Immune Design’s differentiating strength rests in our ability to selectively modulate the immune response to create new treatment modalities.

Through our two proprietary technologies, both of which target human dendritic cells, we are developing novel therapeutics to treat cancer, chronic infectious diseases and allergic disorders.

Our most advanced product, and main focus of our company, is a potential breakthrough cancer vaccine slated for human clinical trials in 2013. This novel therapeutic combines elements of our two technologies and is expected to trigger a powerful and long lasting activation of cytotoxic T lymphocytes (CTLs), the most effective immune cells involved in eliminating tumors and chronic infections. A clear and successful proof of concept in the clinic will likely clear the path for rapid development and registration, in addition to opening an array of innovative cancer therapeutics stemming from our platform.

In addition to oncology, each individual technology also offers the potential to create best- or first-in-class therapeutics and preventative vaccines for infectious diseases and allergy. Some of these possibilities will likely be capitalized through current and future partnerships and collaborations with other Pharma and biotech companies.

**IMMUNE DESIGN TECHNOLOGIES**

The key to our breakthrough technologies came when the late Dr. R. Steinman (Nobel Prize in Medicine, 2011) discovered the dendritic cell in 1960 as the key to presenting antigens to immune cells such as CTLs. This discovery laid the foundation for novel technologies that trigger

A. activation of the dendritic cell
B. de novo production of anti-tumor or anti-infectious disease antigen specific CTLs
C. energizing of existing CTLs to more efficiently eradicate tumors or chronic infections
1. ID-LV

ID-LV is a novel, dendritic cell specific delivery vector that is optimally suited to deliver antigens in the form of DNA to human dendritic cells. Once it has entered the dendritic cell after parenteral injection, it transduces DCs and transcribes the antigen/s which are processed for antigen presentation leading to a de novo production of antigen specific CTLs. Engineered from scratch on a lentivirus backbone, this vector has unique properties not previously seen in other vectors that attempt to deliver antigens to the immune system:

Selective dendritic cell tropism
The main differentiating feature of ID-LV is that it is selective towards human dendritic cells in vivo. Its vector envelope is engineered to selectively bind and enter via the DC-SIGN receptor present in dendritic cells. All other existing vectors bind and enter a number of non-relevant cell types and are non-specific to dendritic cells. The lentivirus vector is uniquely suited to function in non-dividing cells such as dendritic cells.

Absence of pre-existing immunity
With little or no known pre-existing immunity to its envelope, ID-LV can be fully effective from its first administration. This is not the general case for vaccinia or adenovirus-based vectors.

Integration and replication defective
ID-LV has been engineered to avoid these functions and thus provide long-term safety benefits.

Versatility
ID-LV can deliver a number of antigens and other immunological relevant molecules to human dendritic cells in the form of DNA to modulate immune function.

2. TLR4 agonist

A synthetic small molecule Toll Receptor 4 agonist is also delivered to the skin and exerts three related functions.

- TLR4 activates dendritic cells by up-regulating key molecules for efficient antigen presentation, and produces cytokines of the Th1 type that enhance the immune response.
- It can reverse an abnormal Th2 immune response (allergy) to a Th1 type.
- When combined with a protein-based antigen, the TLR4 agonist triggers selective activation of antigen-specific CD4 T lymphocytes (which provide critical support and maintenance of antigen-specific CTLs) and B lymphocytes (which make antibodies against the same antigen). The latter is a key factor in the generation of more effective preventive vaccines against infectious diseases.
THE PRESENT AND FUTURE OF CANCER IMMUNOTHERAPY.

Current cancer therapies rely heavily on cytotoxic agents, radiation and “targeted” therapies, which in many cases may extend patient survival by only a few months and are accompanied by severe side effects.

Many past and present observations affirm our belief that manipulating the immune system to fight cancer has strong potential to become a better therapeutic alternative or valuable complement to traditional approaches for the following reasons:

1. Cancer patients in whom the tumors are infiltrated by immune cells, especially CTLs and/or in whom a CTL response against the tumor is detectable in their blood samples, have a better prognosis, compared to those patients that lack it.

2. Newer and more effective “targeted” agents against specific tumor mechanisms appear to be in part active via activation of CTLs.

3. The novel therapeutic modality termed “Adoptive T cell transfer” supports the therapeutic efficacy of CTLs. Extracting CD8 T lymphocytes from the blood of cancer patients and activating and directing them towards a cancer antigen in the laboratory with subsequent re-infusion to the patient, have resulted in impressive cancer remissions and thus, validated the key role of those CTLs as an effective cancer therapy.

4. Tumors evade the immune system, in part by producing immune suppressive molecules that can abrogate the effective generation and function of CTLs. Blockade of these suppressive mechanisms via new drugs allows pre-existing CTLs present in cancer patients to be more efficient in exerting their anti-tumor function, also resulting in impressive therapeutic effects in some cancers.

5. A first “cancer vaccine” (Provenge®) has been approved in the US for treating prostate cancer. It is a complicated process by which patient dendritic cells loaded with a prostate antigen are reintroduced to the patient in an effort to prolong patient survival. Whether this works via CTL is unclear.

All of the above clearly support the unique opportunity to modulate the immune system in a way that we can envision new, more effective cancer therapies. Moreover, they point to the CTL as the “drug” that mediates the tumor eradication. Importantly, and in contrast with traditional chemotherapy and radiation, many of the above approaches have been deemed extremely safe in comparison.

The goal of Immune Design is to translate these very positive observations into new immunological based therapies grounded on the most advanced scientific knowledge, that not just prolong patient survival but aim at safely eradicating the tumor in larger patient numbers.

IMMUNE DESIGN’S THERAPEUTIC CANCER VACCINE

Having identified the dendritic cell as the generator of CTLs, and these immune cells as the “drug” that will destroy the tumor, we have devised a therapeutic cancer vaccine product that focuses on generating the most effective and long-lasting pool of tumor-specific CTLs.

The goal of the ID-LV:

i. Generate “de novo” CTLs against the tumor antigen/s expressed by the vector, and obviously known to be expressed in the patient’s tumor

The goals of the TLR4 agonist:

i. Activate and mature dendritic cells while providing a Th1 cytokine environment

ii. Generate antigen-specific CD4 T lymphocytes that:
   a) When combined with the same antigen expressed in the ID-LV, will sustain the same tumor antigen-specific CTLs
   b) As a stand alone therapy, can sustain and expand pre-existing CTLs against the same tumor antigens

The potential sequential combination of these two proprietary, cutting-edge technologies (in the vaccine argot defined as heterologous prime-boost) reflect a scientific rationale that is validated in animal models, and is expected to avoid many of the shortcomings of previous attempts to produce cancer vaccines.

Moreover, by using antigen-specific CTLs as our surrogate marker of product concept efficacy, it allows for a faster and smoother product development plan.
PREVENTIVE AND THERAPEUTIC VACCINES FOR INFECTIOUS DISEASES

Prevention of infectious diseases through vaccines has been one of the biggest scientific advancements in the history of mankind. The protective immune response that a traditional vaccine elicits is based on the production of neutralizing antibodies directed to the external component of the invading pathogen.

However, to protect or treat in many infectious disease process requires a more potent and broad antibody response or the production and enhanced function of CTL’s against pathogens.

Therefore, there is an urgent need for new vaccines that are capable of performing two key functions:

1. Enhance and broaden the antibody response to the target and additional “drifted” strains
2. Trigger a cellular immune response such as CD4 T cells and CTLs in the case of intercellular pathogens

These goals can theoretically be achieved by accompanying the antigen/s with the newer “molecular” adjuvants. Immune Design’s synthetic TLR4 agonist fits those characteristics.

Current commercially available adjuvants include conventional ones such as alum-based salts, and in the EU, an oil and water emulsion. These are non-molecular entities and function as a formulation for the pathogen and antigen/s to enhance how specific activation of the immune system as determined by the antibody production. Their mechanism of action is poorly understood but is believed to enhance the antigen uptake by dendritic cells.

A newer adjuvant is now available in a number of successful preventive vaccines, MPL (GSK). This is a crude component of a bacterial cell wall known to activate the TLR4 receptor. Other molecular adjuvants are under development, including some targeting other TLRs such as TLR9, but to date have not been approved for commercial use.

Immune Design’s synthetic TLR4 agonist is under development for preventive and therapeutic infectious desease vaccines and has the advantage of the regulatory path already blazed by MPL as well as much simpler formulation and manufacturing processes.

Targeting the activation of dendritic cells in combination with an antigen results in effective antigen presentation that not only yields higher antibody titers than conventional adjuvants, but also ones that are broader (cross react with other related antigens), more effective in neutralizing the pathogen (Th1 phenotype) and, importantly, provide antigen-specific cellular immunity.

Immune Design’s TLR4 agonist has entered clinical testing as an adjuvant of a number of antigens and pathogens in over 650 healthy volunteers and has shown a very acceptable safety profile (no SAE grade 3 or higher). It has demonstrated efficacy in antibody production and dose sparing (a 35-fold lower antigen concentration yields equal neutralizing antibodies when combined with the TLR4 agonist).

The exciting future of vaccines is to move the field from preventive to therapeutic. Chronic viral infections (hepatitis B or C, herpes and many others) cannot be fully controlled—much less eradicated—through antiviral drugs. Vaccines that only trigger antibody production against these viruses are not effective when administered to patients with active infection. The novel molecular adjuvants such as Immune Design’s TLR4 agonist can trigger a cellular immune response (CD4 and enhance CTLs) which is critical to suppressing the level of viral replication.

ALLERGY

The basic mechanism underlying allergic disorders is a dysfunction of the immune system characterized by a hyper activation of immune cells such as mast cells, eosinophils, anti-allergen antibodies of the IgE class, and cytokines of the Th2 phenotype such as IL5, among others.

Human diseases such as asthma, allergic rhinitis, eosinophilic esophagitis and many others are caused by the above pathogenesis and are major contributors to health costs. Also, current therapies are at large symptomatic and not disease modifying.

The activation of TLR by a number of agonists has been shown in animal models to shift the “Th2 type” immune response to a more balanced one led by a Th1 type. In particular, Immune
Design’s TLR4 agonist has been shown in pre-clinical animal models to effectively reverse the Th2 phenotype and thus it offers the potential for its use as a monotherapy agent to treat or prevent allergic asthma, rhinitis and more. It also has a significant potential to desensitize individuals allergic to known allergies including ragweed and peanut when combined with the allergen, as it is expected to shift the allergen specific IgE to an IgG one, thus avoiding the allergic mechanism.

**IMMUNE DESIGN’s STRATEGY**

As a nascent biotech with a platform of cutting edge technologies that can affect a number of very relevant human diseases, we have made cancer immunotherapy our top priority. Our next goal is to deliver a solid proof of concept clinical validation of Immune Design’s cancer vaccine and subsequently deliver it to commercial success.

In parallel, we are actively pursuing opportunities to ensure that our technologies are advanced in non-cancer fields and help advance clinical medicine. This is being done in partnership with other companies.

**IMMUNE DESIGN PIPELINE**

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**IMMUNE DESIGN PEOPLE**

Our culture is that of breakthrough science translated to breakthrough products in tough to treat diseases. This is a company formed by individuals who believe only in breakthrough advances in science and medicine. We are not after “me better” or “me too” quick wins. We are passionate about what the immune system can do to reverse disease.

Due to the limited nature of the time and resources needed to achieve our lofty goals, we instill ourselves with the following attributes: high sense of urgency, excellence and passion. We work as a team, are flexible, and sponsor the virtual way of executing with best partners and vendors.

Our scientific founders and members of our Scientific Advisory Board include Nobel prize awardees in Medicine and the highest membership in the National Academy of Sciences. Our Board of Directors are seasoned “blue chip” investors and, more importantly, key past executives in successful pharma and biotech companies. Lastly, our management team of seasoned, experienced industry leaders is growing with new talent under recruitment.
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Paul Rickey

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