

## Promising of Immunotherapy against Fungal Infection

Adane Adugna Abate\*

Department of Medical Microbiology, Debre Markos University, Debre Markos, Ethiopia

\*Corresponding author: Adane Adugna Abate, Department of Medical Microbiology, Debre Markos University, Debre Markos, Ethiopia, Tel: 937401165; E-mail: adaneadugna29@gmail.com

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### Abstract

Immunotherapy is a treatment approach that makes use of the immune response of the host in the fight against fungal infection. Innate and adaptive immune responses make up the host's defense against fungus. Cells (neutrophils, monocytes, dendritic cells, Natural Killer (NK) cells, epithelial cells and endothelial cells), cellular receptors (such as Toll-Like Receptors (TLR-2 and TLR-4) all play a role in the innate immune response. TLRs and lectin-like receptors are two categories of Pattern Recognition Receptors (PRRs). When proteins or carbohydrates are found on the fungal wall, a family of receptors known as TLRs recognizes them, activates the cytokine system and regulates the inflammatory response. PRRs are the initial parts of the host defense that the invasive fungus activates and their activation stimulates the innate host defense cells in the first line of defense as well as modulates adaptive cellular responses later on in infection but this system may become weaker or dysfunctional as a result of several illnesses like HIV, cancer, organ transplantation, etc., thus we must strengthen the immune system as a treatment to combat fungus. Recombinant cytokines, granulocyte transfusions, immunization with fungal (glyco) proteins or antigen-loaded dendritic cells and antibody infusion are thus immune-enhancer techniques for the prevention and treatment of fungal infection.

**Keywords:** Fungal infection; Immunotherapy; Immunomodulation; Immunosuppression

due to the increasing of HIV outbreaks and immunomodulatory drugs for the treatment of autoimmune diseases and cancer [2].

People with significant immunosuppression, such as neutropenic patients with acute leukemia and those who have undergone bone marrow transplantation, are most commonly fatally affected by mycoses. Recipients of Bone Marrow Transplantation (BMT) are exposed to mycosis due to prolonged use of immunosuppression drugs like steroids, radiotherapy, Graft Versus Host Disease (GVHD) and immunosuppressive therapy to control and treat GVHD [3].

Both innate and adaptive immune responses are the host defense mechanisms against fungal infection. The innate immune response is mediated by different immune cells such as neutrophils, monocytes, dendritic cells, Natural Killer (NK) cells, epithelial cells and endothelial cells, cellular receptors (*i.e.*, Toll Like Receptors (TLR-2 and TLR-4) and humoral factors such as Tumor Necrosis Factor (TNF). Specifically, the Pattern Recognition Receptors (PRRs) are divided into TLRs and lectin-like receptors. TLRs are a family of receptors that recognize proteins or carbohydrates on the fungal wall, signal cytokine production and regulate the inflammatory response. PRRs such as TLRs, CLRs and NLRs are the primary components of the host defense to be engaged by the invading fungus and their activation leads to stimulation of the cells of the innate host defense in the first line and also to the modulation of adaptive cellular responses later on during infection.

The prognosis for people with fungal infections has only been partially improved by new kinds of antifungal medications. Adjunctive host directed therapy is therefore believed to be the only option to further improve patient outcomes. However, the relatively high efficacies of antifungal drugs disseminative Fungal Infections (IFIs) are still related with tremendous morbidity and mortality, as late diagnosis makes an antifungal drug therapy inefficient [4]. When host immunity isn't restored, the outcome is worse because fungi adapt to stressors in the host and elude the host's defenses. When host immunity isn't restored, the outcome is worse because fungi adapt to stressors in the host and elude the host's defenses. Approaches to modulate the host immune system in fighting against fungal pathogens include the application of effectors and regulatory cells such as granulocytes, antigen-specific T cells or the administration of recombinant cytokines and growth factors including Interferon- $\gamma$  (IFN- $\gamma$ ), granulocyte and granulocyte-

### Introduction

Fungi are eukaryotic single cell or multinucleate organisms that live by decomposing organic materials. They exist in everywhere in the environment. No matter how pathogenic fungi are relatively few in number, they can cause disease with different degrees of severity among individuals whose immunity are normal or impaired. Fungal infections happen in greater than one-four of the world's population [1]. Most mycoses are superficial and easily treatable. However, they can also cause disseminative diseases especially among immunocompromised individuals which are related with greater than 50% mortality and cause 1.5 million deaths. The cases of fungal infections are rising

macrophage colony stimulating factor namely G-CSF, GM-CSF, TNF- $\alpha$ , IL-15 and vaccinations. Modulating host response may be linked with moderate success due to the onset of toxicity, inherent or acquired resistance, excessive immune response and inflammation or pathogen replacement. Pathogen-modulating interventions may benefit from the fact that monoclonal Antibodies (mAb) specifically target antigens [5]. As a result, antifungal immunotherapy to specifically strengthen the host's own immune mechanisms constitute an additional promising strategy in taking action against fungal pathogens.

Know how about the immune pathogenesis of fungal infections has been the way to promising strategies for immunotherapy including strategies that increase phagocyte number, boost antigen-specific immunity and innate host defense mechanisms in phagocytes and dendritic cells (e.g., vaccines). Immunotherapy must be tailored to specific immune compromised states.

## Literature Review

### General concept of promising of immunotherapy against fungal infection

Immunotherapy is an often used term in cancer therapeutics, where immune cell based and antibody mediated mechanisms are employed to directly target cancer cells and/or cut off the various support mechanisms that sustain them. The same concepts is used to take into account immunotherapy of different infectious diseases, including mycoses. The first step of the host immune defense is recognition of an invading pathogen by the innate immune system [6]. Recognition of microorganisms occurs *via* conserved chemical signatures, called Pathogen Associated Molecular Patterns (PAMPs). These PAMPs are recognized by specific innate immune receptors known as Pathogen Recognition Receptors (PRRs). The host is therefore able to coordinate a pathogen specific immune defense.

Immune-enhancer plan for the prevention and treatment of fungal infection include administration of recombinant cytokines, granulocyte transfusions, vaccination with fungal (glyco) proteins or antigen loaded dendritic cells and infusion of antibodies. As responses to cytokines and vaccines can be limited in patients with hematological malignancies especially those with undergoing HSCT, adoptive cell transfer has emerged as a promising therapeutic option for these patients and one such strategy involving transferring fungus primed dendritic cells to trigger fungus specific immunity. Another potential adoptive transfer strategy involves transfer of T cells specific for fungi to reconstitute antifungal immunity [7]. This therapeutic option is also crucial for the treatment of antifungal resistance fungal species like *C. albican*, so the use of immune therapy to augment the host immune response as adjunctive treatment for *Candida* infections is promising approach.

### Cytokine based therapy

Numerous preclinical investigations have demonstrated that cytokines boost the antifungal host defense by increasing or improving phagocyte activity. IL-18 is a pro-inflammatory

cytokine of the IL-1 super family that exhibits broad functional innate and acquired immune responses. IL-18 is secreted by activated macrophages, T and B lymphocytes and dendritic cells. The main function of IL-18 is to induce the proliferation of Th-1 cells and IFN production potentiated by IL-12. IL-10 is an immune regulatory molecule produced by myeloid cells, B cells and Treg. High levels of IL-10 are detected during fungal infections [8]. Clinical findings indicate that IL-10 could be beneficial in controlling the inflammatory response and fungal growth because it enables the development of memory protective immunity. IL-11 has anti-inflammatory activities such as suppression of the proinflammatory cytokine expression of macrophages leading to lowered levels of TNF, IL-12, IL-6 and IFN from Th-1 cells and increasing anti-inflammatory cytokine activity, such as that of IL-4. A T-cell growth factor called IL-2 may improve Th1-type immune responses. The therapeutic potential of IL-2 and IL-12 has been explored, but they are found to cause systemic toxicity. IL-23 is a member of the IL-12 family of cytokines and has a role in chronic fungal infections [9]. In a recent study, IL-23 appeared to have a protective function in the absence of IL-12.

The other important cytokine is IL-17 (IL-17A). It has emerged as a key mediator of protection against extracellular microbes, but this cytokine also drives pathology in various autoimmune diseases. Overwhelming data in both humans and mice reveal a clear and surprisingly specific role for IL-17 in protection against the fungus *Candida albican*, a commensal microbe of the human oral cavity, gastrointestinal tract and reproductive mucosa [10]. The IL-17 pathway regulates antifungal immunity through upregulation of proinflammatory cytokines, including IL-6, neutrophils recruiting chemokines (e.g., CXCL1 and CXCL5) and antimicrobial peptides (e.g., defensins), which act in concert to limit fungal overgrowth. IFN-gamma is the most broad-acting antimicrobial and host-inducing cytokine that is currently available as an immunotherapeutic drug for clinical use [11].

*In vitro*, IFN-g augments the antifungal activity of neutrophils and macrophages and stimulates production of other proinflammatory cytokines. The IFN- $\gamma$ , the prototype Th1 cytokine, enhances Th1 differentiation and skews the immune response towards a protective Th1 phenotype. As such, it has been implicated as a treatment option for disseminative mycoses. In addition, limited evidence suggests that Recombinant IFN- $\gamma$  (rIFN- $\gamma$ ) has a beneficial effect on the outcome of fungal infections in patients with Chronic Granulomatous Disease (CGD) [12]. IFN-g can stimulate pulmonary macrophages for antifungal effects. IFN-g stimulated the killing of *Blastomyces*, *Histoplasma capsulatum* and *Paracoccidioides* organisms (both the yeast and conidial forms) and increased fungistasis against *H. capsulatum*. The antifungal effects of Polymorphonuclear Neutrophils (PMNs) are also enhanced by IFN-g [13].

Cytokine based therapy is Granulocyte Colony Stimulating Factor (G-CSF) and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), Granulocyte colony-stimulating factor, generic names includes filgrastim and lenograstim, primarily stimulates neutrophils production and maturation. Chemotherapy may be myelosuppressive, causing neutropenia and G-CSF can be used

adjunctly to restore neutrophils counts [14]. In brief, GM-CSF stimulates maturation of dendritic cells from monocytes precursors, differentiation of macrophages and proliferation and activation of macrophages, monocytes, neutrophils, eosinophils, dendritic cells and microglia. G-CSF and GM-CSF increase the number and enhance the antifungal function of both intact and immunosuppressed phagocytes. GM-CSF has been used as adjuvant therapy for various fungal infections in cancer patients with relative success. G-effectiveness CSF's as an adjuvant has been investigated in light of the finding that it enhances the killing of fungi by normal PMNs or PMNs from HIV-positive individuals to antifungal therapy for SM in non-neutropenic patients.

GM-CSF also plays a critical role in enhancing numerous activities of mature effector cells, including neutrophils, monocytes, macrophages and dendritic cells. *In vitro* studies demonstrate that GM-CSF enhances the phagocytic activity of neutrophils or monocytes against yeast cells. M-CSF acts on monocytic progenitors, accelerating their differentiation, as well as on mature MNC/macrophages, modulating specific functions [15]. For example, M-CSF enhances the oxidative burst in response to soluble stimuli, up regulates Fe receptor expression and augments phagocytic. GM-CSF can be used alone or in combination with Interferon-G. The combination is mostly used in patients with serious, refractory fungal. Cytokine treatment has also shown promising results when administered along with conventional anti-fungal drugs.

### Granulocyte transfusion based therapy (GXT)

Granulocyte transfusions have a long history of being used in patients with neutropenia or neutrophil dysfunction to prevent and treat invasive fungal infections. Granulocyte transfusion involves transfusion of granulocytes, including neutrophils, from a donor to the patient. Neutrophils are required for killing fungal pathogens restores the neutrophil count and augments the host's defenses against fungi. As prolonged neutropenia is a major risk factor for invasive fungal infections, transfusion of granulocytes from healthy donors is a logical adjunct to antifungal therapy [16]. Granulocyte antimicrobial activity may be enhanced by co-treatment with recombinant growth factors and proinflammatory cytokines such as G-CSF, GM-CSF and IFN-g. Although generally well tolerated, granulocyte transfusions may cause alloimmunization and subsequent failure of hematopoietic stem cell transplantation.

Several patient groups can benefit from granulocyte transfusion. This strategy can be used in patients with profound and prolonged neutropenia (<100/mL for >10 days) who have developed severe fungal infections refractory to standard antimicrobial therapy, provided these patients are likely to recover their hematopoietic functions. The most important predictor of efficacy for granulocyte transfusions is the number of granulocytes transfused. The daily production of granulocytes in an uninfected adult is  $5 \times 10^{10}$  cells and giving less than that will not be effective. The target for granulocyte transfusions should be  $10 \times 10^{10}$  cells. G-CSF has long been recognized as a potent immediate activator of neutrophils *in vivo*.

Neutrophils recognize and respond to fungal pathogens using pattern recognition receptors, including toll-like receptors and dectin-1. After phagocytosis of the pathogen, the contents of the cytoplasmic granules are released into the vacuole and expressed onto the surface of the organism. The azurophil (primary) granules contain Myeloperoxidase (MPO) and three predominant neutral proteases; cathepsin G, elastase and proteinase 3. The movement of compensating potassium ions produces conditions in the vacuole conducive to microbial killing and digestion by the enzymes released from the cytoplasmic granules.

### Dendritic cell based therapy

Dendritic cells are now recognized to play a primary role in the induction of T cell responses to fungal pathogens. Fungus-pulsed dendritic cells have been shown to induce activation of protective CD4 Th1 responses on adoptive transfer in a murine model of hematopoietic stem cell transplant aspergillosis. Specific induction of plasmacytoid dendritic cells with FLT3-ligand rather than GM-CSF/IL-4 resulted in protection of mice from infection as well as preventing graft versus host disease.

Dendritic Cells (DCs) coordinate the lungs' overall antifungal immune defense. The respiratory tracts have been described as having a dense network of DCs. The possibility exists that local immunoregulatory events may impact the ability of pulmonary DCs to direct the appropriate T-cell responses to invading fungal infections by mediating unresponsiveness to respiratory antigens through the generation of Interleukin 10 (IL-10).

*In vitro* and *in vivo*, Dendritic Cells (DCs) have the unique ability to process information relevant to fungi and translate it into qualitatively different T helper (Th) immune responses. As a result of the activation of particular recognition receptors that primarily influence cytokine production and costimulation, DCs detect fungus in a morphotype-specific manner. Adoptive transfer of various DC types induces regulatory T cells, protective and non-protective Th cells and influences how infections turn out. In hematopoietic transplantation, DCs transfected with fungal RNA also restore antifungal resistance.

Like macrophages, Dendritic Cells (DC) express a range of phagocytic receptors, such as Complement Receptors (CRs) and Fc Receptors (FcRs). It has become clearer and clearer that DC have the ability to phagocytose and destroy living microorganisms in addition to their well-known roles as powerful antigen presenting and cytokine secreting cells. A large influx of DC into local lymph nodes following immunization with cryptococcal antigens is associated with a protective immune response against *C. neoformans* because human DC are able to phagocytose and destroy *C. neoformans* for presentation to T cells [17]. Strong evidence suggests that *C. neoformans* Manno Proteins (MPs) are important for triggering the T-cell mediated immune response, which is essential for antifungal defense.

### Natural Killer (Nk) cell based therapy

The transfer of NK cells from a donor to a patient is known as natural killer cell treatment often referred to as adoptive transfer of NK cells. Unlike T-cells, NK cells are activated

whenever they do not receive the inhibitory self-MHC I receptor binding, hence they do not require antigen priming. Potential exists for NK cell therapy as an immunotherapeutic approach to treat systemic fungus infection. They either directly use cytotoxic chemicals like perforin or granzyme B, which are stored in granules, to destroy their potential targets or they use death receptor mediated apoptosis to do it. Generally speaking, the production of Self-Recognizing Inhibitory Receptors (SRIR) causes the maturation of NK cells into a fully functional state, a process known as "licensing".

The idea of adoptively transferring Natural Killer (NK) cells to recipients of hematopoietic stem cells is gaining popularity since these cells eliminate infections and tumor cells. NK cell function against *Aspergillus* species, the main culprit behind invasive fungal infection in stem cell recipients, in humans. The promise of an NK cell to the host is crucial for resolving C. due to the fact that it generates gamma interferon. Additionally, Pneumocystis murina and other opportunistic fungal infections are protected against by it. Through the creation of gamma Interferon (IFN-) by NK cells, IL-12 and IL-18 jointly stimulate fungicidal activity of murine peritoneal exudate cells against *C. neoformans*. By producing a variety of soluble immunoregulatory factors including GM-CSF, IFN or rants, NK cells can control many immune system components [18].

## Discussion

### Neutrophil based therapy

The primary tissue forms of opportunistic fungi during invasive infections, fungal hyphae and pseudohyphae, are greatly harmed and ultimately killed by neutrophils (Polymorphonuclear Leukocytes, PMNLs). The main risk factors for opportunistic mycotic infections include prolonged neutropenia and impaired neutrophil function. Granulocyte infusions have been used for a long time as a treatment for severe protracted neutropenia and invasive fungal infection.

Other white blood cells are outnumbered by neutrophils in circulation and they are attracted in great numbers to infection sites by chemokine gradients, where they act as the first line of defense. Through pattern recognition and cytokine receptor activation in diseased tissues, neutrophils release the weapons housed in their granules, either by secreting them outside of the cell or by fusing them with vesicles that contain the pathogen or phagosomes. Short Antimicrobial Peptides (AMPs), proteolytic or nucleolytic enzymes, as well as other antimicrobial agents are present in the granules. Downstream kinase activation and Ca<sup>2+</sup> mediated signaling cause neutrophils to build a large protein complex known as Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase or phagocyte oxidase in response to stimulation of pattern recognition receptors (Phox). Membrane-bound and cytoplasmic (p40, p47 and p67) components make up this complex (gp91 and p22). A functional enzymatic multimeric protein that converts molecular oxygen to superoxide anion is produced following assembly on plasma and granular membranes. Reactive Oxygen Species (ROS), a group of intermediates that include hydrogen peroxide and hypochloric acid and are further converted into these highly reactive radicals

by the neutrophil enzymes superoxide dismutase and Myeloperoxidase (MPO), act as both effective antimicrobials and transient signaling molecules [19]. Reactive oxygen species actively encourage the activation of pro-inflammatory mechanisms and the removal of ingested microbes.

When dendritic cells were exposed to a fungal infection like *Aspergillus in vitro*, neutrophils significantly increased the upregulation of costimulatory molecules on the cells. Neutrophils are actively drawn into the vaginal cavity during the inflammatory response caused by Sap during vaginal candidiasis.

### Cellular based therapies

T-cell treatment involves taking T-lymphocytes from a patient or donor's blood, causing the cells to multiply and expand in an *in vitro* system and then reinfusion the patient with the ready to use cells. The injection of cytokines can boost T-cell immunity against fungus infection. Type-1 (Th1) and Type-2 (Th2) adaptive T helper-cell responses are categorized as "protective" and "non-protective," respectively. Th1 cytokines, such as Interferon (IFN)- $\gamma$  and Interleukin (IL)-2, IL-12 and IL-18, are produced as part of the type 1 response. These cytokines drive macrophage activation, the formation of cytotoxic CD4<sup>+</sup> T cells, the development of opsonizing antibodies and delayed type hypersensitivity. The synthesis of Th2 cytokines, such as IL-4, IL-5, IL-10 and IL-13, is a component of the type 2 response and causes the formation of non-opsonizing antibodies and allergic reactions while also suppressing the protracted inflammatory response brought on by Th1 cytokines. In addition to the Th1 and Th2 T cells that are involved in the aforementioned kinds of adaptive immunity, regulatory T cells (Treg) have recently been shown to play a part in the immune response against fungus. Treg cells reduce inflammation, promote tolerance and mediate resistance to reinfection by attenuating Th1 responses.

Through the production of tumor necrosis factor and Interferon (IFN)- $\gamma$ , Th1 cells are crucial for activating phagocytes (TNF). The etiology of autoimmune and allergy diseases is linked to Th17 cells. The Th17 cells' release of IL-17A activates neutrophils and triggers the synthesis of defensins, both of which help to quickly and effectively control the infection at the site. Failure to suppress TH17 leads to chronic inflammation and ineffective infection treatment. For the body to be resistant to fungus, balanced Th1 and Th17 responses are crucial. Other immune cell types involved in antifungal immunity include Th22 cells, which release IL-22, which triggers epithelial cells to generate antimicrobial peptides.

### Antibody based therapy

The development of hybridoma technology, which enables mAb synthesis, about 40 years ago helped to clarify the role of antibody mediated immunity in fungal infections. Invasive mycoses are known to cause the production of a variety of polyclonal antibody populations that, depending on their specificity and isotype may lessen the effects of fungal infections. Notably, these populations can either be protective or non-protective or they can worsen the disease in the host. Since antibodies can be protective by encouraging biological

mechanisms including complement-mediated lysis, stimulation of the pathogen phagocytic process by opsonization, cytokine release mediated by Fc or a direct antibacterial impact, MAbs are extremely selective and adaptable molecules. MAbs can also change how extracellular virulence factors are released from vesicles, which can affect how biologically active fungi are. In the absence of functional cellular immune systems, passive antibody transference enables the injection of protective mAbs against a particular pathogen, preventing infection. The large antigenic variations between and among fungi and humans support the use of MAbs based immunotherapy in treating fungal infections. Particularly cell wall glycoproteins are attractive candidates for therapeutic antifungal vaccinations. Additionally, creating mAbs against intracellular targets seems to be a successful method for enhancing host protection.

Through genetic rearrangement and somatic hypermutation of their variable regions, antibodies or immunoglobulins identify a variety of antigens. Constant areas, which are identified by an immunoglobulin isotype, are recognized by C1q, a component of the complement cascade that can result in bacterial lysis but not fungal lysis and Fc Receptors (FcR) on immune cells. A target molecule's biological activity can be directly modified by the antibody-antigen binding, which is a highly specific interaction, for example, by neutralizing a toxin. Aside from secreted substances, antibodies can also block the activity of adhesins and other surface-bound proteins on microbes. Additionally, surface reactive antibodies can function as opsonins to flag bacteria for eradication. The cytoplasmic membrane of phagocytes contains Fc receptors that detect bound IgGs. This increases phagocytosis, improves phagosomelysosome fusion and leads to a more effective microbial death when combined with the parallel detection of conserved microbial structures by determined pattern recognition receptors.

Antibody injection can boost humoral adaptive immunity against fungal infection. Fungal infection is more likely in those with primary antibody deficiency, such as those with X-Linked Agammaglobulinemia (XLA) or Common Variable Immunodeficiency (CVID). For example, immunotherapeutic research describing protective monoclonal antibodies (mAbs) for *A. fumigatus*, *C. albicans*, *Histoplasma* (H.) *capsulatum* or *Paracoccidioides* (P.) *brasiliensis* have been described.

Indirect therapeutic use of antibodies is possible and they may play a role in the development of some fungal infections. For the prevention of biofilm development by encapsulated yeast (*C. neoformans*) infection, antibodies-mediated therapy against fungal infection, particularly *C. neoformans*, is important. Polysaccharide capsule antibodies can increase survival, encourage phagocytosis and influence complement activation. Modulate expression of immunologically significant molecules, clear serum polysaccharide antigen, improve antigen presentation and alter cytokine expression *in vivo*.

### Vaccine based therapy

Immunity to fungus can be increased and strengthened through vaccination. For a number of fungal infections, including *C. albican*, *C. neoformans*, *A. fumigatus* and dimorphic fungi, the development of vaccines is a top priority. No one antigen can be

anticipated to be employed in a "pan-fungal" vaccine; rather, the main fungal infections will require customized, specialised vaccinations.

A *C. neoformans* vaccination that induces antibodies to the capsular polysaccharide Glucuronoxylomannan (GXM) is justified by the fact that these antibodies can enhance the host's defenses against experimental cryptococcosis. The effectiveness of a compound made of a decapeptide mimotope (P13) of GXM and a carrier protein in extending mice's lives following a fatal challenge with *C. neoformans*. Some vaccinations directly produce fungicidal antibodies, whereas others provide protection in animals with serious fungal infection risk factors, such as neutropenia or CD4<sup>+</sup> T-cell insufficiency.

Plasmid DNA encoding sequences are being used in novel ways in vaccine development to express foreign antigens like peptides and proteins in order to trigger a particular immune response. DNA vaccines contain genes that code for immune modulatory substances to boost the immune system's ability to fight off fungal infection by adjusting the cellular and humoral immune responses. Because they interfere with both innate and adaptive processes, Heat-Shock Proteins (HSPs) are appropriate molecules to use as antigens. In comparison to giving the usual form of the naked plasmid DNA vaccine, the nanoscale-controlled release mechanisms are a potential method for delivering vaccinations. Protection against the antigen's degradation *in vivo* and the nanobiotechnological approaches to delivery of DNA vaccine against fungal infection are two enhancements for vaccines created by these technologies.

The apparent existence of two immunological processes in providing protection is one of the fungus vaccines' most intriguing features. The primary mechanisms that have been suggested are an antibody mediated immune response, a Th1-based and/or Th17-based response [20]. With little clinical success, a variety of recombinant proteins and genetic constructs, entire fungi, cell wall or cytoplasmic extracts, antigen-pulsed Dendritic Cells (DCs) and other preparations have been tested.

### Conclusion

Generally, fungal immunotherapy involves the administration of exogenous immune agents, such as white cells, antibodies, T-cells and cytokines, natural killer cells and dendritic cells to immunocompromised individuals to enhance their immune system against fungal infection. As individuals with HIV, diabetic, cancer, organ-recipients and chronic disease become immunosuppressed. Thus; they have a chance to expose fungal infection. As a result; modulation of their immune system as a therapy is significant in order to with stand against fungal infection.

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