indicators of potential benefit. If the Chambers cannot be validate then a Phase II will have to be performed, increasing time and costs.*

5.4 Detailed Clinical Activities and Timelines

Development of Investigational Product [Completed]:

Time Estimate: 3-5 months

- a. Research & Development of rationale for product. [Completed]
- b. Construction of Plasmid Vector [Completed]
 - i. Choice of plasmid vector backbone (in-licensed vector) [Completed]
 - ii. Choice of allergen nucleotide sequence [Completed]
 1. Public domain [Completed]
 - iii. Gene sequences are optimized using software and synthesized, then cloned into chosen plasmid vector backbone [Completed]

- c. Small scale expression and purification of plasmid construct with LAMP and allergen sequence **[Completed]**
- d. Validation of DNA-LAMP-allergen expression
 - i. **In vitro expression validation by transient transfection** of cell line **[Completed]**
 - ii. In vivo validation (mouse model primary immunization with secondary boost) **[Completed]**
 - 1. **prophylactic model:**
 - antibody expression (comparing plasmid control, plasmid pLAMP control and plasmid-LAMP-allergen investigational product) **[Completed]**
 - gross toxicity assessment **[Completed]**
 - 2. **therapeutic model:**
 - sensitization of mice by SC, followed by vaccination of cohorts with controls and investigational product **[Completed]**
 - ELISA antibody determination of IgG1, IgG2a, & IgE **[Completed]**
 - iii. **In Vitro cytokine Profile:** Mouse model expression of recombinant Allergen induced IL-4, IL-5 & IFN- γ performed by ELISA (Th1 biomarkers) **[Completed]**
 - iv. **Anaphylactic IgE Rat Basophil Degranulation (RBL) Assay:** Rat cell cultures in vitro, desensitized with immune mouse sera, then challenged with Allergen **[Ongoing]**
 - v. **Anaphylactic IgG by Passive Cutaneous Anaphylaxis (PCA)** using immune mouse sera to sensitize naïve mice, then challenging with recombinant Allergen. **[Ongoing]**
 - vi. Development and validation of PCR assays for plasmid-LAMP-allergen detection for use in preclinical biodistribution study **[Completed]**
 - vii. Detection of LAMP nucleotide sequence **[Completed]**
 - viii. Detection of Allergen nucleotide sequence **[Completed]**
 - ix. Detection of Plasmid vector nucleotide sequence **[Completed]**
 - x. Development of immunoassay for detection of specific anti-allergen IgG antibodies induced by vaccine in animal model **[Completed]**
 - xi. First preference given to using established RAST or explore use of the Phadia ImmunCAP InvitroSight system **[Ongoing]**
 - xii. ITI has also obtained several plasmid constructs from its vector manufacturer to use as controls in the above research experiments:
 - 1. Plasmid alone
 - 2. Plasmid – LAMP

Investigational Product Manufacturing under cGMP [Completed]

Time Estimate: 5-6 month

- a. Contract manufacturing – 2 grams of one plasmid vector (DNA-LAMP-CryJ 2). **[Completed]**

- b. ITI will execute an agreement with a cGMP vendor by the end of May that can supply pilot batches before the end of June in animal safety studies and the clinical batches by September/October. **[Completed]**

Preclinical Testing [Completed]

Time Estimate: 5-6 month

- a. FDA stated in their Pre-IND responses to ITI that “...toxicity testing of two DNA plasmids may support the use of a single plasmid in humans, ...” March 10, 2008. In a prior Pre-IND response for a 3-4 plasmid anti-HIV product, FDA gave the same response. The ITI proof-of-concept study will use the major allergen of Japanese Red Cedar(Cry J1/J2); however, it has also developed a DNA-LAMP-CryJ1 plasmid for future studies and can license both to any Japanese partner.
- b. 85 day **General Toxicology Study** using multiple 4-6 dose regimen in Rabbits (protocol developed and would be performed by contract laboratory organization), study would run concurrently with biodistribution study protocol.
- c. **Biodistribution Study** in Rabbits 1 dose with distribution in tissues assessed at 3 time points to look at presence of the plasmid vector in cells of target tissues verse clearance 7, 30 & 90 days, after immunization with a single dose.
- d. ITI plans to avail itself of an offer from FDA/CBER to have an **informal dialogue** to confirm the design of the 85 day toxicology and biodistribution studies, before initiating these studies in July.
- e. ITI has proposal from several contract laboratory vendors and will be finalizing a relationship with one of them, then using the draft protocol to informally confirm with FDA the acceptability of the two animal protocols *before* initiating the studies.

Clinical Development Phase Ia

Time Estimate: 4 months

- a. Phase Ia - Safety & Immune titer in patients sensitivity to Cry J1/J2 allergen.
 - i. 24-36 patients with moderate to severe allergen reactivity ages from 16 to 50 years
 - ii. 2 treatment cohorts - 2 mg v 4 mg dose. It is likely that the 4 mg dose cohort will reach its maximum IgG anti-Cry J1/J2 antibody titer levels, before the cohort receiving 2 mg doses.
 - iii. Recruit 24-36 US resident Japanese expatriates and sensitized US patients
 - iv. 4-6 doses at 7-14 day intervals between doses
 - v. Endpoints for Phase Ia
 - vi. Safety – General Safety criteria
 - vii. IgG (O day, then prior to each of the subsequent 3-5 immunizations, then 60 & 90 days)
 - viii. Total
 - ix. Specific anti-Cry J1/J2 IgG antibodies [assay to be developed]
 - x. IgG subtypes (IgG1, IgG2, IgG3 & IgG4)

- xi. IgE (O day, then prior to each of the 4-6 immunizations, then 60 & 90 days)
 - xii. Total
 - xiii. Specific anti-Cry J1/J2 IgE antibodies [assay to be developed]
 - xiv. Clinical symptoms evaluation using validated clinical questionnaires
 - xv. Nasal
 - xvi. Non-nasal
 - xvii. Phase Ib – patients in Phase Ia would be rolled over to a longer term follow-up protocol so that a final report can be written for the Phase Ia and submitted to FDA to support the protocol design for a Phase III.
- b. Allergen Challenge Chamber Time Estimate: 3-4 **(optional)**
- i. ITI understands this it will have to validate the use of such chambers to establish pollen exposure levels and that it can quantify allergic responses induce in the chamber.
 - 1. 3-4 consecutive days allergen exposure (@3 hours) to prime allergic patients before immunization for maximum baseline sensitivity level
 - 2. 1-2 consecutive days (@ 3 hours) Cry J1/J2 exposure to assess clinical responses 14-30 days after completion of dosing regimen.
 - 3. ITI and Dr. Larry Weiner will be meeting in June with a principle investigator who has used Allergen Challenge Chambers extensively and will try and further refine a clinical protocol design

Clinical Development Phase Ib

Time Estimate 9-12 months

- a. Phase Ib Rollover Safety & Booster Study.
 - i. Once patients have been tested 60-90 days after initial immunization, they would be rolled-over to a follow-up study to continue monitoring for an additional 5-6 months to assess:
 - 1. General safety monitoring Clinical symptoms and Anti-LAMP antibodies
 - 2. Immune Response
 - a. Titer of specific anti-Cry J1/J2 IgG and IgE antibodies
 - a. Sera would be saved for future IgG subtype assessment
 - iii. Once patient specific anti-Cry J1/J2 IgG and IgE antibody titers fell below 50% of their titer after the primary immunization in Phase Ia, the patients would receive a booster dosing regimen (2 immunizations 14 days apart of 4 mg @).
 - ii. Patient follow-up monitoring for general safety & antibody levels for an additional 6 mo.
 - iii. ITI is considering making an assessment of patient sensitivity to Cry J1/J2 using the Allergen/Chamber Exposure, before the booster immunization and 14-21 days after the booster to assess clinical therapeutic benefit.

Regulatory Development

Time Estimate 3-5 months

- a. ITI had a Pre-IND meeting scheduled with FDA on March 10, 2009, and received written answers to all of its questions outlined in the ITI Briefing Package, prior to the scheduled date. Based on the adequacy of the answers received from FDA/CBER, ITI agreed to cancel the scheduled meeting provided it could talk further with the reviewers if it had specific questions.
- b. ITI is planning to discuss the draft preclinical protocols with the CBER toxicology reviewer before finalizing the contract with animal laboratory testing vendor selected to perform the two tests.
- c. ITI believes, based on scheduling of manufacturing and preclinical studies, that it will have all the necessary information and sufficient clinical supplies to file an Investigational New Drug (Biologic) application [IND] by early in the first quarter of 2011 and have authorization to proceed into clinical studies with Japanese Red Cedar DNA vaccine by November, 2011.
 - iv. ITI intends to use the piloted validation batches from its contract manufacturer available by June, to use in preclinical studies to commence animal dosing in early July.
 1. Samples of these pilot validation batches will be analytically compared to the final cGMP batches for use in the clinical study
 - v. ITI will be requesting each vendor provide a Master Drug (Biologic) File [DMF] to cross reference for the IND, or the actual documents to insert into the IND.
 - vi. The costs shown here also include the preparation of the Institutional Review Board (IRB) package including the draft Informed Consent document.
- d. ITI during the Phase Ia & Ib clinical trial period will seek to obtain an Orphan Drug Designation for the DNA-LAMP-Cry J1/J2 vaccine to treat patients sensitive to Japanese Red Cedar. One advantage with obtaining the Orphan Drug Designation is that it will obviate paying the FDA User Fee for a BLA application which is likely to be in excess of \$1,400,000 by 2014
- e. The US. Food & Drug Administration [FDA]/Center of Biological Evaluation & Research [CBER] and the European Medicines Evaluation Agency (EMA) have stated that the use of Allergen Challenge Chambers is an acceptable protocol vehicle for use in Phase II studies. They have not accepted them for use in pivotal Phase III Efficacy studies to support licensure. The two groups, who have Allergen Challenge Chambers with whom ITI is now negotiating have done extensive clinical testing of allergen sensitive patients to against weed, tree and other allergens, as well as assessed the therapeutic effects of drugs in lowering the levels of allergic sensitivity. ITI through the Cry J1/J2 vaccine program intends to develop a basis for using the chambers for assess clinical reactivity to each allergen within the multivalent vaccine.

5.5 Development of Multivalent DNA Allergy Vaccine for Conifers: Oak, Birch, Cedar/Juniper, Ash & Elm

- a. **Product Rationale:** The R & D development protocols, the manufacturing, preclinical and clinical data and experience gained with the Cry J1/J2s vaccine should provide a strong safety and efficacy basis for development of the multivalent DNA allergy vaccine for conifers. ITI

believes that many of the R & D models, manufacturing issues, preclinical protocol design and clinical protocol design experience with the Cry J1/J2 vaccine are directly relevant to the development of the multivalent conifer vaccine, especially the ability to demonstrate immunogenicity. There is also a growing literature in the DNA vaccine area and clinical study basis to support the potential safety and efficacy of multivalent DNA vaccines, especially ones using the same plasmid vector backbone. ITI believes that the development of the DNA Conifer vaccine will also provide a model for similar multivalent allergen vaccines: e.g., grasses, animal dander, house mites.

- b. Assuming that the nucleotide sequences for the major allergens are publically available, ITI could prepare plasmid vectors (Plasmid-LAMP-Tree Allergen) for each of the above listed major tree allergens as described in detail in Section A. If ITI has a partner for a multivalent DNA Conifer vaccine and there is agreement on what allergens to use, ITI will work with its partner to identify sources of each allergen nucleotide sequence.
- vii. If the size of the individual tree allergen nucleotide sequence is small, it may be possible to place two allergens on each major tree allergen plasmid
- viii. As described above Section A, each of the five tree DNA vaccine plasmids could be prepared and manufactured in research amounts and also then its immunologic performance validated individually [as described in Section A (d)].
- ix. The final product composed of the five (5) DNA LAMP-allergen plasmids would also be tested using the same validation methodology using the same *in vitro* and *in vivo* assays [as described in Section A (d)].
- b. It is suggested that once the research data as described in Section A is available that a substantive Pre-IND meeting be held with FDA before moving forward into cGMP manufacturing or preclinical studies. The regulatory risk is whether FDA/CBER would have any objections to a multivalent allergy vaccine composed of 5 plasmids with unrelated allergens? They have previously allowed multivalent DNA vaccines with multiple plasmids containing related antigens. The regulatory strategy is to generate the R & D data on the individual and multivalent DNA vaccine, then seek the pre-IND meeting with FDA and possibly EMEA, before proceeding into manufacturing, preclinical and clinical work.
- c. Projected Estimated Costs for the Multivalent DNA Conifer Vaccine:
 - i. **Research & Development Phase:** during this phase, ITI will make and test each of the five individual conifer vaccine plasmid constructs, as well as to test the multivalent conifer vaccine to develop sufficient information for a Pre-IND meeting to support the acceptability of a multivalent DNA vaccine. ITI believes that the preclinical and clinical development to support a Phase Ia/Ib using sensitive patients, will be equivalent to those requirements for Cry J1/J2.

Project Break Point – Have FDA Pre-IND Meeting to Validate Strategy and Requirements

- a. **Manufacturing cGMP of 5 plasmids for multivalent Conifer Vaccine:** ITI's strategy would be to have the minimum quantities manufactured sufficient to support the preclinical safety studies and for Phase Ia/Ib using a limited number of 30 -40 patients.
- b. **Preclinical Safety and Biodistribution Studies:** The projected costs would be quite similar to those for the single Cry J1/J2 DNA vaccine. This cost estimated is based on prior FDA statements that a 4-5 plasmid containing vaccine will be treated as a single product.
- c. **Clinical Development Protocol:** ITI will use the same clinical design that it used for the Cry J1/J2 DNA vaccine Phase Ia and Ib, but anticipates greater costs in screening patients for the inclusion criteria and also increased costs regarding use of Allergen Challenge Chambers for screening for the sensitivity levels to each of the five tree allergens in the 30 - 40 patients.

Appendix 1

Immunomic Therapeutics Key Personnel

William Hearl, Ph.D., President & CEO

Dr. William Hearl, the founder of ITI, is an experienced and successful scientific businessman and entrepreneur. He worked closely with Dr. Tom August, Capital Genomix and Johns Hopkins University to capture the LAMP technology for ITI and start operations in 2006. His extensive experience in intellectual property management and business development led to the speedy sub-license of the LAMP technology to Geron within 30 days of initiating operations.

Dr. Hearl is also the founder of Capital Genomix (CGI), a Maryland-based biomarker and drug discovery company and served as its first CEO from inception in 2000 until late 2002 when he assumed the role of Chief Scientific Officer. Dr. Hearl raised seed and Series A & B funding for CGI (~\$5 million in cash/debt) and acquired the Dynex Technologies division of Thermo in a leverage acquisition deal. (Dynex was subsequently divested yielding a 10-fold return to the Company). He is also responsible for the acquisition and development of the core technologies of Capital Genomix: GeneSystem320 was licensed exclusively from MD Anderson Cancer Center and the ImmunoMouse was invented by Dr. Hearl.

He also has an established record of scientific productivity over his 20 years of work in the biotech industry. He started his career as a bench scientist at Electro-Nucleonics and developed blood based diagnostics for HIV, HTLV-I and Hepatitis C. He later worked at Life Technologies (LTI, now Invitrogen) and directed the Immunodetection Group. His lab developed a number of innovative antibody based detection kits and reagents. He moved into scientific management when he became the Director of R&D at Kirkegaard & Perry Laboratories in 1994. Dr. Hearl has a Ph.D. in biochemistry from the University of Tennessee (Oak Ridge, Knoxville) and a B.S. from East Tennessee State University

W. Barry McDonald, Vice President, Business Development, Chairman of the Board

In over 30 years in healthcare, Mr. McDonald has held executive management positions with U.S., European and Japanese health care companies which include venture-funded start-ups, mid-size independent companies and subsidiaries of international health care conglomerates. His experience encompasses a broad range of human diagnostics and biotechnology products, services and markets worldwide. Among his management experiences and capabilities are general management skills, acquisition, divestiture, corporate alliance expertise, technology assessments, strategic planning, and development of supply chain delivery and service networks to global health care

Prior to joining The Sage Group, Mr. McDonald was President and CEO of MAST/Hitachi and simultaneously headed an executive staff within Hitachi Chemical corporate, which was responsible for new technology assessments, acquisitions, and business development activities for Hitachi Chemical's life sciences business worldwide. Previously, he was with Hycor Biomedical, as Senior Vice-President of Sales, Marketing and Business Development, where he was instrumental in establishing a new strategic direction for the company, and developing its global distribution network and in acquiring two companies, which expanded Hycor's business globally. Mr. McDonald's entrepreneurial experience was gained as President and CEO of Photest Diagnostics, a company concentrating on novel, homogeneous fluorescent immunoassays for the point-of-care (POC) market. As a venture capital backed emerging company, he was responsible for the turnaround in Photest, commercialization of its technology, and its ultimate sale to a European corporation.

Mr. McDonald's technical and scientific competencies were developed through academic degree programs and medical school experiences. His broad health care business expertise has been augmented through participation

in international strategic management schools in France, Japan, and in the United States at Wharton Business School and Columbia University. Mr. McDonald's academic experiences include an M.D./Ph.D. program at the University of Kentucky, Albert Chandler Medical School, an M.S. in Microbiology and Genetics and a B.S. in Biochemistry and pre-med from The University of Southern Mississippi.

Bruce F. Mackler, Ph.D., J.D., Vice President, Regulatory Affairs & Development

Dr. Mackler's 27 years of FDA legal/regulatory experience in biomedical products includes biologics, drugs, medical and in vitro diagnostic devices, manufactured by traditional and biotechnology processes (recombinant proteins, genomics, allergens, active and passive vaccines, cell and gene therapy). Dr. Mackler has advised financial groups on integrated FDA, technical and business issues, when performing due diligence assessments on biomedical opportunities prior to their making initial investments and during bridging. These due diligence activities integrate his business acumen from working in sales/manufacturing in a family textile business, owning and managing several bioservice businesses and being an university/NIH researcher for 15 years, prior to his 27 years in a FDA legal/regulatory practice with premier law firms. He has founded biomedical companies, established and implemented their regulatory strategies and also assisted in securing early stage funding.

Dr. Mackler has a Ph.D. and M.S. in the area of Immunology/Microbiology and has authored more than 100 published scientific papers and abstracts in immunology, immunopathology, allergy and diseases, as well as numerous additional articles and briefing papers on FDA and FDA-related legal and regulatory issues. Dr. Mackler has advised clients and venture capital groups on FDA regulatory approval strategies for their portfolio companies, regulatory/quality problems regarding establishing manufacturing facilities and how to effectively initiate product development and interact with FDA. Dr. Mackler has experience drafting and evaluating numerous FDA regulatory documents (e.g., INDs/NDAs, DMFs, and BLAs, Accelerated and Fast Track Approvals, Orphan Drug Designation applications. He has, as a U.S. agent, held IDEs/INDs and secured Treatment-INDs with substantial cost reimbursement, and has written successful Orphan Drug Development/SBIR grants and Designation applications; therefore, he is familiar with the nuances of these regulatory procedures. Dr. Mackler received his J.D. from the South Texas College of Law (magna cum laude, 1979), his Ph.D. (Immunology/Microbiology) from the University of Oregon Medical School (1970), his M.S. (Immunology/Microbiology) from the Pennsylvania State University (1965), and his B.A. (Biology) from Temple University (1964).

Teri Jones Heiland, Ph.D., Vice President, Research & Development

Dr. Heiland is currently the Vice President of Research and Development at ITI and was one of the founding employees of the Company. Dr. Heiland is an experienced molecular biologist and holds multiple patents in the field of genomics. Prior to assuming the post as Vice President at ITI, Dr. Heiland led multiple research teams at Capital Genomix developing and validating GeneSystem320 and applying this technology to identify biomarkers associated with cancer. She has also worked closely with the development of the ImmunoMouse and is an expert in molecular biology and genomic analysis. Prior to joining Capital Genomix, Dr. Heiland worked as a senior scientist in R&D at Kirkegaard & Perry Labs (KPL) where she spent four years as a project leader on development and commercialization of six major kits and she was responsible for the utilization of GS320 with both cytokine and HIV model systems. She has facilitated the optimization of the GS320 assay and has been involved in work involving eukaryotic gene regulation since 1989. She has expertise in the fields of signal transduction, amphibian development, and gene regulation. Dr. Heiland is primary author on a number of publications that utilized extensive work with mRNA and cDNA and assays such as RT-PCR, RNase Protection Assays, Northern Blotting, and library cloning and screening. Dr. Heiland obtained her Ph.D. in molecular biology at the University of Missouri-Columbia in 1993. Dr Heiland also currently has an appointment at Johns Hopkins University as a Visiting Scientist.

Appendix 2

Selected References on LAMP

Title	Ref	Comment
Intramuscular immunization with DNA construct containing Der p 2 and signal peptide sequences primed strong IgE production	Vaccine 2006	Chua demonstrates that DNA vaccine containing LAMP drives immune response to IgG / antigen rather than IgE / allergen
HIV-1 p55Gag Encoded in the Lysosome-associated Membrane Protein-1 as a DNA Plasmid Vaccine Chimera Is Highly Expressed, Traffics to the Major Histocompatibility Class II Compartment, and Elicits Enhanced Immune Responses	J. Biol. Chem. Vol. 278, No. 39, 37926–37936, 2003	Paper from August Lab showing the importance of including the luminal domain of LAMP – the preferred plasmid construct for LAMP vaccines
Dendritic Cell-Lysosomal-Associated Membrane Protein (LAMP) and LAMP-1-HIV-1 Gag Chimeras Have Distinct Cellular Trafficking Pathways and Prime T and B Cell Responses to a Diverse Repertoire of Epitopes	J. Immunology 2006	Compares response to DC-LAMP with LAMP-1 and expands on role of luminal domain
Telomerase mRNA-Transfected Dendritic Cells Stimulate Antigen-Specific CD8 and CD4 T Cell Responses in Patients with Metastatic Prostate Cancer	J Immunology 2005	Clinical study showing the value of the LAMP targeting sequence in Prostate Cancer Patients
Robust CD4+ and CD8+ T cell responses to SIV using mRNA-transfected DC expressing autologous viral Ag	Eur. J. Immunol. 2007. 37:1	Further work from the lab of Eli Gilboa showing importance of LAMP targeting sequence
DNA Encoding an HIV-1 Gag/Human Lysosome-Associated Membrane Protein-1 Chimera Elicits a Broad Cellular and Humoral Immune Response in Rhesus Macaques	PLOSone 2006	August & Marques demonstrate the use of LAMP vaccines in monkeys
Expansion of HIV-specific CD4 ₊ and CD8 ₊ T cells by dendritic cells transfected with mRNA encoding cytoplasm- or lysosome-targeted Nef	Blood, 1 March 2006 Volume 107, Number 5	Kavanagh continues his work with HIV and LAMP vectors. He pursues doses HIV patients with LAMP-nef mRNA into DC's
West Nile pre-membrane-envelope genetic vaccine encoded as a chimera containing the transmembrane and cytoplasmic domains of a lysosome-associated membrane protein: increased cellular concentration of the transgene product, targeting to the MHC II compartment, and enhanced neutralizing antibody response	Virology 332 (2005) 66–77	Excellent study on the use of LAMP in formulating a preventive DNA vaccine against an infectious agent
Both antigen optimization and lysosomal targeting are required for enhanced anti-tumour protective immunity in a human papillomavirus E7-expressing animal tumour model	Immunology, 116, 255–266	Korean group shows value of LAMP vector in building HPV vaccine (Wu collaborator).

DNA vaccines for cervical cancer: from bench to bedside	Experimental & Molecular Medicine, Vol. 39, 679-689 2007	Review article summarizing progress towards a therapeutic DNA vaccine for cervical cancer. Comments on value of lysosomal targeting
Enhancing DNA Vaccine Potency by Combining a Strategy to Prolong Dendritic Cell Life and Intracellular Targeting Strategies with a Strategy to Boost CD4 T Cells	2007 Human Gene Therapy 18:1129–1139	Wu continues his work on a DNA vaccine for HPV. In this study he combines his MHC-I targeting with LAMP to improve CD8 activation
DNA Vaccination Can Break Immunological Tolerance to PrP in Wild-Type Mice and Attenuates Prion Disease after Intracerebral Challenge	Journal Of Virology, 2006, p. 9970–9976	Work showing LIMP (closely related to LAMP and covered by LAMP IP) is able to overcome tolerance to prions in BSE – like disease.