Prospects of vaccines for medically important fungi

This is the third in a series of reviews that detail the basic science progress in the quest to achieve vaccines for several of the medically important fungi.

Review

Progress in vaccination for histoplasmosis and blastomycosis: Coping with cellular immunity

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Human infection with *Histoplasma capsulatum* or *Blastomyces dermatitidis* is sufficiently frequent to warrant exploring the development of vaccines. This review examines the advancements that have been accomplished over the last few years. The availability of molecular tools to create recombinant antigens or mutant strains has produced a small number of useful vaccine candidates. More importantly, the studies summarized herein demonstrate that understanding the host response to a protein or mutant fungus is critical to creating a vaccine that may be useful for the immunocompromised patient.

**Keywords** vaccines, T cells, cytokines, histoplasmosis, blastomycosis

Introduction

A previous review posed a salient question regarding vaccination for a particular fungus. Is it needed? The focus was on *Candida albicans*, the most common causative agent of fungal infection in man [1]. Unlike many other causes of fungal diseases in humans, *Candida* is a natural resident of the human host. *Histoplasma capsulatum* and *Blastomyces dermatitidis*, on the other hand, are quite different in that regard. As soil-based fungi, infection of humans is largely dictated by chance. These fungi do not seek the human host to survive or propagate, and humans are largely incidental hosts in the lifecycle of each of these species. The question raised by the authors of the review of vaccination for *C. albicans* has more urgency than the two fungal diseases listed above. One of the major impediments in deciding if human vaccines for histoplasmosis and/or blastomycosis are cost-effective is the lack of epidemiological data regarding incidence and prevalence of infection. Although the state of Wisconsin does track blastomycosis, there is no national effort on behalf of these fungal diseases or of any of the other systemic mycoses. Thus, the field of mycology and in particular the arena of systemic mycoses needs this epidemiological information. The major effort in vaccinology in the past concentrated on causative agents of childhood diseases such as rubella, rubeola, and polio. The scientific approach was to create hypovirulent or attenuated strains that would cause mild illness but induce protective immunity that was durable. The primary mediator of that immunity is the generation of neutralizing antibodies. For histoplasmo-
Many cases of disseminated blastomycosis are present. Unlike Histoplasma, Blastomyces more often spreads to bone and skin. Unlike Histoplasma, Blastomyces can produce a pneumo-

Clinical manifestations

Infection with H. capsulatum or B. dermatitidis is acquired by incidental inhalation of conidia or mycelial fragments upon exposure to soil laden with the fungus. Following exposure, the organisms transform into the yeast phase which is responsible for the clinical and pathological manifestations of the diseases. Most exposures are asymptomatic or induce an influenza-

Elements of the protective immune response to histoplasmosis and blastomycosis

The rational design of vaccines for histoplasmosis and blastomycosis requires a fundamental understanding of their immunobiology. Both fungi rely on a Th1 or type I response for protective immunity. The complexities of Th1 and Th2 immunity have been published in a previous review in this journal and will not be further elaborated herein [5]. Interleukin (IL)-12, interferon (IFN)-γ and tumor necrosis factor (TNF)-α are essential constituents for the ontogeny of protective immunity in a naïve host [6–18]. In their absence, animals succumb to infection. IL-12 is one of the principal stimuli for inducing a Th1 response, and it does so by inducing the production of IFN-γ. Thus, the IL-12-IFN-γ axis is a critical feature of protective immunity to these fungi.

Likewise, TNF-α is required for survival of infected mice. In mice infected with H. capsulatum, the major immunological defect associated with a lack of TNF-α is a deficiency in production of nitric oxide [9,14]. This molecule is crucial in the generation of protective immunity. One mechanism is that it binds iron and, thus, removes this essential growth element from the fungus. Infection of murine macrophages with a virulent isolate of B. dermatitidis induces the production of transforming growth factor (TGF)-β, a cytokine known to express potent deactivating properties. The BADI (for Blastomyces adhesin-1) molecule on the surface of this fungus is the major culprit in inducing production of this cytokine [6,7]. A hypovirulent mutant strain that has a deletion of the BADI gene does not induce TGF-β, but rather a strong TNF-α response. Thus, there is a correlation between virulence, cytokine production, and the surface molecule BADI. Yeast cells lacking this surface molecule are killed by murine macrophages and this killing is associated with production of TNF-α. The wild-type strain or a revertant of the mutant is not readily killed by macrophages. This scenario is accompanied by vigorous TGF-β production and weak TNF-α release. The countervailing forces of high TGF-β and dysfunctional macrophages and high TNF-α and functional macrophages provide an understanding of the influence of TNF-α in the protective immune response.

Other molecules are key in primary host defenses to H. capsulatum. Leukotrienes are required for an effective cellular immune response [19]. Likewise, defensins contribute to the clearance of H. capsulatum, although their in vivo role remains to be defined [20,21]. Endogenous granulocyte macrophage colony-stimulating factor (GM-CSF) is another cytokine that is essential for protective immunity in primary infection [20–23]. In vivo neutralization leads to uncontrolled infection and ultimately the death of animals. The absence of this cytokine leads to numerous perturbations in cytokine levels including decreases in IFN-γ, TNF-α, and nitric oxide and elevations in IL-4 and IL-10. The latter two are potent inhibitors of cellular immunity to this fungus.

In secondary histoplasmosis, IFN-γ appears to be largely dispensable [14]. Neutralization of this cytokine in combination with blockade of its cognate receptor in immune animals does not markedly alter the protective immune response in secondary infection. On the other hand, TNF-α is vital and its absence leads to the death of mice. In mice infected with H. capsulatum, the major immunological perturbation appears to be a pro-
nounced elevation in IL-4 and IL-10 [9]. Both are required for the impaired immunity since in vivo neutralization of either one alone did not improve the outcome of infection. However, neutralization of both restores protective immunity in TNF-α-deficient mice.

TNF-α mediates its biological activities through two receptors, TNF receptor (R) 1 and 2. The lack of either one is detrimental to host resistance to H. capsulatum [24]. However, mice that are deficient in TNFR1 are much more susceptible to infection than those that are missing TNFR2. Infection with as few as 10³ yeasts resulted in death of TNFR1 knockout mice, whereas 10⁵ yeasts are handled by TNFR2 knockout mice. Yeast numbers greater than 10⁵ lead to unremitting infection in both groups. The mechanisms that lead to impaired immunity differ between the two strains of mice. TNFR1 knockout mice manifest impaired inflammatory responses, whereas those that lack the other receptor fail to generate IFN-γ. Immunity is restored in TNFR2 knockout mice by treatment with recombinant IFN-γ [24].

**Vaccination for histoplasmosis**

The history of a vaccine for H. capsulatum dates to studies in the 1960s in which injection of yeasts conferred a protective immune response upon subsequent challenge. Others demonstrated that an ethylenediamine extract of the yeast and a ribosomal-protein complex vaccinate mice against inoculation with yeasts [25–27]. Following those reports, little had been pursued concerning a vaccine. Several years later, in an analysis of antigen recognition by H. capsulatum-reactive T cell clones, one protein emerged as a immunodominant antigen. This antigen is recognized by 67–100% of monoclonal populations of T cells raised against a detergent extract from the cell wall and cell membrane of yeasts [28]. This antigen was originally called His 62 because of its approximate molecular weight of 62 kDa. Immunization with this antigen produced a marked response by T cells from injected animals. Moreover, immunization with native His 62 confers a protective immune response in C57BL/6, BALB/c, and CBA/J mice to a lethal intravenous challenge with H. capsulatum yeasts [29]. This finding produced the first report of a putatively single antigen from this fungus that could confer protection in an animal model.

The antigen was originally identified by Edman degradation of peptide fragments as homologous to heat shock protein (hsp) 60. Recombinant protein was generated, and it also conferred protection in mice to an intranasal challenge [30]. This finding was somewhat surprising since hsp are highly homologous to one another. The H. capsulatum protein was approximately 75% homologous to hsp 60 from Saccharomyces cerevisiae, Mus musculus, and Homo sapiens, and approximately 50% homologous to this family from bacteria.

Immunological dogma posits that most if not all potent immunogens from microbial pathogens are surface-bound. Classically, hsp 60 is a cytosolic protein although it has been reported to be on the surface of some pathogens [31,32]. H. capsulatum yeasts adhere to the CD11/CD18 family of integrins on the surface of macrophages [33,34]. In a search for the ligand on the surface of the yeasts that engage the macrophage receptors, hsp 60 emerged as a leading candidate on the basis of the following information [31,35]. Native and recombinant protein bound complement receptor 3 in a Far Western blot. Immunelectron microscopy and flow cytometry both indicated that hsp 60 was on the surface of yeasts. Recombinant hsp 60 but not H antigen could block binding of yeasts to the surface of macrophages.

A major unanswered question is how this molecule transits to the surface. One possibility is that it is shed from dying organisms and attaches to the surface of viable yeasts. This scenario is similar though not identical to that of BAD1 from B. dermatitidis. This molecule is shed and attaches via chitin to the surface of the fungus [36]. An alternative explanation is that there is a transport signal, as yet unidentified, that promotes trafficking to the surface. Nevertheless, the appearance of hsp 60 on the surface provides an explanation for its potent immunogenic properties. Moreover, the findings indicate that not only is this protein a target of the cellular immune response, but it may also be considered a virulence determinant since it promotes the entry of yeasts into macrophages where the organisms can survive.

**Mapping the determinants of hsp 60**

Additional work has demonstrated that all the immunological activity of hsp 60 is located within a stretch of amino acids 172–443 [37]. This knowledge was acquired by generating overlapping fragments of the protein and testing them not only for ability to induce a cellular immune response but also to protect mice. Four fragments were generated by recombinant technology and tested in this manner. All four induced a cellular immune response in mice as assessed by T cell proliferation assays. However, only one fragment, termed F3, was protective. These results suggest that
a correlation between ability to induce a cellular response and a protective response may not exist.

**Other antigens from H. capsulatum**

Two additional proteins from this fungus have been reported to be protective against a challenge with *H. capsulatum* in mice. One is a member of the hsp 70 family that was called HIS 80 [38]. Vaccination with it mediated a modest protective effect in mice whereas vaccination with hsp 70 was not protective [39]. The other protein was H antigen, which had been used for years in immunodiagnosis. The antigen was cloned and found to be a member of the β-glucosidase family. Originally, vaccination did not induce a protective immune response against an intravenous challenge [40]. Studies performed later revealed that the antigen was protective in an intranasal model [41]. This result indicated that the route of exposure to a pathogen may alter vaccine effectiveness. When yeasts were delivered in a manner similar to that of natural infection, the H antigen exerted protection whereas it failed to do so in a model of systemic infection induced by intravenous inoculation. At present, the reasons for this discrepancy are not known. One potential explanation is that the high and rapid burden delivered to the spleen via the intravenous route may require a more vigorous T cell-dependent immune response.

A cell free extract of *H. capsulatum* yeasts induces a protective immune response when used as a vaccine [42]. This material is prepared by vortexing yeasts in a small volume of buffer and removing the particular material. The identity of the protective molecules has not been determined.

**Hsp and vaccination**

The high homology of fungal hsp to their mammalian counterparts raises the concern that immunization with these molecules might induce autoimmunity as a result of cross-reactivity with the mammalian proteins. There is little evidence to support this theoretical adverse effect. In fact, T cells from mice that have not been exposed to this fungus or the *H. capsulatum* hsp do not respond to *H. capsulatum* hsp 60 or 70 [29,30,39].

**Antibodies and vaccination**

There are scant data regarding the efficacy of antibodies in naturally acquired infection, but that does not preclude a role for them in vaccination. In this regard, a recent report suggests that a monoclonal antibody to the surface of *H. capsulatum* can be useful as immunotherapy when injected concomitant with fungus [43]. The antigen recognized by this antibody has been identified as a histone, H2B-like protein. Administration of the antibody alone produced only a modest effect in reducing fungal burden or improving survival. However, when the antibody was combined with subtherapeutic amounts of the antifungal amphotericin B, there was a dramatic improvement in survival of mice that received the antifungal plus the antibody when compared to those that received the antifungal alone. These results substantiate the utility of antibody for this infection, and the data suggest that the immunomodulatory properties of amphotericin may enhance the efficacy of the antibody. Additional studies are needed to determine if immunization with the antigen induces any protective antibodies in a pool of those produced.

**Immunological requirements for efficacy of hsp 60**

One of the primary goals of vaccinology should be to understand at the immunological level what makes a vaccine efficacious. Immunization with hsp 60 stimulates strong production of IL-10, IL-12, and IFN-γ by splenocytes from immunized mice [44]. IL-4, TNF-α, and GM-CSF were either not detected or weakly produced when compared to animals injected with hsp 70 or bovine serum albumin. The levels of IL-12 following vaccination with hsp 60 exceeded those of hsp 70 and this may be one explanation for the efficacy of the former antigen.

These findings prompted studies to examine the necessity of those cytokines both in the afferent phase of immunization (the phase when the vaccine is given) and the efferent phase (postvaccination). IL-12, IFN-γ, and IL-10 were required for vaccine efficacy in the afferent phase. The surprising finding was that IL-10, which is often associated with inhibiting immune responses and potent anti-inflammatory effects, was necessary for hsp 60 to protect. The source of IL-10 appeared to be largely from non-T cells. IL-10 has been reported to be necessary for additional vaccines [45–47]. In the afferent phase, IL-12 and IFN-γ were required for protection mediated by hsp 60.

CD4+ cells must be present during the afferent phase in order that hsp 60 function optimally. Elimination of CD8+ -bearing cells at this time does not alter the efficacy of vaccination with this antigen. On the other hand, elimination of either population in the efferent phase only modestly to moderately impacted the utility of hsp 60. Elimination of both T cell subsets
abrogated the protective efficacy mediated by hsp 60 [44].

**T cell receptor (TCR) repertoire to hsp 60 and F3**

Given the importance of T cells in immunization with hsp 60, studies were conducted to determine if particular T cell receptor (TCR) families were involved. The approach was to create T cell clones and by reverse transcriptase-polymerase chain reaction (RT-PCR) identify the β chain of the variable (V) region of the TCR. The advantage of this method is that monoclonal antibodies (mAb) exist to confirm the RT-PCR findings and that the mAb can be used to eliminate the population. The majority of T cells from mice immunized with hsp 60 expressed Vβ 8.1/8.2 [48]. Other families included Vβ 4, 6, or 11. When the Vβ 8.1/8.2+ cells were eliminated by treatment with mAb in immunized mice, all T cell clones that were reactive to hsp 60 expressed Vβ 4. Furthermore, depletion of the Vβ 8.1/8.2+ cells abrogated the protection conferred by hsp 60. Upon further examination using T cell clones, a subset of this family was responsible for protection. Vβ 8.1/8.2+ cells that were Th1 and reacted to the protective fragment, F3, were responsible for protection. If the cells did not react to F3, they were not protective. Th2 clones, even if they expressed Vβ 8.1/8.2+, were not protective, but did exacerbate infection.

Since IL-10 and IFN-γ are central in the functional integrity of hsp 60, IL-10 or IFN-γ knockout mice were immunized with this protein to ascertain if the TCR repertoire was altered. Indeed, in both groups the absence of one of those cytokines produced a shift in the TCR profile [49]. This alteration was more pronounced in IFN-γ knockout mice as compared to mice deficient in IL-10. Adoptive transfer of either T cell subset did not mediate a protective immune response. These results established the importance of both IL-10 and IFN-γ in shaping the TCR repertoire during the protective immune response induced by hsp 60.

The TCR repertoire of T cell clones from mice immunized with F3, the protective fragment of hsp 60 also was explored. The initial report indicated that nearly all the T cell clones expressed the Vβ 6 family and each of them was of the Th1 phenotype [50]. The only additional Vβ present was 14. Interestingly, T cell lines derived from mice whose Vβ 6 cells were eliminated did not recognize the antigen. This finding is in contradistinction to that of elimination of Vβ 8.1/8.2+ from mice immunized with hsp 60 in which another family, Vβ 4, arose that could recognize the antigen. Vβ 6+ cells could transfer protection if they were Th1, whereas Vβ 14+ cells did not [50]. Thus, protection was confined to a single family. The importance of this family was extended by showing that elimination of Vβ6+ cells during vaccination abrogated protective immunity mediated by F3. This finding highlights the significance of a single Vβ family in the protective immune response to vaccination.

After the original report regarding the TCR usage in mice immunized with F3, additional T cell clones were analysed, and, surprisingly, this panel was more heterogeneous than the original group in terms of Vβ expression. Moreover, Th2 clones were also found. When adoptive transfer studies were performed, only the Vβ 6+ clones that were Th1 mediated protection [51]. If Th2 clones were transferred, they induced exacerbation of infection. Unlike the protective response mediated by Vβ 6+ cells that are Th1, several Vβ families that are of the Th2 phenotype heightened the severity of infection.

What is the importance of these studies concerning the TCR usage? Data clearly show that upon immunization of a host, an antigen that causes T cell outgrowth induces a bias in the phenotype of T cells that emerge. In fact, the evidence from these studies strongly suggests that only a small number of T cells may be requisite for the protective immune response. If these cells are congenitally absent from an immunized host, the vaccine may not be functional, as indicated by the above studies. The findings may be one explanation for the failure of the vaccine to be efficacious in a given individual.

An intriguing extension of the above data is that patients who develop disseminated histoplasmosis might have a ‘hole’ in the TCR repertoire, thus rendering them more susceptible for progressive disease. There are no data in this regard, and most cases of disseminated histoplasmosis occur in immunocompromised patients that either lack T cells, such as in AIDS, or possess dysfunctional T cells induced by immunosuppressive therapeutics. However, if there is a subset of individuals that are predisposed to disseminated disease because of a missing TCR family, it may be possible to vaccinate them if the absent family is not identical to the one engaged by the vaccine.

Another finding that emerges is that hsp 60 and F3 elicited both a Th1 and Th2-expressing T cell clones. Since Th1 cells are necessary for clearance of *H. capsulatum*, the question arises as to whether a protein that stimulates the expansion of both Th1 and Th2 cells is not the optimal candidate. Perhaps, it can be argued
that a protein or peptide that strictly induces Th1 cells is the best candidate. However, two key features of Th2 response need to be considered in vaccine design. First, sole generation of Th1 cells may lead to a hyper-inflammatory response when the host confronts the invading pathogen. The presence of Th2 cells may inhibit the aggressiveness of inflammation without dampening the protective effect. Secondly, data are emerging about the central role of antibodies to several fungal pathogens including *H. capsulatum*. The Th2 response may, therefore, promote the protective response by inducing the expansion of B cell clones that release protective antibodies.

**Vaccination with BAD1**

The surface molecule of *B. dermatitidis* was originally identified as a dominant target of the human humoral and cellular immune response to this fungus [52,53]. Upon discovery, it was named WI-1 and subsequently changed to BAD1. The molecular composition was determined by cloning and sequencing [54]. The structure of the protein can be divided into three domains: (1) a hydrophobic amino terminus that harbors a secretion signal, (2) a central region with numerous tandem repeats that display B-cell epitopes and bind complement type 3 receptors [55], and (3) a carboxy end that has homology to epidermal growth factor and fixes the protein to the yeast cell surface [56]. The central region containing the tandem repeats also possesses homology to the *Yersinia* virulence factor invasin, which is important for this bacterium to enter mononuclear phagocytes and non-phagocytic cells via β1 integrin receptors [54,57]. The BAD1 antigen has similarly been found to be a virulence determinant as well as a target of the immune system. Gene deletion reduced the virulence of this fungus dramatically and was associated with poor binding to phagocytes [58]. BAD1 can mediate virulence by mechanisms in addition to cellular adherence, since the molecule modulates the profile of pro-inflammatory cytokines and shapes the composition of leukocytes that migrate into inflamed lung. In either a soluble form, or when bound to the yeast surface, BAD1 binding of CR3 ‘exploits’ natural mechanisms that phagocytes employ to dampen inflammation on ingesting apoptotic cells [59]. Pathogen suppression of TNF-α released by host phagocytes in this manner may thereby subvert host defense [6,7].

It had been postulated that engendering an immune response to a major virulence factor such as BAD1 could provide the host a selective advantage and prevent against infection, either through prompt pathogen recognition, or possibly by neutralization of BAD1 function. In an early series of studies, recombinant BAD1 was utilized to vaccinate mice [60]. Despite the fact that the protein was immunodominant, the effect was not striking. In multiple experiments, immunization with this protein prolonged the mean time of survival when compared to controls, but the number surviving over 30 days was modest. The lack of efficacy could not be correlated with an inability to stimulate a T cell-dependent and a B cell-dependent response. The protective effect of BAD1 as a vaccine was augmented when it was given with IL-12 as an adjuvant. Administration of both BAD1 and the cytokine was associated with a shift in the antibody response and an improvement in delayed-type hypersensitivity responses to this antigen. Yet, even with this regimen, the immunogenicity was not overwhelming. Mean time to death was prolonged and CFU were diminished when compared to animals vaccinated with only BAD1, but the number of animals that survived was low.

An alternative approach designed to explore anti-BAD1 antibody-mediated immunity investigated the efficacy of BAD1 monoclonal antibodies in prevention of infection [61]. *In vitro*, mAbs to BAD1 increased binding and entry of *B. dermatitidis* yeast into macrophages, but this did not enhance killing of the yeast. *In vivo*, none of a series of mAbs protected mice against experimental pulmonary infection, and B-cell knockout mice demonstrated significantly enhanced resistance to *B. dermatitidis* infection. Hence, there is no evidence to date that inducing an antibody response against BAD1 or other *B. dermatitidis* determinants will protect susceptible hosts or improve the outcome of infection in a measurable way.

The inability of recombinant BAD1 to rescue mice from a pulmonary challenge with *B. dermatitidis* stimulated a search for other approaches to vaccination. The *BAD1*-null mutant, as mentioned above, is hypovirulent in a mouse model. This finding suggested that it might induce an immune response in mice and hopefully a protective immune response. When live yeast of the mutant strain were injected subcutaneously in the absence of adjuvant there was a marked improvement in the survival of mice challenged intrapulmonary with this fungus [62]. The survival was associated with a sharp decrease in the number of CFU found within lungs. Remarkably, the majority of the vaccinated mice survived a lethal challenge and demonstrated sterilizing immunity. The effect of the mutant could be mimicked by injection of a cell wall and cell membrane preparation from the knockout strain. Protection was correlated with vigorous production of IFN-γ and with T cell activation and proliferation. This
Report was the first to indicate that a genetically engineered strain of fungus could be employed as a vaccine.

Immunological requirements for vaccine efficacy

Studies of vaccine mechanisms in immune-competent and immune deficient mice uncovered plasticity of residual immune elements in compromised hosts both at the cellular and molecular level. In immune-competent mice, CD4+ cells mediated resistance chiefly by production of TNF-α and IFN-γ [12,63]. Surprisingly, although both of these regulatory cytokines were crucial mediators of vaccine expression, the effectiveness of vaccination with the mutant strain did not require the pre-existing presence of IFN-γ or TNF-α. The efficacy of vaccination in IFNγ−/− or TNF-α−/− mice did require either the reciprocal cytokine or GM-CSF since neutralization of these cytokines reversed the immunogenicity of the vaccine. The vaccine did require TCR γ/β+ cells but functioned well in the absence of either CD4+ or CD8+ cells. Moreover, production of oxygen intermediates, but not nitrogen intermediates, were required for the vaccine to protect [12]. Immunization of mice lacking the inducible nitric oxide synthase gene or the adenine dinucleotide phosphate (NADPH) oxidase system (phox) produced quite different results. The absence of the nitric oxide synthase gene did not alter the utility of the vaccine, whereas the absence of phox did. This finding strongly suggests that the vaccine must protect through generation of oxygen intermediates that most likely damage the virulent isolate. More importantly, this study unequivocally demonstrates that vaccination of immunodeficient hosts can be accomplished.

The investigators extended these studies and reported that the efficacy of the BAD1-null mutant vaccine in CD4−/− mice relied on competent CD8+ cells [63]. This finding was extended to H. capsulatum, although with that organism the wild-type strain was used to immunize subcutaneously. The CD8+ cells required interaction with major histocompatibility complex I antigens. These cells functioned appropriately in the absence of either TNF-α or IFN-γ. In the absence of TNF-α, GM-CSF compensated and, in the absence of the IFN-γ, TNF-α and GM-CSF regulated the expression of immunity. Vaccine immunity to Blastomyces and Histoplasma thus overcame a requirement for CD4 help, and that immunity was durable for at least 8 weeks post-vaccination. This is in contrast to the findings of recent studies with CD4-help independent CD8 memory responses against viral and bacterial infections, which waned over a similar interval of time, indicating that CD8 memory to fungi may be durable and biologically distinct from CD8 memory against viruses and bacteria. The most likely mechanism to explain the effect of CD8+ cells is through cytokine production [63]. There is no evidence in either infection that cytotoxicity exerted by CD8+ cells influences the course of infection.

Who and when to vaccinate

A crucial issue that must be addressed for these two fungi is who and when to vaccinate. These will not be ‘universal’ vaccines since the fungi do have a geographic limitation. Both infections pose a risk only for those in the endemic areas of the world. Certainly, vaccinees should include those who are engaged in outdoor activities in which either their métier or their recreational activities brings them into contact with the soil or caves. Thus, workers in construction, especially those refurbishing older buildings, are at risk. Others at risk include agricultural workers, those building roads, etc. Recreational activities such as spelunking also pose a risk.

The age of vaccination is a major issue. In the absence of solid epidemiological data that indicate the age of disease acquisition it is difficult to prescribe a specific age. Moreover, the need to induce robust T cell immunity requires a mature immune system. Large-scale skin testing has shown that delayed type hypersensitivity indicative of prior exposure is evident in most school-aged children living in the endemic region. Thus, the earliest ages for vaccination are probably within the 2–3 year-old range.

Conclusions

These findings represent a significant step forward in vaccination, since many individuals who may profit the most from a vaccine may be immunosuppressed either by underlying disease such as AIDS or by pharmacological agents given to treat malignancies, autoimmune conditions, and organ rejection. These individuals are the ones who are most likely to acquire complicated fungal infections. Thus, a vaccine that can be used for the ever expanding numbers of immunosuppressed patients is a real boon to the armamentarium of the clinician. Not only may lives be saved, but the total cost of health care may be sharply reduced. What is now required is a thorough cost-benefit evaluation.

The future of vaccination for histoplasmosis and blastomycosis requires a thorough knowledge of the epidemiology of these fungal infections. This knowl-
edge will provide information regarding the age at which vaccination should be initiated. Additional work needs to be conducted to determine the durability of vaccines and their utility not only as preventive, but also therapeutic vaccines.

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