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Review on Immunotherapy Strategies against Infectious and Noninfectious Diseases

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Abstract
Immunotherapy, in its broadest sense, encompasses the treatment and prevention of a large number and variety of immunologic and non immunologic diseases. Immunization may be active, in which administration of antigen (usually a modified infectious agent or toxin) results in active production of immunity, or passive, in which administration of antibody containing serum or sensitized cells provides passive protection for the recipient. Several mechanisms to stimulate immune system of host through different types of cell or cell extract, such as cellular therapy, immunomodulators, and antibody therapy. The potential for prophylaxis and therapy for veterinary medicine and human medicine comprise the following: control of infectious disease, cancer therapy, specific treatment of autoimmune disease, immunomodulation of allergic disease. However, risks associated with immunotherapies, such as toxicity and hypersensitivity, also have been documented.
Keywords: Immunotherapy, allergy, Antibody, Immunomodulator, Cancer, Plasmid DNA therapy

1. INTRODUCTION

The living animal's body contains all the components necessary to sustain life. It is warm, moist, and full of nutrients. As a result, animal tissues are extremely attractive to a vast array of microorganisms. This can be readily seen when animals die. It begins to smell and decay as microbial invasions occurs. The tissue of living, healthy animals are resistant to microbial invasions because of the presence within the body of a vast array of defense mechanisms. Indeed, the survival of an animal depends on the successful defense of the body against microbial invasions (Tizard, 1996).

The best way to prevent and remove infections is through the natural 'sterilizing' action of the immune response that combines elements of both innate and adaptive immunity toward off foreign pathogens without medical intervention. The immune system 'remembers' the cleared foreign antigens to speed up its response to re-infection. The immune system in most cancer patients can still completely destroy viruses and bacteria. The ferocity and specificity of this response can be witnessed in the way an inadequately suppressed immune system can completely destroy a large transplanted organ, while sparing one's own (self) tissues. This destructive effect would be beneficial for cancer therapy if it could be directed at tumors (Matzinger, 2001).

Immunotherapy is a form of *biologic therapy* or *biotherapy*. It is treatment that uses certain parts of the immune system to fight diseases. This can be done in a couple of ways either stimulating own immune system to work harder or smarter or giving immune system components, such as man-made immune system proteins that triggers the body's immune system to recognize and respond to cancerous cells. Some forms of immunotherapy include interferons, vaccines, and monoclonal antibodies (Prehn *et al.,* 1996).

Therefore, the objectives of this paper are to review current immunotherapy strategies against infectious and noninfectious diseases and to forward appropriate recommendation on the applications and challenges of immunotherapy.

2. IMMUNOTHERAPEUTIC STRATEGIES

The development of immunotherapy technology is more recent. There are two main types of immunotherapy. Active immunotherapies stimulate body's own immune system to fight the disease. Passive immunotherapies do not rely on body to start the attack on the disease; instead, they use immune system components (such as antibodies) made in lab (Stites *et al.,* 1994). The types of immunotherapy described in the following section include: T cell therapy, therapeutic antibodies, immunomodulation and plasmid DNA therapy (Har-Noy *et al.*, 2009).

2.1. Cellular Therapy

It is clear from observations of immune responses that some cells must be able to recognize foreign antigens and then respond to them (Tizard, 1996). Professional antigen presenting cells include Dendritic Cells (DCs), Macrophages, and B-cells. Of these DCs are the most potent antigen presenters given their morphologic and phenotypic properties (Igyarto and Kaplan, 2013). The response of these antigens – sensitive cells must act either in the production of antibodies or in the production of cells that can participate in the cell-mediated immune responses. Cells must also be generated that can respond even more effectively on second exposure to same antigen memory cells (Tizard, 1996).

2.1.1. Improving (stimulation) T cell therapy /Dendritic cell-based immunotherapy

This novel approaches for increasing the efficacy of T cell therapy through genetic modification of specific T cells to improve their biological function (Rooney *et al.*, 1998). The poor immunogenic of most tumor antigens largely reflects the non conductive context in which these antigens are naturally presented, as well as tolerance resulting from most tumor antigens being normal proteins aberrantly expressed by tumor. Therapeutic vaccines have attempted to evade these problems by presenting tumor antigens in a more enticing fashion, generally through activated dendritic cells (DCs). This has been achieved either by isolating DCs and introducing the antigen *ex vivo* before returning the DCs to the hosts, by inoculating dead tumor cells modified to secrete factors such as granulocyte-macrophage-colony stimulating factor (GM-CSF) that promote local accumulating of DCs, by injecting activators of DCs such as tumor like receptor (TLR) ligands or monoclonal antibodies (Mab) to CD40 with the antigen, or by injecting recombinant vectors that provide both the antigen and a stimulus to the innate immune system (Waldman, 2005; Overes *et al.*, 2009). Upon transfusion back into the patient these activated cells present tumour antigen to effector lymphocytes (CD4+ T cells, CD8+ T cells, and B cells). This initiates a cytotoxic response to occur against cells expressing tumour antigens against which the adaptive response has now been primed (Overes *et al.*, 2009). The cancer vaccine Sipuleucel-T is one example of this approach (Di Lorenzo et al., 2011).

2.1.1.1. Blockage of the actions of CTLA-4 and PD1 Inhibitory Receptors induced after cell activation

Among the best studied of the immunological checkpoints is the cytokine T lymphocyte antigen – 4 (CTLA-4, CD152), a negative costimulatory molecule (Kwon *et al.*, 1999; Rosenberg, 2004). The initial interaction of B7 family members such as CD80 or CD86 with the CD28 costimulatory receptors provides a fundamental costimulatory signal that is required to initiate the T cell immune response, in addition to signaling that occurs through the T cell receptor for antigen. However, the expression of CTLA-4, a receptor that has a much higher affinity for B7 than CD28 is induced after T cell activation. CTLA-4 inhibits T cell activation and interleukins-2(IL-2) production. Allison and coworker demonstrated that transient antibody-mediated blockade of B7-CTLA-4 interaction enhanced the antitumor immunity provided by a GM-CSF transduced vaccine (Kwon *et al.*, 1999). This coordinate strategy led to the regression of established transplanted syngeneic tumors and has induced remission in some patients with malignant melanoma (Waldmann, 2005).

The immune system employs a series of checkpoints to protect normal, healthy tissue from an immune response. These consist of receptors on the surface of activated T cells and their corresponding ligands on the surface of antigen presenting cells. A key immune checkpoint is created when PD-1 (programmed cell death protein 1) engages its ligand PD-L1. As a result of this interaction, T cell activation is attenuated and an active immune response is prevented (Curran *et al.,* 2010). This mechanism is also used by tumors. PD-L1 is upregulated in several tumor types and contributes to the malignancy of these cancers by interacting with PD-1 and inhibiting T cell activation. In this way, the tumors avoid detection and destruction by the immune system. Accordingly, PD-1 and PD-L1 have garnered much attention for their roles in tumor immunology and as potential immune-based therapeutic targets. The interaction of PDl with programmed cell death ligand-l (PDL-1) or PDL2 dramatically inhibited T cell receptor mediated proliferation and cytokine secretion by CD 4+ T cells (Waldmann, 2005; Gameiro *et al.,* 2014).

2.1.1.2. Elimination of CD4 +CD25+ foxp 3 expressing Tregs (Regulatory T cell)

Another immunological check point is mediated by Tregs that express CD4+ CD25+ fork head protein 3 (foxp3). These Tregs, or regulatory T cells, can compromise immune responses to tumor antigen (Randolph *et al.*, 2006; Shevach, 2000). As is true of the other check points, CD4+ CD25+ Tregs are engaged in the control of self-reactive T cells and there by contribute to the maintenance of immunological self tolerance. In mice, administration of Pc61, a CD25 (Interleukin-2 Receptor alpha/IL-2Rα) species Mab, led to the depletion of Tregs, which was associated with an augmented immune response to certain syngeneic tumors (Hurwitz *et al.*, 2000). In particular, Pc61 was associated with the induction of Cytotoxic T Lymphocytes (CTL) and Natural killer cell (NK- cell) mediated cytotoxicity that in turn led to tumor rejection. As noted above, CD25 is expressed not only by Tregs but also by activated effector T cells. Therefore, CD25 directed therapy to remove Tregs must preceded the administration of an antitumor vaccine that induces CD25 expression effector T cells. The triggering CTLA-4 blockade augments Tregs expression. However, anti- CTLA-4 therapy with an associated depletion of CD4+ CD25+ Tregs mediate by the simultaneous administration of Pc61 provided synergistic antitumor therapy in a murine B16 melanoma (Sutmuller *et al*., 2001).

2.1.1.3. Targeting the Inhibitory Cytokine TGFβ

Yet another mode of inhibition of cancer immunosurveillance is mediated by the CD4+, NK-T cell and production of IL-13. This induces the expression of Tumor necrosis factor-β (TGFβ) to inhibit the antitumor cytotocicity lymphocytes(CTL) mediated by CD8+ CTLs. Blockage of this negative regulatory pathway by inhibiting IL-13 action using an IL-13 receptor IgFc fusion protein enhanced antitumor responses and potentiated the efficacy of vaccines (Berzofsky *et al*., 2001). More broadly, as noted below, these checkpoints and others can be blockage using antibodies directed toward TGFβ (Gorelik *et al*., 2002). A number of

biologically active agents either synthesized directly by tumor cells or secreted by host cell in association with tumor growth exert suppressive effects on the immune system (Gorelik *et al*., 2001). As just noted, TGFβ is one of the most prominent. It is produced not only in association with the CD4+ NK-Tell and IL-13 system but also in association with the actions of Tregs, NK cells, macrophage, epithelial cells, and stromal cells (Gorelik *et al*., 2002).

TGFβ is a pleiotropic cytokine that inhibits T cell proliferations and differentiation into CTLs and helper cells, and thereby prevents an effective immune response to the tumor. TGFβ is produced not only by host cells but by a wide array of tumor tissues. Such TGFβ production can have an important role in the suppression of antitumor immune response. Gorelik and Flavel utilized CD8 T cell genetically altered so that they could not respond to TGFβ, to demonstrate that T cells specific blockade of TGFβ signaling allows the generation of tumor specific CTL responses (Gorelik *et al*., 2002). Such T cells were able to eradicate tumors in mice challenged with melanoma tumor cells. Thus, the use of Mabs or TGFβ-RII- directed blockade of TGFβ action on T cell signaling could be translated to clinical situations to improve existent cell-mediate antitumor immunity (Gorelik *et al*., 2001).

Table 1: Blockage of immunoregulatory negative checkpoints that impede immunotherapy

Host negative immunoregulatory mechanism	**Potential intervention to release Checkpoint on the immune response**
Signal mediated by negative T cell costimulatory molecule CTLA-4 after interaction with CD80,86 family on APCs deliver signals that terminate T cell activation	Antibody-mediated blockage of CTLA-4 to enhance antitumor immunity induced by vaccine
PD1 interaction with PDL1 or PDL2 inhibits T cell receptor –mediated proliferation and activation of CD4 + T cells	*Anti-PDL1 antibody*
CD4+CD25+ negative regulatory Tregs (suppressor T cells) inhibit antitumor immune responses	Oncotoxin (IL-2 diphtheria toxin, anti-2Rα *pseudomonas* toxin. orCD25-directed antibody (PC61) therapy to deplete Tregs
CD4+ NK T cell generation of IL-13 that Indirectly (through the action of TGFβ) inhibit CD8+ cell-mediate antitumor responses. TGFβ is also synthesized directly b tumor cells or by host cells via other mechanisms	IL-13Ra IgFc or anti-TGFβ monoclonal antibody

Source: Waldmann, 2005

2.1.2. Adoptive cell therapy

Transplantation of immunocomptent cells from normal donor or patient with cancer is the method used to achieve immune function in immune deficient diseases and tumor. Adoptive cell therapy approaches to date have used tumors, peripheral blood malignant effusion, and draining lymph node as the anatomic source of input T cells for adoptive transfer. However, mainly using of CD8+ T cell for adoptive therapy as opposed to other cytolytic cells such as natural killer cell is their ability to specifically target cells through the recognition of differentially expressed proteins presented on the surface. Using T cell for adoptive therapy is also attractive due to the long clonal life spans of T cells which allow both therapeutic and immunoprophylactic scenarios to be envisioned. In addition T cells are well suited for genetic manipulation and its safe, effective and protective *in vivo* (June, 2007).

An alternative to using allogeneic T cells to mediate antitumor responses has been to isolate autologous tumor- reactive T cells, expand the cells *in vitro*, and then reinfuse the cells back into the patient. Analogous adoptive therapy trials for immunosupressed hosts have demonstrated increased *in vivo* proliferation and persistence of CD8 effector T cells in the presence of specific CD4+ helper cells. Such CD4+ T cells likely provide many beneficial functions including cytokine production and APC activation which can improve the quality and quantity of the CD8+ responses, as well as direct effector activities against infected or tumor targets. Consequently, the largest experience is with IL-2 which clearly prolongs persistence and enhances the antitumor activity of transferred CD8+ cells (Riddle, 1995). Alternative cytokines such as IL-15, IL-7, and IL-21 as well as activations of APCs with antibodies to CD40 are currently being evaluated in clinic. The transfer of antigen specific CD8+ T cell clones has been shown to be effective for prevention of viral infections and treatments of malignant diseases (Salvin, 2001).

2.2. Therapeutic Antibodies

Therapeutic antibodies are lab engineered substances that recognize and bind onto a protein on the surface of cell. Each therapeutic antibody recognizes different protein or antigen, and in general can be used alone, in combination with chemotherapy or as carrier of substance such as toxins or radiation. After being to the targeted site, the therapeutic antibody can block the growth of tumor and/or recruit body's immune system to attack the target, and

can also sensitize a cancer cell to chemotherapy (Tizard, 1996).

2.2.1. Monoclonal antibodies

Monoclonal antibodies are monospecific antibodies that are made in laboratory from a single clone of B cell. These proteins are designed to attach to area on the surface of pathogenic agents and interfere with their growth and spread. Once the antibodies are given, they can then recruit other parts of the immune system to destroy the cancer cells. Two types of monoclonal antibodies are used in cancer treatments (Witzig, 2002).

2.2.1.1. Naked monoclonal antibodies

Naked Mabs are the most commonly used Mabs at this time. Although they all work by attaching themselves to specific antigens, they can be helpful in different ways.

i) Markers for destruction

Some naked Mabs attach to cancer cells to act as a marker for the body's immune system to destroy them. Antibodies now in use in this group include: Rituximab (Rituxan), Ofatumumab, Alemtuzumab (Campath) (Witzig, 2002).

ii) Activation blockers

Some naked Mabs don't really interact with a person's own immune system. Their effects come from their ability to attach to the specific antigens that are working parts of cancer cells or other cells that help cancer cells grow, and stop them from working. These Mabs are also referred to as targeted therapies. Examples of FDA-approved Mabs of this type include: Cetuximab (Erbitux), Trastuzumab (Herceptin) for cancer (Waldmann, 2005).

2.2.1.2. Conjugated monoclonal antibodies

Conjugated Mabs are monoclonal antibodies that are attached to drugs, toxins, or radioactive substances. The Mabs are used as homing devices to take these substances directly to the cancer cells. The Mab circulates in the body until it can find and hook onto the target antigen. It then delivers the toxic substance where it is needed most. This lessens the damage to normal cells in other parts of the body (Denny, 2004).

Conjugated antibodies may pack more of a punch than naked Mabs, but for this reason they often cause more side effects, too. The side effects depend on which type of substance they're attached to. For example, Ibritumomab tiuxetan (Zevalin) delivers radioactivity directly to cancerous B lymphocytes. It is used to treat B-cell non-Hodgkin lymphoma that has not responded to standard treatment (Waldmann, 2003).

Strategies and Targets of Monoclonal Antibody Action

A diverse array of strategies and cellular targets of antibody action have been employed in patient with cancer. Cellular targets include the tumor cells themselves, tumor vasculature, and various host-negative immunoregulatory elements (check points). The mechanism of action antibodies directed toward the tumor cells themselves include: One mechanism of action is a direct cytotocic action on the tumor cells mediated by the Mabs. For example, CD30-directed Mabs facilitate a target cell's death-signaling path -way rather than the cell-proliferation pathway mediated constitutively by the tumor necrosis factor-α (TNFα) receptor. By eliminating the proliferation and survival path way, the antibody kills CD30-expressing anaplastic large cell lymphoma cells (Mir *et al*, 2000).

A second mechanism is antibody-dependent cellular cytotoxicity (ADCC) mediated target- cell killing – a process that involves the redirection of host cytotoxic mononuclear cells to the tumor. Clynes *et al*., (2000) demonstrated that antibody engagement of receptors utilizing the FcRγ subunit plays a major role in the tumor-cell effector function of select Mabs in murine xenogeneic models of human malignancy. They showed that the efficacy of antibodies directed toward malignant melanoma cells was greatly diminished (Clynes *et al*., 2000).

A third strategy is to use cytokines (e.g., IL-2, IL-4, IL-12, and GM-CSF) genetically linked to Mabs to induce NK cell and T cell proliferation at the tumor site (Lode *et a*l, 2000). A fourth is to the antigen specifically of the Mabs to deliver cytocidal agents to the surface of the tumor cell (Witzig *et al*., 2002). For example, pretargeting strategies have been used to for the selective delivery of enzymes that activate prodrugs within the tumor, thereby diminishing the toxicities of the active drug through administer antibody-dependent enzyme-mediated prodrug therapy (ADEPT), an antibody-fragment-enzyme fusion protein is allowed to localize in the tumor. After the fusion protein is cleared from the circulation, the prodrug is administered and converted to an active drug by the enzyme focused within the tumor (Denny, 2004).

Table 2. Monoclonal antibodies for cancer treatment.

Year approved	Brand name	Generic name	Type of mAb	Target	Indication
1997	Rituxan	Rithximab	Chimeric	CD-20	Non-Hodgkin's lymphoma
1998	Herception	Trastuzumab	Humanized	HER-2	HER-2/neu positive metastatic breast cancer
2000	Mylotarg	Gemtuzumab Ozogamicin	Humanized	CD-33	Acute myelogenous leukemia
2001	Campath-I	Alemtuzumab	Humanized	CD-52	B-cell chronic lymphocytic leukemia
2002	Zevalin	Ibritumomab Tiuxetran	Murine Radiolabeld	CD-20	Non-Hodgkin's lymphoma
2003	Avastin	Tositumomab	Murine Radiolabeled	CD-20	Non-Hodgkin's lymphoma
2004	Erbituxx	Bevacizuma	Humanized	VEGF	Colorectal cancer
		Cetuximab	Chimeric	EGFR	Colorectal cancer
2006	Vectibix®	Panitumumab	Radiolabeled	(HER1)	Colorectal cancer
2004	Erbitux®	Cetuximab	Chimeric	EGFR (HER-1	Colorectal cancer head & neck cancers
2006	Avastin®	Bevacizumab	Humanized		Breast & kidney cancer
2009	Arzerra®	Ofatumumab	Radiolabeled		chronic lymphocytic LL)

Key: VEGF Vascular endothelial growth factor
Source: Hay-Novy (2009) and Waldman (2005)

2.2.2. Polyclonal antibody

Polyclonal antibodies are antibodies that are derived from many different B cells or B cell lines, similar to the mixture of antibodies found in sera. Polyclonal antibodies are therefore a mixture of much different specificity. This is in contrast to monoclonal antibodies which are derived from one clone. Immunization may be accomplished passively by administering either performed immune active serum or cell (CDC, 2009).

Antibody, either as whole serum or as fractionated, concreted immune globulin that is predominantly IgG, may be obtained from human or animal donors who have recovered from an infectious disease or have been immunized. These antibodies may provide immediate protection to antibody-deficient individual. Passive immunization is thus useful for individuals who cannot form antibodies or for the nonimmunocompromised host who might develop disease before active immunization could stimulate antibody production, which usually requires at least 7-10 days (Stites *et al.,* 1994).

Additionally, passive immunization is useful when no active immunization is available, when passive immunization is used in conjunction with vaccine administration (e.g. in rabies vaccination), in the augment of specific effects of certain toxins and venom, and, finally, as immunosuppressant. Antibody may be obtained from humans or animals sera give rise it an immune response that leads to rapid clearance of the protective molecules from the circulation of the recipient and the risk of allergic reaction, particularly serum sickness or anaphylaxis. Thus, to obtain similar protective effect, much more animal antiserum must be injected compared with human antiserum (Stites *et al.,* 1994).

2.3. Immunomodulatory Strategies

Immunomodulators are biology response modifying compound that affect the immune response in either a positive or negative fashion. There are many ways in which the cytokine network might be exploited therapeutically, whether positively by cytokine administration or negatively by inhibition or by more suitable modulation through therapeutic intervention in the cytokine network (Kelso, 1998).

2.3.1. Inhibition (Elimination) of endogenous cytokine production or action

This action is achieved using neutralizing antibodies against soluble cytokine receptors, antisense oligonucletides, pharmacologic inhibitors of signal transduction, natural and synthetic receptor antagonists permanently by gene inactivation as a result of natural mutation or generating in embryonic stem cells (Walker, 1999). For example, IL-4 and IL-5 where both transient neutralization and gene targeting have confirmed the key selective role of these cytokines in IgE synthesis and eosinophilia respectively, in the immune response to air way allergens and gut nematodes. In these examples the consistency of outcome of the two approaches to cytokine elimination reflects the fact that IgE synthesis and eosionophilia are induced responses to infection or allergenic change (Weiner, 1997).

2.3.2. Stimulation or modulation of endogenous cytokine production

Different immunogen induce the synthesis of different cytokines which in turn activated different immune

effector mechanisms. These include a large number of compounds, which can be divided into 3 broad categories (Stites *et al*., 1994).

2.3.2.1. General immunostimulatory agents

These are mostly of bacterial origin such as BCG (attenuated mycobacterium bacillus calmatte Guerin). BCG stimulates macrophage, T and B lymphocyte, and natural killer (NK) cells function and to augment interleukin 1 (IL-1) production. An injection of BCG into lesion of malignant melanoma has led to remission of the local tumor as well as distant metastases (Chirigos, 1992).

2.3.2.2. Eukaryotic source substance

Especially we focus on cytokines. The term cytokine define a large group of non enzyme protein hormones whose actions are both diverse and overlapping and which affect diverse and overlapping target cell population. They are generally subdivided into four groups (Stites *et al*., 1994).

i) Interferons

Although interferons (IFNs) were first recognized for their effect on viral infections, their clinical usefulness as immunomodulators has been demonstrated in certain neoplastic diseases (e.g. leukemia lymphoma) as well. For example IFNα, natural product of macrophage, has demonstrated antitumor activity in a numbers of neoplastic disorders. Also, IFNγ, a product of lymphocytes has extensive activity in a variety of tumors and viral infections (Rees, 1992).

ii) Haemopoietic colony- stimulation factors

They are erythropoietin, now used routinely to treat anemia in patients with chronic renal disease, granulocyte colony stimulating factor (G-CSF), macrophage, colony-stimulating factor (M-CSF), and granulocyte macrophage colony stimulating factor (GM – CSF) (Blackwell *et al*., 1992).

iii) Growth and differentiation factors

Perhaps the best studied growth and differentiation factor is transforming factor beta (TGFβ), which has a wide range of effect on the immune response. It has potential benefit as an accelerator of wound healing, and markedly inhibits the IL-4 stimulated synthesis of IgE and may be clinically useful as an antiallergy drug (Stites *at el*., 1994).

iv) Interleukins (ILs)

Interleukins are a diverse group of cytokines exhibiting a broad array of actions on the immune system. These have potential usefulness as therapeutic immunomodulators. For instance, Interleukin 2 (IL-2) has been used successfully in the treatment of certain tumor (such as malignant melanoma, renal cell carcinoma). This is possibility due to activation and proliferation of lymphocyte activated killer cells (LAK) derived from the patient peripheral blood leukocytes. Recently, IL-2 has been used to productive ex vivo activation of a subset of lymphocytes derived from soidtumors, known as tumor- infiltrating lymphocytes (TIL) (Thompson,1992).

Tumor necrosis factor (TNF), a cytokine that has antitumor activity both in vitro and in vivo through: directly slowing the growth of cancer cells, slowing down *angiogenesis*, the growth of new blood vessels that tumors must have in order to grow, causing cancer cells to produce more antigens, making them easier for the immune system to see and destroy, boosting the cancer cell-killing ability of natural killer (NK) cells and of other immune system cells that attack cancer with help from antibodies(Prehn,1996).

2.3.2.3. Biochemical agents

They act via their ability to induce the production of interferons (Amery, 1992). For instance, the best known biochemical immunoimodulator is levamisole, an imidathiazole compound originally studied for its anthelmintic activity. It is immunotrophic; however, its mechanism of function is unknown and it exhibits no direct cytotoxic activity. It has little effect in immunocompetent individuals it has been shown to reverse post viral energy associated with measles and influenza and has some benefit in chronic infections, and neoplastic diseases (Amery, 1992).

2.4. Plasmid DNA therapy

Plasmids are autonomously replicating entities which can be found essentially in all bacterial species and which play a significant role in bacterial adaptation and evolution. Furthermore, plasmids are studied for their own sake and serve as important tools in studies of molecular biology (Summer, 1996). Plasmids are normally circular, although linear forms have also been described, and vary widely in size from 1 kb to 200 kb. Larger plasmids of up to 1000 kb, termed mega plasmids, have also been identified. The copy number per chromosome also varies among plasmids, and bacterial cells can carry more than one type. Like chromosomes, plasmids code for RNA molecules and proteins, replicate as the cell grows, and equal numbers are normally distributed to the two daughter cells upon cell division. However, plasmids do not code for functions which are essential to bacterial growth in the absence of any stressful situation, e. g., in the absence of an antibiotic (Schorr *et al*., 1996).

The experimental work on DNA vaccines in preclinical animal models explores its potential for prophylaxis and therapy in four areas that are of interest in human and veterinary medicine. These comprise the following: control of infectious disease, immune therapy of cancer, specific treatment of autoimmune disease, immunmodulation of allergic disease (Schneide *et al*., 1998).

For example, consider allergy treatment. Immune reactions underlying allergy are characterized by a strong Th2 phenotype, and DNA vaccination often introduces a strong Thl-bias into the immune responses it primes or boosts. In mouse models, allergy-inducing Th2 responses have been converted into non-pathogenic Thl responses against the allergen by DNA vaccination (Schneide *et al*., 1998; Ziegelhof *et al.,* 1997; Schorr *et al*., 1996). The inhibition of IgE antibody formation by plasmid DNA immunization has been shown to be mediated by both CD4+ and CD8+ T cells (Lee *et al*., 1997). DNA vaccination is an exceptionally potent strategy to stimulate T cell responses. This makes DNA-based immunization an interesting strategy for vaccination against intracellular pathogens and cancer. Different mechanisms seem to be involved in priming T cells by genetic vaccination (Schorr *et al*., 1996). Also immunomodulatory roles of plasmid DNA is mediated through the following mechanisms: potent inducer of *protective anti-viral CTL responses; override non- or low responder status* in anti-viral T cell reactivity; overcome low responsiveness or tolerance induction in *neonatal* immune system convey *cross-strain protection* against viruses and support priming of *anti-viral CTL despite deficient* CD4' T *cell helper activity* (Schneide *et al*., 1998).

3. APPLICATION OF IMMUNOTHERAPY

Most of immunotherapy is ideal treatment but some strategies are practical applied (Morgan, 2004).

3.1. Viral therapy

In persistent virus infections where viral replication is controlled by specific CTL such as Epstein Barr Viruses (EBV) and cytomegalovirus (CMV), adaptive transfer of CTL generated from the origin marrow donor to patients immunosuppressed following allogeneic SCT had prove beneficial in reducing the incidence of serious viral disease (Roony *et al*., 1998).

3.2. Cancer Therapy

Cancer immunotherapy attempts to stimulate the immune system to reject and destroy tumors. Immuno cell therapy for cancer was first introduced by Rosenberg and his colleagues of the National Institutes of Health in the United States in the late 1980s. They reported a low tumor regression rate (2.6–3.3%) in 1205 patients with metastatic cancer who underwent different types of active specific immunotherapy (ASI), and suggested that immuno cell therapy along with specific chemotherapy is the future of cancer immunotherapy(Rosenberg,1984). Initially Immunotherapy treatments involved administration of cytokines such as Interleukin. Thereafter the adverse effects of such intravenously administered cytokines lead to the extraction of the lymphocytes from the blood and expanding in vitro against tumour antigen before injecting the cells with appropriate stimulatory cytokines. The cells will then specifically target and destroy the tumor expressing antigen against which they have been raised (Yang *et al*., 2003; Egawa et al., 2004; Li et al., 2005). T Lymphocytes play a key role in maintaining antitumor immunity and provide an important opportunity for the immunotherapy of cancer. For example, transfer of T lymphocytes with antitumor activity via tumor infiltrating lymphocytes (TILs). There are lymphocytes that have been obtained from tumor tissue by mechanical means and enzymatic digestion of tumor specimens. A single-cell suspension is then cultured for several weeks before TILS can be harvested. TLIS cultured in the presence of IL-2 produce cytotoxic effects in colon carcinoma melanoma, and bladder carcinoma (Dudley, 2000).

3.3. Allergy Desensitization Therapy

Immunotherapy is also used to treat allergies. While other allergy treatments (such as antihistamines or corticosteroids) treat only the symptoms of allergic disease, immunotherapy is the only available treatment that can modify the natural course of the allergic disease, by reducing sensitivity to allergens. Immunotherapy does not work for everyone and is only partly effective in some people. The therapy is indicated for people who are extremely allergic or who cannot avoid specific allergens. For example, they may not be able to live a normal life and completely avoid pollen, dust mites, mold spores, pet dander, insect venom, and certain other common triggers of allergic reactions. Immunotherapy is generally not indicated for food or medicinal allergies. This therapy is particularly useful for people with allergic rhinitis or asthma (Durham et al., 1999).

The therapy is particularly likely to be successful if it begins early in life or soon after the allergy develops for the first time. Immunotherapy involves a series of injections (shots) given regularly for several years by a specialist /allergists. The first shots contain very tiny amounts of the allergen or antigen to which one is allergic. With progressively increasing dosages over time, one's body adjusts to the allergen and becomes less sensitive to it, in a process known as desensitization. In many allergic diseases may be controlled through the use of "allergy shots". It was originally believed that injection of the allergen stimulate the production of IgG antibodies. It was anticipated that these would compete with IgE for antigen and, therefore, prevent the antigen from reaching the mast cells. Although partially correct, it is also probable that allergy shots stimulate Th1 cells to release IFNγ. This IFNγ blocking stimulation of IgE antibody synthesis by IL-4 from Th2 cells (Stites *at e*l.,

1994).

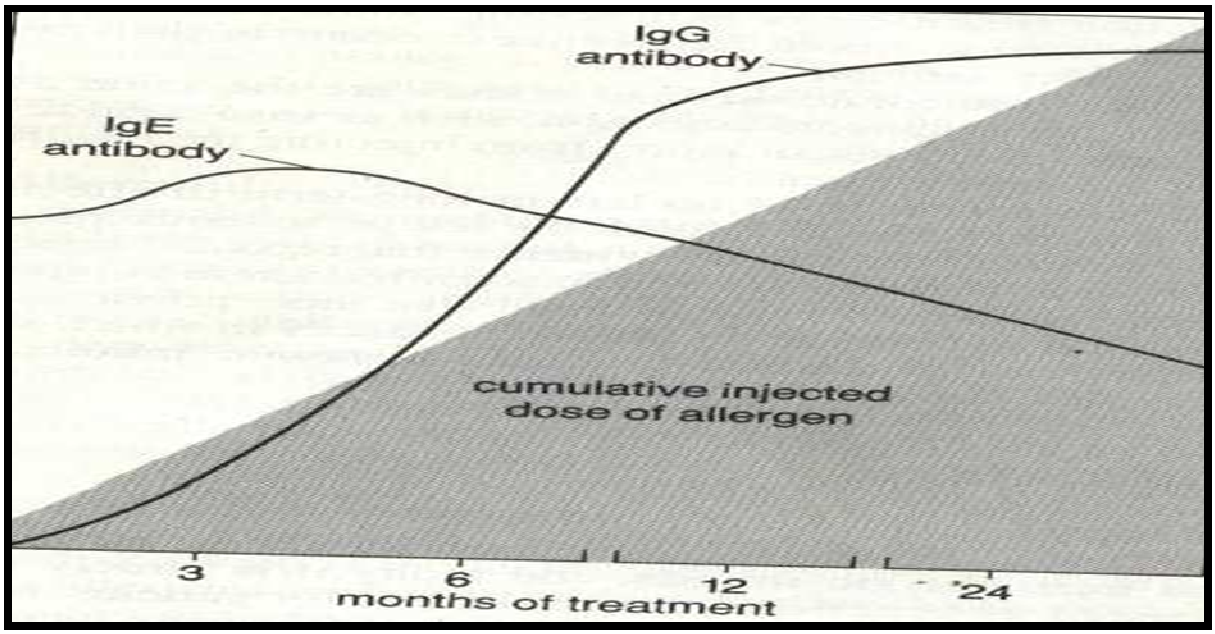

Figure 1: Allergy Desensitization Therapy
Source: Stites *at e*l., 1994

4. CHALLENGES OF IMMUNOTHERAPY

Immunotherapeutic have risks that are, at this early stage of development of the novel vaccination technique, difficult to assess critically. The limited experience with safety considerations obtained in animal models suggests the following potential risks (Waldman, 2003).

4.1. Toxicity

One major difficulty in cytokine therapy has been toxicity. For example, TNF produces clinical signs similar to those induced by endotoxin. IL-2 and IL-4 are extremely toxic when administered alone. In low doses it induces fever, chills, nausea, and anemia, thrombocytopenia and eosinophilia. Patients may develop a severe, very itchy rash and endocrine abnormalities (Michilak *at el.,* 2004).

4.2. Hypersensitivity

An IgE response is a potential hazard that may result from the administration of any antigen, including vaccine. The term hypersensitivity is used to denote a severe reaction that occurs in response to normally harmless materials. For instance, normal animal do react to antigen then activated immunoresponse to release histamine and prostaglandin (Tizard, 1996).

4.3. Graft-versus Host Rejection

If healthy lymphocytes are injected into the skin of an allogeneic recipient, the lymphocyte attach the host cells leading to a local acute inflammatory response provided the recipient has a functioning immune system This graft-versus-host (GVH) reaction is not serious, since the recipient is able to destroy the foreign Lymphocytes and thus terminate the reaction. However, the recipient cannot reject the graft Lymphocyte because it has been immunosuppressed or immunodeficient, these cells may cause uncontrolled destruction of the host's tissues and eventually death (Tizard, 1996).

4.4. Mutation

Another problem of immunotherapy is emergence virus escape mutants are major concern during viral replication will lead to resistance to antiviral drug (Fung *et al*., 2006). For example, activation of B cell by HCV envelope protein (E2) CD81 is through to be a cellular receptor for HCV based on its ability to bind E2 (Zham *et al*., 2004). Binding of CD81 with E2 or certain Mab against CD81 induces B cell aggregation; inhibit NK cell functions (Crotta *et al*., 2002).

5. CONCLUSION AND RECOMMENDATIONS

The best way to prevent and remove infections is through the natural 'sterilizing' action of the immune response that combines elements of both innate and adaptive immunity to ward off foreign pathogens without medical intervention. Innovation in immunology in the form of prophylactic and therapeutic vaccines has been used to treat a variety of infectious and non infectious disease. Immunotherapy is a highly desirable alternative to current treatment strategies than surgery, radiation and chemotherapy due to well suited for genetic manipulation and its safe, effective and protective *in vivo* with low toxicity and a durable treatment response. Two main types of immunotherapy strategies are passive and active. But most of them are ideal treatment and some strategies are practical like cancer therapy and allergic desensitization. Among the risk immunotherapeutic strategies are toxicity, hypersensitivity, graft-versus host rejection, and Mutation are the major one. In the light of the above conclusive remakers the following point are recommended: further studies should be carried out on desirable and side effects of immunotherapeutic and Technology should be refined in a way to minimize well-being and ethical concerns.

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