Biotechnology International 3 (1) : 4-17, March 2010
ISSN 0974-1453

Published by Biotechnology Society Online www.bts.org.in

Candida albicans Vaccines

Aditi Grover, B. S. Bhandari, Nishant Rai*, Pramesh C Lakhera

Department of Botany & Microbiology,HNB Garhwal University,Srinagar, (Garhwal) 246174, Uttarakhand, India,* Department of Biotechnology,Graphic Era University, Clement Town, Dehradun, Uttarakhand, India.
***Author for Correspondence, email:** nishantrai1@gmail.com

Summary: Since most fungal infections occur in immunocompromised patients, the generation of tools relying on host immunity for effectiveness is a notable challenge. Nevertheless, with improved knowledge of the host-fungus relation, and the spectacular advances in genome sequencing, genetic engineering, and proteomics, strong progress in fungal vaccine research has been made. Some vaccines induce the generation of directly antifungal antibodies; others are protective in animals carrying major risk factors for fungal infections. Together with demonstrated efficacy of various antibodies in passive vaccination approaches, there is growing confidence in the future availability of safe and efficacious immunological tools to combat deadly microbes in a weak host.

Key Words: Vaccines, *Candida albicans*, Immunity.

Introduction

Candida albicans is the most common cause of opportunistic fungal diseases in human (Schaberg *et al*., 1991). In the immunocompromised patients, disseminated candidiasis is a serious disease which often results in death, even in patients treated with antifungal agents such as amphotericin B (Anttila *et al*., 1994 ; Komshian *et al*., 1989) (Table 2). Difficulties associated with both the diagnosis of disseminated candidiasis and treatment of the disease by conventional means argue in favor of pursuing the development of preventive strategies and alternative forms of treatment (Berenguer *et al*., 1993; Reboli, 1993). In experimental animal models of candidiasis, optimal antifungal protection has been achieved by vaccination with an attenuated low-virulence strain or after spontaneous recovery from the initial infection (Bistoni *et al*., 1986; Cassone *et al*., 1995; Fidel *et al*., 1998; Romani *et al*., 1992). Since candidiasis is especially prevalent among immunocompromised subjects, however the use of inactivated whole cell or subunit vaccines should be, in principle, a safer and more convenient approach. Vaccines against fungal diseases are gaining ever increasing medical attention due to development of new virulent strains and their impacts thereafter. This review aims to discuss

the medical need for candida vaccine, the challenging nature of candida as vaccine targets, and new approaches in the generation of candida vaccines and protective antibodies.

The case of fungal vaccines

Available figures support the alarming impact of fungal infections on human health. Fungal infections rank among the first five causes of infections, with an absolute incidence rate above 1% (Wisplinghoff *et al*., 2004 ; Nucci *et al*., 2005). The spectrum of fungal pathogens is widening in parallel with a rise in immunosuppression caused by other factors including HIV infection, population ageing, and treatments requiring or inducing breakage of cutaneous and mucosal integrity. Candida species, in particular have become the fourth most common nosocomial bloodstream isolate in the USA and in most European countries (Pfaller *et al*., 2007 ; Sims *et al*., 2005; Morris *et al*., 2006; Wenzel *et al*., 2005). Invasive fungal infections are frequent and severe in the settings of hematological malignancies and organ transplant, where they cause substantial mortality. Patients undergoing hematopoietic stem cell transplant appear to be particularly vulnerable to a variety of fungal pathogens with mortality exceeding 60% (Nucci *et al*., 2005; Safdar, 2006; Pagano *et al*., 2006). Improvements have been made in fungal infection chemotherapy with the availability of new azole-derivatives and inhibitors of glucan synthase (Cappelletty et al., 2007; Polak, 2003; Wengard, 2007). Although the introduction of these new agents may improve the efficacy of antifungal prophylaxis in at-risk patients and provide a valid alternative to old drugs in refractory or resistant cases (Deep *et al*., 2005; Cornely *et al*., 2007; Segal *et al*., 2007 ; Ullmann *et al*., 2007), it is not yet clear to what extent the new drugs will affect the overall incidence and mortality caused by fungal disease. This is the result of their limited antifungal spectrum, the emergence of new, poorly susceptible filamentous fungi, and the difficulties encountered in rapid and accurate diagnosis of invasive infection. Furthermore, drug interactions and environmental moulds continue to be challenging aspects of disease control (Maertens, 2007; Bodey, 2005). Thus, the mortality rate for invasive candidiasis, one of the most common fungal infections, has remained stable from 1997 to 2003 (at around 0.4 per 100 000 population in the USA despite the introduction of the new agents, which are almost all effective against *Candida* sp (Pfaller *et al*., 2007). In experimental animal models of candidiasis, optimal antifungal protection has been achieved by vaccination with an attenuated low-virulence strain or after spontaneous recovery from initial infection (Bistoni *et al*., 1986; Cassone *et al*., 1988 ;Fidel *et al*., 1998; Romani *et al*., 1992). Since candidiasis is especially prevalent among immunocompromised subjects, however, the use of inactivated whole-cell or subunit vaccines should be a safer and more convenient approach.

Immune Response Against *Candida*

The importance of antibody immunity against a pathogen is usually inferred from one or more of the following criteria:

♦ Correlation of the presence of specific antibody with protection against infection.

♦ Prevention or modification of infection by antibody administration.

♦ Association of susceptibility to infection with antibody deficiencies.

In vitro studies demonstrating antibody- mediated killing or enhancement of cellular activity provide supportive evidence for protective antibody immunity. The term 'protective antibody' is applied here to antibodies that either prevent infection or modify the cause of infection to the benefit of the host (Robbins *et al*., 1995). The protective role of innate immunity, such as mechanical barriers and phagocytes, is indirectly but extensively illustrated by the existence of classic risk factors for opportunistic fungal infections, including indwelling central venous catheters, neutropenia , and use of corticosteroids. Complement and other humoral factors of innate immunity, such as antifungal peptides and the mannose-binding lectin have also been shown to have a role (Ip *et al*., 2004; Lillegard *et al*., 2006). Recent studies have highlighted the crucial role of dendritic cells in linking the innate to adaptive immunity and organizing the nature and extent of antifungal defense (Shoham *et al*., 2005; Levitz, 2004; Bernardis *et al*., 2006). Cell mediated immunity is commonly believed to be the primary defense against fungal diseases (Cutler *et al*., 2007; Deepe *et al*., 2005 ; Morris *et al*., 2006).

Important points to consider in antifungal immunity and its relevance to vaccination are:

♦ usually fungi display only moderate virulence (Gow *et al*., 2002; Latge *et al*., 2002).

♦ antifungal immune responses are usually redundant.

Although almost all pathogenic fungi have mechanisms to evade or intoxicate immune responses residual immunity may still be beneficial to the host (Monari *et al*., 2006; Gartner *et al*., 2005; Wheeler *et al*., 2006). Finally there is no need for a vaccine to be fungus-eradicating: neutralization of adhesins and enzymes or other low- penetrance virulence traits may be sufficient to avoid disease (Cassone *et al*., 2006).

Mechanism of antibody- mediated protection

Protective immune sera, mucosal antibodies, some murine and human monoclonal antibodies, and genetically engineered antibody fragments have all shown remarkable efficacy in fighting fungi (Cutler *et al*., 2007; Cassone *et al*., 2006; Casadevall *et al*., 2002). In principle, antibodies can be induced by vaccination in at risk patients before they become immunocompromised. Furthermore, Because of the longevity of Ig G (weeks to months depending on the Ig G subclass), antibodies might persist with a protective titre even during prolonged immunosuppression.

Antibodies to *Candida albicans* agglutinate yeast cells could theoretically contribute to host defense by localizing infection. However, an agglutinating nonprotective Ig M MAb to *Candida albicans* has been described suggesting that the ability to agglutinate yeast cells is not sufficient for protection (Han *et al*., 1995). Ig G to *Candida albicans* prevent serum-induced clumping, a phenomenon of

uncertain physiological significance(Chilgren *et al*., 1968). Interference of *Candida albicans* with attachment is a potent mechanism of antibody protection (Cassone *et al*., 1995; Epstein *et al*., 1982, Han *et al*., 1995; Scheld *et al*., 1983 ; Umazume *et al*., 1995; Vudhichamnong *et al*., 1982). For *Candida albicans* there is minimal phagocytosis by host effector cells in the absence of either antibody or complement-derived opsonins (Chilgren *et al*., 1968). Antibodies to *Candida albicans* are potent opsonins; however, opsonic antibody is not an absolute requirement for phagocytosis because the yeast can stimulate the complement pathway (Solomkin *et al*., 1978). Specific Ig G has no direct effects on *Candida albicans* growth (Chilgren *et al*., 1968), but Fab fragments to a hyphal antigen can inhibit germ tube formation (Casanova *et al*., 1990). Antibodies to *Candida albicans* can absorb immunosuppressive polysaccharide antigen from sera, suggesting a role for antibody in neutralization of immunomodulating fungal products (Fischer *et al*., 1978). Thus for *Candida albican ,* Antibody immunity may contribute to host defense by direct candidacidal activity (Poloneilli *et al*., 1994), Prevent attachment (Epstein *et al*., 1982; Han *et al*., 1999; Scheld *et al*., 1983; Umazume *et al*., 1995), Providing opsonins for more efficient phagocytosis (Chilgren *et al*., 1978), Binding to immunomodulating polysaccharides (Fischer *et al*., 1978), Neutralizing extracellular proteases (Cassone *et al*., 1995), Inhibiting the yeast-to-mycelium transition(Casanova *et al*., 1990), which is associated with increased adherence and invasion.

Antibody mediated enhancement of fungal infection

Some antibody responses to fungal antigens may be deleterious to the host. Rabbits treated with immune sera had more severe lesions than controls (Hurd *et al*., 1953). *In vitro* observations suggest mechanisms by which antibody could contribute to the pathogenesis in *Candida albicans* infections. Sera from certain patients with Candidiasis with high titers of antibody to *Candida albicans* can interfere with neutrophils candidacidal activity (LaForce *et al*., 1975; Walker *et al*., 1980). Non-specific IgA can enhance *Candida albicans* adherence to epithelial cells (Vudhichamnong *et al*., 1982).The phenomenon of antibody mediated inhibition of serum-induced clumping (Preilser *et al*., 1969) may contribute to dissemination by promoting mycelial transformation (Louria *et al*., 1972). Antibody to *Candida albicans* can inhibit human lymphocyte proliferative responses to *Candida albicans* antigen, possibly by interfering with macrophage antigen presentation (Witkin, 1986). An Ig G like molecule has been implicated in the chemotaxis defect of a patient with mucocutaneous candidiasis (Cates *et al*., 1980).

Important considerations in studies of antibody protection

The evaluation of the role of antibody immunity in animal systems involves complex experiments in which the outcome is dependent on multiple variables including antibody quantity, specificity, and isotype composition, inoculum, the timing of infection and antibody administration; route of infection

and antibody administration, the virulence of the experimental strain, and the susceptibility of the animal host to infection with the organism (Table 1).

Specific vaccines and antibodies

Table 3 summarizes some of the anticandida vaccines that have successfully provided both active and passive immunization. Almost all types of chemical and antigenic formulations, including antigen-encoding DNA, have been considered for active vaccination. With present day regulatory hurdles, it is quite unlikely that vaccines based on complex and ill-defined antigenic mixtures will be approved, even if they are shown to be immunogenic and protective in the preclinical setting. Advances in whole genome sequencing and proteomics are now making it possible to know most- if not the whole set-of fungal proteins; this knowledge allows for selection of a discrete number of antigens to test for protection, exactly as it has been done for bacterial vaccines (Giefing *et al*., 2007; Thomas *et al*., 2006; Rappuoli *et al*., 2004). Recent examples of the application of this "antigenome" approach (Giefing et al., 2007) have been provided by Thomas *et al* (2006) for anticandidal vaccine. Attenuated fungal cells are potently protective vaccines in animal models (eg, the CA2 strain of *Candida albicans*) (Romani, 2004; Bistoni *et al*., 1986) but could not be used in immunocompromised patients.

Subunit vaccines remain the most researched types of fungal vaccines and are most likely to result in an approvable product. They consist of one or more purified proteins (usually recombinant in nature), or one or more polysaccharided render sufficiently immunogenic through conjugation with a protein carrier (mostly bacterial toxoids) (Torosantucci *et al*., 2005; Han *et al*., 1999; Oscarson *et al*., 2005). Polysaccharide subunit vaccines include those based on original approaches such as peptide mimotopes (Datta *et al*., 2006; Maitto *et al*., 2004) and yeast killer toxin-neutralising antibody (Polonelli *et al*., 1993; Cassone *et al*., 1997; Polonelli *et al*., 1994). Some subunit vaccines are based on antigens that are common in different fungal species (Ibrahim *et al*., 2001; Spellberg *et al*., 2006) or even genera (Torosantacci *et al*., 2005; Cassone *et al*., 2006), raising the possibility of immunization against several fungi with a single antigenic formulation (the so called universal antifungal vaccine) (Torosantacci ., 2005). Since protection against most fungal diseases is provided by cellular effectors, passive vaccination has mainly been tested in diseases where more extensive and pioneering work on the protective role of antibodies has been done-namely andidiasis.

Table1: Variables, experimental considerations, and design of antibody protection experiments (Casadevall, 1995).

Variable	Experimental considerations	Suggestions
Antibody preparation	Polyclonal preparations are complex mixtures which may contain protective, nonprotective, and deleterious antibodies; the amount of specific antibody in polyclonal preparations may be	Use MAbs to defined antigens; if MAbs fail to modify infection, consider isotype switching since antibody efficacy may depend on constant-region functions; switching from IgG3 to IgG1

	insufficient to modify infection.	converts a nonprotective antibody to C.neoformans into a protective antibody (Yuan *et al*., 1995).
Antibody dose	Small doses may be insufficient for protection; very high doses may result in diminished antibody efficacy (i.e prozone phenomena described with antipneumococcal antibodies (Felton, 1928)).	Titrate antibodies dose and inocula.
Timing of antibody administration	Antibody efficacy may depend on timing of antibody administration; antibody prophylaxis is usually more effective than therapy..	Administer antibodies before infection to maximisze likelihood of demonstrating antibody protection
Fungal strains	Fungal strains can vary in susceptibility to antibody immunity (Mukherjee *et al*., 1995).	Test multiple strains of pathogen in question.
Inoculum	Small inocula may not produce reliable infections; large inocula may result in overwhelming infection refractory to antibody administration.	Use smallest inocula required to infect the majority of animals and produce the intended outcome (i.e., death, tissue infection etc.)
Experimental animal	Demonstration of antibody efficacy may be easier in some animal species; a GXM MAb prolonged survival in complement-deficient DBA/2J but not BALB/c mice (Dromer *et al*., 1989).	Consider testing antibody reagents in various animal models
Route of infection	Antibody efficacy may depend on the route of infection; for example, antibody efficacy against some pneumococcal strains was greater in i.v. infection than in i.p. infection (Briles *et al*., 1992).	Consider various routes of infection in experimental design; for example, rabbit polyclonal immune sera against *C. neoformans* prolonged survival in i.p. infection but not i.v. infection (Graybill *et al*., 1981).
Parametere of antibody efficacy	Survival, CFU, and severity of pathological lesions are frequently used parameters of antibody efficacy; organ CFU may be a more sensitive parameter of antibody efficacy than survival (Mukherjee *et al*., 1995)	Test multiple parameters; antibodies to *C. neoformanscan* reduce tissue CFU without prolonging survival (Mukherjee *et al*., 1995 ; Sanford *et al*., 1990)

Table 2:The biological and pathological features of *Candida* spp. currently considered as important target for vaccines.

	Biology	**Pathogenecity**	**Disease**
Candida spp.	Several species of which *Candida albicans* is the most pathogenic. *C. albicans* can grow as both yeast and mycelial forms (hyphae), which are prevalent at 37Oc.Pseudohyphae can also be formed. C. albicans are commensal organisms of the human gastrointestinal tract with a worldwide distribution.	Extracellular pathogens possess well defined virulence traits such as various adhesins and aspartic proteinase enzymes. Hyphae formation also contributes to virulence in vivo.	Cause superficial infections (skin and various mucosae, particularly vaginal and oral) and deep-seated infections, in nearly all internal organs. Vaginal infection with *Candida spp* is estrogen dependent, and probably the most diffuse fungal infection worldwide, affecting around 75% of all women in fertile age at least once.

Table 3: Major fungal vaccines for active and passive immunization against canididiasis (Cassone, 2008).

	Antigens	**Underlying immunity**	**References**
Whole cells and cell extracts	Strain CA2, live-attenuated	T-helper 1, cell-mediated immunity	(Bozza et al., 2004; Bistoni et al., 1986)
	Ribosomal cell fraction	Antibodies and cell mediated immunity	Segal *et al*., 2006; Levy *et al*., 1989
	Inactivated whole cells	Undefined	Cardenas *et al*., 1999
Antigen pulsed cells and T cells	Dendritic cell loaded with Candida antigen	Cell mediated immunity, T-helper 1	Bozza *et al*.,2004; Perrucio *et al*., 2004; Bacci *et al*., 2002
Subunit and glycoconjugates	Agglutin like sequences	Cell mediated immunity	Cutler *et al*., 2007; Ibrahim *et al*., 2006; Spellberg *et al*., 2006
	Secreted aspartic proteases 2	Anti sap2 antibodies	Cassone *et al*., 1995
	65Kda mannoprotein	Adhesin neutralizing antibodies	Sandini *et al*., 2007
	β-1,3-glucan	Growth inhibitory and cytocidal antibodies	Torosantucci *et al*., 2005; Cassone *et al*., 2006
	β-1,2-mannosides	Antibodies (Opsonophagocytic; possibly adherence	Cutler *et al*., 2007; Cutler *et al*., 2005; Han *et al*., 1999

		blocking)	
Idiotypes and mimotopes	Killer-toxin neutralizing mAb KT4	Fungicidal antibodies	Poloneilli *et al*., 1993; Cassone *et al*., 1997; Poloneilli *et al*., 1994
Antibodies	Mycograb, anti-Hsp peptide	Unknown	Matthews *et al*., 2004; Matthews et al., 2003; Pachl et al., 2006
	Anti- β-1,3-glucan Mab 2G8	Growth inhibitory	Torosancttui et al., 2005; Cassone et al., 2006
	mAb C7(Stress mannoprotein)	Candidacidal	Moragues et al., 2003
	Single chain fragment variable of anti-idiotypic antibodies	Candidacidal antibodies	Magliani et al., 2005
	Anti-mannan mAb C6	Opsonophagocytic Candidacidal	Cutler et al., 2005; Han et al., 1999
	Anti-glycosyl mAb	Enzyme and adhesion	Kawishwar et al., 2006
	Anti-sap2 and anti-MP65 domain antibodies.	neutralising	De Bernardis et al., 2006

Clinical trials of active and passive vaccination

There is no fungal vaccine approved or currently undergoing advanced clinical trials for active immunization in human beings. However, several vaccine manufacturers have fungal antigens under development as candidate vaccines. Vaccine formulation that have undergone limited phase I and phase II trials is against vulvovaginal candidiasis by a candida ribosome preparation (Levy et al., 1989). The result of this trial offered valid data on immunogenicity and, in the case of vulvovaginal candidiasis, the vaccine also showed some partial protection, but did not encourage further progress.

References

Bacci, A., Montagnoli, C., Perruccio. K. (2002). Dendritic cells pulsed with fungal RNA induce protective immunity to *Candida albicans* in hematopoietic transplantation. *J Immunol*.**168:** 2904–2913.

Bistoni, F., Vecchiarelli, A., Cenci, E., Puccetti, P., Marconi, P., Cassone, A. (1986). Evidence for macrophage-mediated protection against lethal *Candida albicans* infection. *Infect Immun*. **51:** 668–674.

Bodey, G. P. (2005). Managing infections in the immunocompromised patient. *Clin Infect Dis*. **40** (suppl 4)**:** S239.

Bozza, S., Montagnoli, C., Gaziano, R. (2004). Dendritic cell-based vaccination against opportunistic fungi. *Vaccine*. **22:** 857–64.

Briles, D. E., Forman, C., Crain. M. (1992). Mouse antibody to phosphocholine can protect mice from infection with mouse-virulent human isolates of *Streptococcus pneumoniae*. Infect. Immun. **60:** 1957–62.

Cappelletty, D., Eiselstein-McKitrick, K. (2007). The echinocandins. *Pharmacotherapy*. **27:** 369–88.

Cardenas-Freitag, L., Cheng, E., Mayeux, P., Domer, J. E., Clemens. J. D. (1999). Eff ectiveness of a vaccine composed of heat-killed *Candida albicans* and a novel mucosal adjuvant, LT(R192G), against systemic candidiasis. *Infect Immun*. **67:** 826–833.

Casadevall, A. (1995). Antibody Immunity and Invasive Fungal Infections. Infection and Immunity.63: 4211-4218.

Casanova, M., Martinez, J. P., Chaffin, W. L. (1990). Fab fragments from A monoclonal antibody against germ tube mannoprotein block the yeastto-mycelium transition in *Candida albicans*. Infect. Immun. **58:** 3810–3812.

Cassone, A. (2008). Fungal vaccines: real progress from real challenges.Lancet Infect dis. 8:114-124.

Cassone, A., Boccanera, M., Adriani. D., Dantoni, G., De Bernardis, F. (1995). Rats clearing a vaginal infection by *Candida albicans* acquire specifi c, antibody-mediated resistance to vaginal reinfection. *Infect Immun*. **63:** 2619–2624.

Cassone, A., Conti, S., De Bernardis, F., Polonelli, L. (1997). Antibodies, killer toxins and antifungal immunoprotection: a lesson from nature? *Immunol Today*. **18:** 164–69.

Cassone, A., Torosantucci, A. (2006). Opportunistic fungi and fungal infections: the challenge of a single, general antifungal vaccine. *Expert Rev Vaccines*; **5:** 859–67.

Cassone, A., Boccanera, M., Adriani, D.A., Santoni, G., De Bernardis. F (1995). Rats clearing a vaginal infection by *Candida albicans* acquire specific,antibody-mediated resistance to vaginal infection. Infect. Immun. **63:** 2619–2624.

Cates, K. L., Grady, P.G., Shapira, E., Davis, A. T. (1980). Cell-directed inhibition of polymorphonuclear leukocyte chemotaxis in a patient with mucocutaneous candidiasis. J. Allergy Clin. Immunol. **65:** 431–435.

Chilgren, R. A., Hong, R., Quie, P.G. (1968). Human serum interactions with *Candida albicans*. J. Immunol. **101:**128–132.

Cornely, O. A., Maertens, J., Winston. D. J. (2007). Posaconazole *vs*fl uconazole and itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. **356:** 348–59.

Cutler, J. E., Deepe, G. S., Klein, B. S. (2007).Advances in combating fungal diseases: vaccines on the threshold. *Nat Rev Microbiol*. **5:** 13–28.

Cutler, J. E. (2005). Defining criteria for anti-mannan antibodies to protect against candidiasis. *Curr Mol Med*. **5:** 383–92.

Datta, K., Pirofski, L. (2006). Toward a vaccine for *Cryptococcus neoformans*: principles and caveats. *FEMS Yeast Res*. **6:** 525–36.

De Bernardis, F., Liu, H., O'Mahony, R. (2006). Human domain antibodies against virulence traits of *Candida albicans* inhibit fungus adherence to vaginal epithelium and protect against experimental vaginal candidiasis. *J Infect Dis*. **195:** 149–57.

De Bernardis, F., Lucciarini, R., Boccanera, M. (2006). Phenotypic and functional characterization of vaginal dendritic cells in a rat model of *Candida albicans* vaginitis. *Infect Immun*. **74:** 4282–4294.

Deepe, G. S., Wuthrich, M., Klein, B. S. (2005). Progress in vaccination for histoplasmosis and blastomycosis: coping with cellular immunity. *Med Mycol.* **43:** 381–89.

Dromer, F., Perrone, C., Barge, J., Vilde, J.L., Yeni, P. (1989). Role of IgG and complement component C5 in the initial course of experimental cryptococcosis. Clin. Exp. Immunol. **78:** 412–417.

Epstein, J. B., Kimura, L. H., Menard, T.W., Truelove, E. L., Pearsall, N. N. (1982). Effects of specific antibodies on the interaction between the fungus *Candida albicans* and human oral mucosa. Arch. Oral Biol. **27:** 469–474.

Felton, L. D. (1928). The units of protective antibody in anti-Pneumococcus serum and antibody solution. J. Infect. Dis. **43:** 531–542.

Fidel, P.L., Jr., Sobel. J. D. (1998). Protective immunity in experimental *Candida* vaginitis. Res. Immunol. **149**:361-373.

Fischer, A., Ballet, J. J., Griscelli, C. (1978). Specific inhibition of in vitro *Candida*-induced lymphocyte proliferation by polysaccharide antigens present in the serum of patients with chronic mucocutaneous candidiasis. J. Clin. Invest. **62:** 1005–1013.

Gartner, B. N., Simmons, R. M., Underhill, D. M. (2005). Dectin-1 mediates macrophage recognition of *Candida albicans* yeasts but not filaments. *EMBO J*. **24:** 1277–86.

Giefing, C., Nagy, E., von Gabain, A. (2007). The antigenome: from protein subunit vaccines to antibody treatment of bacterial infections? In: Guzman CA, Feuerstein G, eds. Pharmaceuticalbiotechnology.Vienna: Landes Biosciences,. http://www.eurekah.com/book/1030#chapters (accessed Dec 17, 2007).

Gow, N. A., Brown. A. J., Odds, F. C. (2002). Fungal morphogenesis and host invasion. *Curr Opin Microbiol*. **5:** 366–371.

Graybill, J. R., Hague, M., Drutz, D. J. (1981). Passive immunization in murine cryptococcosis. Sabouraudia **19:** 237–244.

Han, Y., Ulrich, M. A., Cutler, J. E. (1999). *Candida albicans* mannan extract-protein conjugates induce a protective immune response against experimental candidiasis. *J Infect Dis*. **179:** 1477–84.

Han, Y., Cutler, J. E. (1995). Antibody response that protects against disseminated candidiasis. Infect. Immun. **63:** 2714–2719.

Hurd, R. C., Drake. C. H. (1953). *Candida albicans* infections in actively and passively immunized animals. Mycopathol. Mycol. Appl. **6:** 290–297.

Ibrahim, A. S, Spellberg, B. J, Avanesian V., Fu, Y., Edwards, J. E. (2006). The anti-candida vaccine based on recombinant N-terminal domain of Als1p is broadly active against disseminated candidiasis. *Infect Immun*. **74:** 3039–41.

Ip, W. K., Lau, Y. L. (2004). Role of mannose-binding lectin in the innate defense against *Candida albicans*: enhancement of complement activation but lack of opsonic function in phagocytosis by human dendritic cells. *J Infect Dis*. **190:** 632–640.

Kawishwar, A., Shukla, P. K. (2006). Candidacidal activity of a monoclonal antibody that binds with glycosyl moieties of proteins of *Candida albicans*. *Med Mycol*. **44:** 159–67.

LaForce, F. M., Mills, D. M., Iverson, K., Cousins, R., Everett, E.D. (1975). Inhibition of leukocyte candidacidal activity by serum from patients with disseminated candidiasis. J. Lab. Clin. Med. **86:** 657–666.

Latge, J. P, Calderone, R. (2002). Host-microbe interactions: fungi invasive human fungal opportunistic infections. *Curr Opin Microbiol*. **5:** 355–58.

Levitz, S. M. (2004). Interactions of Toll-like receptors with fungi. *Microbes Infect*. **6:** 1351–1355.

Levy, D. A., Bohbot, J. M., Catalan, F. (1989). Phase II study of D,651, an oral vaccine designed to prevent recurrences of vulvovaginal candidiasis. *Vaccine*.**7:** 337–40.

Lillegard, J. B., Sim, R. B., Thorkildson, P., Gates, M. A., Kozel, T. R. Recognition of *Candida albicans* by mannan-binding lectin in vitro and in vivo. *J Infect Dis*. **193:** 1589–1597.

Louria, D. B., Smith, J. K., Brayton, R. G., Buse, M. (1972). Anti-*Candida* factors in serum and their inhibitors. I. Clinical and laboratory observations. J. Infect. Dis. **125:** 102–114.

Maertens, J. (2007). Evaluating prophylaxis of invasive fungal infections in patients with haematologic malignancies. *Eur J Haematol*. **78:** 275–82.

Magliani, W., Conti, S., Salati, A. (2004). Engineered killer mimotopes: new synthetic peptides for antimicrobial therapy. *Curr Med Chem*. **11:** 1793–800.

Maitta, R. W., Datta, K., Lees, A., Belouski, S. S., Pirofski, L. A. (2004). Immunogenicity and effi cacy of *Cryptococcus neoformans* capsular polysaccharide glucuronoxylomannan peptide mimotope-proteinconjugates in human immunoglobulin transgenic mice. *Infect Immun*. **72:** 196–208.

Matthews, R. C., Burnie, J. P. (2004). Recombinant antibodies: a natural partner in combinatorial antifungal therapy. *Vaccine*. **22:** 865–71.

Matthews, R. C., Rigg, G., Hodgetts, S. (2003). Preclinical assessment of the effi cacy of mycograb, a human recombinant antibody against fungal HSP90. *Antimicrob Agents Chemother*. **47:** 2208–16.

Moragues, M. D., Omaxtebarria, M. J., Elguezabal, M. J. (2003). A monoclonal antibody directed against *Candida albicans* cell wall mannoprotein exerts three anti-*C albicans* activities. *Infect Immun*. **71:** 5273–79.

Morris, A., Masur, H., Huang, R. (2006). Current issues in critical care of the human immunodefi ciency virus-infected patient. *Crit Care Med*. **34:** 42–49.

Mukherjee, J., Scharff, M. D., Casadevall, A. (1995). Variable efficacy of passive antibody administration against diverse *Cryptococcus neoformans* strains. Infect. Immun. **63:** 3353–3359.

Nucci, M., Marr, K. A. (2005). Emerging fungal diseases. *Clin Infect Dis*. **41:** 521–26.

Oscarson, S., Alpe, M., Svahnberg, P., Nakouzi, A., Casadevall, A. (2005). Synthesis and immunological studies of glycoconjugates of *Cryptococcus neoformans* capsular glucuronoxylomannan oligosaccharide structures. *Vaccine*. **23:** 3961–72.

Pachl, J., Svoboda, P., Jacobs, F. (2006). A randomized, blind,multicenter trial of lipid-associated amphotericin B alone versus in combination with an antibody-based inhibitor of heat-shock protein 90 in patients with invasive candidiasis. *Clin Infect Dis*. **42:** 1404–13**.**

Pagano, L., Caira, M., Candoni, A. (2006). The epidemiology of fungal infections in patients with hematologic malignancies: the SEIFEM-2004 study. *Hematologica*. **91:** 1068–75.

Perruccio, K., Bozza, S., Montagnoli, C. (2004). Prospects for dendritic cell vaccination against fungal infections in hematopoietic transplantation. *Blood Cells Mol Dis*. **33:** 248–55.

Pfaller, M. A., Diekema, D. J. (2007). Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev*. **20:** 133–63

Polak, A. (2003). Antifungal therapy—state of the art at the beginning of the 21st century. *Prog Drug Res*. spec no: 59–190.

Polonelli, L., De Bernardis, F., Conti, S. (1994). Idiotypic intravaginal vaccination to protect against candidal vaginitis by secretory yeast killer toxin-like anti-idiotype antibodies. *J Immunol*. **152:** 3175–82.

Polonelli, L., Lorenzini, R., De Bernardis, F. (1993). Idiotypic vaccination: immunoprotection mediated by anti-idiotypic antibodies with antibiotic activity. *Scand J Immunol*. **37:** 105–10.

Polonelli, L., Gerloni, M., Conti, S., Fisicarp, P., Cantelli, C., Portincasa, P., Almondo, F., Barea, P. L., Hernandao, F. L., Ponton, J. (1994). Heat-shock mannoproteins as targets of secretory IgA in *Candida albicans*. J. Infect. Dis. **169:** 1401–1405.

Preilser, H. D., Hasenclever, H. F., Levitan, A. A., Henderson, E .S. (1969). Serologic diagnosis of disseminated candidiasis in patients with acute leukemia. Ann. Intern. Med. **70:**19–25.

Rappuoli, R. (2004). From Pasteur to genomics: progress and challenges in infectious diseases. *Nat Med*. **10:** 1177–1185.

Romani, L., Mencacci, A., Cenci, E., Mosci, P., Vitellozzi, G., Grohmann, U., Puccetti, P and Bistoni, F. (1992). Course of primary Candidiasis in T-cell-depleted mice infected with attenuated variant cells. J. Infect. Dis. **166**: 1384-1392.

Safdar, A. (2006). Strategies to enhance immune function in hematopoietic transplantation recipients who have fungal infections. *Bone Marrow Transplant*. **38:** 327–37.

Sandini, S., La Valle, R., De Bernardis, F., Macri, C., Cassone, A. (2007). The65 kDa mannoprotein gene of *Candida albicans* encodes a putative beta-glucanase adhesin required for hyphal morphogenesis and experimental pathogenicity. *Cell Microbiol*. **9:** 1223–1238.

Sanford, J. E., Lupan, D .M., Schlageter, A. M., Kozel, T .R. (1990).Passive immunization against *Cryptococcus neoformans* with an isotype switch family of monoclonal antibodies reactive with cryptococcal polysaccharide.Infect. Immun. **58:**1919–1923.

Schaberg, D. R., Culver, D. H., Gaynes, R. P. (1991). Major trends in the microbial of nosocomial infection. *Am J Med*. **91** (suppl 3B)**:** 72S–75S.

Scheld, W. M., Calderone, R. A., Brodeur, J. P., Sande, M.A. (1983). Influence of preformed antibody on the pathogenesis of experimental *Candida albicans* endocarditis. Infect. Immun. **40:** 950–955.

Segal, E., Elad, D. (2006). Fungal vaccines and immunotherapy. *J Mycolog Med.* **16:** 134–151.

Shoham, S., Levitz, S. M. (2005). The immune response to fungal infections. *Br J Haematol*; **129:** 569–582.

Sims, C. .R, Ostrosky-Zeichner, L., Rex, J. H. (2005). Invasive candidiasis in immunocompromised hospitalized patients. *Arch Med Res*. **36:** 660–71.

Solomkin, J. S., Milis, E. L., Giebink, G. S., Nelson, R. D., Simmons, R., Quie, P. G. (1978). Phagocytosis of *Candida albicans* by human leukocytes: opsonic requirements. J. Infect. Dis. **137:** 30–37.

Spellberg, B. J., Ibrahim, A. S., Avanesian, V. (2006). Efficacy of the anti-candida rAls3p-N or Als1p-N vaccines against disseminated and mucosal candidiasis. *J Infect Dis*. **194:** 256–260.

Thomas, S. W., Viudes A., Monteagudo, C., Lozell, A.L, Saville, S. P, Lopez-Ribot, J. L. (2006). A proteomic-based approach for the identification of *Candida albicans* protein component present in a subunit vaccine that protects against disseminated candidiasis. *Proteomics*. **6:** 6033–41.

Torosantucci, A., Bromuro, C., Chiani, P. (2005). A novel glyco-conjugate vaccine against fungal pathogens. *J Exp Med*. **202:** 597–606.

Ullmann, A. J., Lipton, J. H., Vesole, D. H. (2007). Posaconazole or fl uconazole for prophylaxis in severe graft-versus-host-diseases *N Eng J Med*. **356:** 335–47.

Umazume, M., Ueta, E., Osaki, T. (1995). Reduced inhibition of *Candida albicans* adhesion by saliva from patients receiving oral cancer therapy. J. Clin. Microbiol. **33:** 432–439.

Vudhichamnong, K., Walker, D. M., Ryley, H. C. (1982). The effect of secretory immunoglobulin A on the *in-vitro* adherence of the yeast *Candida albicans* to human oral epithelial cells. Arch. Oral Biol. **27:** 617–621.

Walker, S. M., Urbaniak, S. J. (1980). A serum-dependent defect of neutrophil function in chronic mucocutaneous candidiasis. J. Clin. Pathol. **33:** 370–372.

Wenzel, R. P., Gennings, C. (2005). Bloodstream infections due to *Candida* species in the intensive care unit: identifying especially high-riskpatients to determine prevention strategies. *Clin Infect Dis*. **41** (suppl 6)**:** S389–93.

Wheeler, R. T., Fink, G. R. (2006). A drug-sensitive genetic network masks fungi from immune system. *PLoS Pathog*. **2:** 328–37.

Wingard, J. R. (2007). New approaches to invasive fungal infections in acute leukemia and hematopoietic stem cell transplant patients. *Best Pract Res Clin Haematol*. **20:** 99–107.

Wisplinghoff, H., Bischoff, T., Tallent, H., Seifert, R., Wenzel, F., Edmond, M. B. (2004) Nosocomial bloodstream infections in US hospitals: analysis of 24 179 cases from a prospective nationwide surveillance study. *Clin Infect Dis*. **39:** 309–17.

Witkin, S. S. (1986). Inhibition of *Candida*-induced lymphocyte proliferation by antibody to *Candida albicans*. Obstet. Gynecol. **68:** 696–699.

Yuan, R., Casadevall, A., Spira, G., Scharff, M. D. (1995). Isotype switching from IgG3 to IgG1 converts a non-protective murine antibody to *C. neoformans* into a protective antibody. J. Immunol. **154:**1810–1816