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Immunization Strategies for the Control of Histoplasmosis

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Abstract

Histoplasmosis is an infection caused by the dimorphic fungus *Histoplasma capsulatum*. Histoplasmosis is typically self-limited and presents asymptomatically in most people. Nevertheless, histoplasmosis can cause severe pulmonary disease and death. Histoplasmosis is increasingly found worldwide; however, it is best documented in the endemic region of the Mississippi river valley system in the Eastern part of the United States (US). Epidemiological studies from the US detailing the morbidity, mortality, and cost associated with histoplasmosis underscore the need to develop a vaccine.

Purpose of review: This review will detail some of the major developments in potential vaccines against histoplasmosis, with particular emphasis on those that could be used to immunize immunocompromised hosts. Additionally, this review will highlight some non-traditional vaccine-like ideas for the prevention of diverse mycoses.

Recent findings: Historically, immunization strategies against histoplasmosis have largely focused on identifying immunogenic proteins that confer protection in animal models. More recently, novel active, therapeutic, and immunomodulatory strategies have been explored as potential alternatives for those with various immune-deficiencies.

Summary: The studies summarized in this review demonstrate that more research is needed to clarify the immunobiology, clinical role and efficacy of each candidate vaccine in the ever-expanding potential armamentarium against histoplasmosis.

Keywords

histoplasmosis; *H. capsulatum*; vaccine; T cells; antibodies; immune-therapy

Introduction

Histoplasmosis is an infection caused by *Histoplasma capsulatum* (*H. capsulatum*), a thermally dimorphic ascomycete fungus. *H. capsulatum* and, correspondingly, histoplasmosis is increasingly found worldwide [1–3]. Of all the systemic mycoses, histoplasmosis is the most common in North America, with the majority of cases occurring

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Conflict of Interest

Maxwell T. Roth, Daniel Zamith-Miranda, and Joshua D. Nosanchuk declare no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

within the endemic region of the Mississippi river valley system in the Eastern part of the United States (US) [4–6]. From 2011 to 2014, a total of 3,409 cases of histoplasmosis were documented in health surveillance records across 12 states, including those within and outside the classically defined endemic region of the continental US. State-specific annual incidence rates of histoplasmosis ranged up to 4.3 cases/100,000 population and were relatively consistent over the 4 year period [6]. Due to a lack of reporting and robust public health surveillance data, however, the true incidence and burden of histoplasmosis in the US may be underestimated.

H. capsulatum infection is a serious public health issue as it can cause severe disease and has a significant risk of mortality. Of all the cases of histoplasmosis reported in the aforementioned study, 57% of patients were hospitalized for severe infection, of which 7% died [6]. These recent findings are consistent with a previous epidemiological study, conducted in 2002, which found a mortality rate of around 7% for adult patients hospitalized for histoplasmosis within the endemic region of the US [4]. Moreover, significant costs are incurred by patients and the health care system at large for hospitalizations related to histoplasmosis (average hospital charge per adult patient in 2002: $20,300) [4]. The current morbidity, mortality and cost associated with histoplasmosis, in combination with the emergence of drug resistant varieties of *H. capsulatum*, suggest that a robust immunization strategy to prevent cases of histoplasmosis is indicated [6,7].

Histoplasmosis

H. capsulatum infection typically occurs after incidental exposure to either contaminated soil or the decaying excreta of bats or certain bird species. *H. capsulatum* enters the host through the inhalation of spores or mycelial fragments into the alveolar spaces of the lung. Spores or active mycelia readily differentiate into budding yeast cells at physiological temperature and are phagocytosed by dendritic cells (DC), polymorphonuclear phagocytes (neutrophils), and alveolar macrophages [8]. Dendritic cells are able to rapidly phagocytose and kill yeast phase *H. capsulatum* in the lung; neutrophils also play a role in the acute response to *H. capsulatum* infection by inhibiting fungal growth through the release of azurophilic granule contents [9,10]. A few days after initial infection, phagocytosed *H. capsulatum* yeast cells are principally found within inflammatory macrophages, wherein they are able to survive and proliferate as facultative intracellular pathogens [8]. Control of histoplasmosis is thus classically dependent on the *activation* of infected mononuclear phagocytes by various Type 1 pro-inflammatory cytokines such as IFN-γ, TNF-α, and GM-CSF to kill phagocytosed yeasts or form granulomas encapsulating the infected tissue [11].

The severity of histoplasmosis is largely dependent on the degree of exposure and the patient's immune status. Histoplasmosis is typically asymptomatic and self-limited in immunocompetent hosts. More severe, symptomatic infections characteristically involve some degree of pulmonary disease. *H. capsulatum* infection can also cause a lethal disseminated disease. Disseminated *H. capsulatum* infection is most commonly seen in immunocompromised hosts (e.g. those with comorbid HIV infection, hematologic malignancies, or those receiving some type of immunosuppressive therapy) [12–14]. Nevertheless, disseminated disease can occur in otherwise immunocompetent hosts as well,

particularly in the setting of a heavy inoculum exposure. *H. capsulatum* can also establish a latent phase in humans. In this capacity, *H. capsulatum* is able to operate as an opportunistic pathogen causing infection as host conditions permit (e.g. organ transplant, anti-TNF-α therapy) [13,15,16]. Thus, the ability to vaccinate even those with various immune deficiencies is paramount in the search for an effective immunization strategy against histoplasmosis.

Currently, there are no vaccines available for the prevention or treatment of any mycosis. However, there are numerous strategies under study. This review will detail developments in both active and passive immunization strategies against histoplasmosis.

Active Immunization Strategies

rHsp60

In an early pioneering study, a detergent extract of the cell wall and membrane of yeast phase *H. capsulatum* was identified to confer protective immunity against lethal intravenous challenge with *H. capsulatum* in murine models [17]. Subsequent research narrowed in on specific fractions of the extract, testing them systematically for antigenicity and immunogenicity [18,19]. HIS62, a glycoprotein isolated from the 62kDa fraction of the extract, was identified as an immunogenic antigen. Additional experiments showed that purified native HIS62 could induce a delayed type hypersensitivity reaction (DTHR) in mice that had been previously immunized with a sublethal inoculum of *H. capsulatum* [18]. Moreover, splenocytes from mice that had been previously immunized with live *H. capsulatum* proliferated in response to exposure to HIS62. Most importantly, however, approximately 80% of mice immunized with purified HIS62 survived subsequent lethal intravenous challenge of *H. capsulatum* [18].

After documenting the protective capacity of HIS62, the gene encoding the protein was identified and cloned in order to better understand the biology of the native protein and assess the antigenicity and immunogenicity of its recombinant counterpart. The amino acid sequence revealed that HIS62 is about 70% homologous to heat shock protein 60 (Hsp60) found in *S. cerevisiae*; HIS62 was also recognized by a rabbit antiserum raised against *E. coli* Hsp60. Thus, HIS62 was re-named heat shock protein 60 (Hsp60) from *H. capsulatum* and its recombinant counterpart, rHsp60. rHsp60 was documented to have a similar antigenicity and immunogenicity to its native cousin. 100% of mice vaccinated with rHsp60 survived a lethal intranasal challenge with live *H. capsulatum* yeast cells [20].

Subsequent studies were carried out to isolate the specific amino acid sequence of rHsp60 responsible for its immunogenicity. To do this, rHsp60 was broken down into 4 overlapping polypeptide fragments, all of which could stimulate cell proliferation of pre-sensitized splenocytes. Only fragment three (F3), however, ranging from amino acids 172–443, conferred protection, albeit in only 50% of mice, against lethal intranasal challenge with live *H. capsulatum* yeast cells. By comparison, the full length recombinant protein, rHsp60, provides greater protection against histoplasmosis in murine models than the immunologic fragment, F3, in and of itself [20,21].

rHsp60 vaccination in murine models works by priming a CD4+ Th1 effector response against histoplasmosis. Induction of the Th1 effector response to *H. capsulatum* infection is classically dependent on the interleukin 12 (IL-12)/IFN-γ axis. In simplest terms, macrophages and dendritic cells respond to *H. capsulatum* infection by secreting IL-12. IL-12 induces the differentiation of naïve (Th0) CD4+ T cells into Th1 cells, which in turn secrete IFN-γ among other pro-inflammatory cytokines. IFN-γ plays a pivotal role in promoting the cellular immune response to *H. capsulatum* as it is a potent activator of effector macrophages; its absence is correlated directly with decreased survival in murine models of primary histoplasmosis [22–24]. Vaccination with purified rHsp60 requires the presence of CD4+ T cells, a functioning IL-12/IFN-γ axis and IL-10 for an effective inductive phase. Neutralizing any of these mediators with mAb results in a 100% mortality rate upon subsequent lethal challenge with *H. capsulatum* in murine models [25].

The expressive phase of vaccination after lethal challenge with *H. capsulatum* requires the presence of either CD4+ or CD8+ T cells. This finding suggests that even though CD8+ T cells are not necessary in the afferent phase of rHsp60 vaccination, these cells, when present, can also be primed by rHsp60 immunization to carry out an effector response in the expressive phase of the vaccine, even if the CD4+ T cell population has been depleted. MAb induced depletions of both CD4+ and CD8+ T cell populations after vaccination results in the failure to control a lethal *H. capsulatum* infection in murine models. [25].

Vaccination with rHsp60 is critically dependent on a functional host CD4+ T cell population in the afferent phase, and thus would have limited efficacy in those with significantly depleted CD4+ T cell counts (e.g. individuals with AIDS). Theoretically, the evidence suggests that vaccination with rHsp60 might still be effective if given before the acquisition of such an immunodeficiency. Though most importantly, this discovery indicates that it may be possible to immunize those with seriously depleted CD4+ T cell counts by directly activating CD8+ T cells to carry out an effector response [25].

Molecular indicators for vaccine efficacy for rHsp60 and F3 of rHsp60 have been studied in some detail. Vaccination of mice with rHsp60 or F3 induces the differentiation and clonal expansion of different subsets of T cell clones. In either case, elimination of the specific clonally expanded Th1 cell population nullifies the protective effect of vaccination. Despite the differences in the T cell clones isolated after vaccination with either rHsp60 or F3, common *protective* epitope binding domains were identified in the T-cell Receptors (TCRs) of both populations. Thus, if the same phenomenon holds true in humans, common TCR domains could potentially serve as primary indicators for effective induction of vaccination, reducing the need for extensive primary clinical efficacy trials [26].

F3 of rHsp60 has additional value in that it is a small protein fragment. It may well be possible to generate immunogenic peptide fragments of F3 as potential subunit vaccines. Peptides are advantageous in that they can be manufactured in mass, readily modified to improve their stability and enhance their immunogenicity; and most importantly, they are non-infectious [27]. Thus, even in the face of potentially diminished protection from the subunit in and of itself, the pros of using a peptide may outweigh the cons. In the context of a defined biologic marker for efficacy, immunogenic peptide fragments of F3 represent

potentially powerful, modifiable, and scalable clinical options for active vaccination against *H. capsulatum*.

H Antigen

An additional protein immunogen, H antigen, has also been shown to confer protective immunity against *H. capsulatum* in murine models. H antigen, a member of the β-glucosidase family, is a surface protein component of the cell wall of *H. capsulatum* [28]. Studies have revealed that H antigen is indeed antigenic [29–31]; however, mice immunized with recombinant H antigen were not protected against sublethal or lethal *intravenous* inoculums of live *H. capsulatum* yeast cells [32]. Nevertheless, it was subsequently shown that immunization with recombinant H antigen does confer protection against sublethal and lethal *intranasal* challenge with *H. capsulatum*. The mechanism by which this differential response occurs is not currently understood [33]. These studies highlight the fact that the efficacy of H antigen vaccination, at least in murine models, is dependent on the route of infection. This is a critical finding in that it identifies a potential limitation of H antigen vaccination against histoplasmosis. More importantly, however, it suggests that future active immunization strategies against histoplasmosis should be assessed in terms of their efficacy against different potential routes of infection.

Cross-Priming

Dendritic cells play a critical role in the control of histoplasmosis in murine models. Dendritic cells can phagocytose and kill intracellular *H. capsulatum*; and, as principle multimodal antigen presenting cells, they are able to stimulate effective CD4+ or CD8+ T cell responses to *H. capsulatum* infection. *In vitro* priming of dendritic cells with apoptotic macrophages, which have previously phagocytosed heat inactivated *H. capsulatum*, followed by auto-transplantation has been shown to produce protective CD4+ or CD8+ T cell responses in murine models of histoplasmosis. This active immunization strategy, although technically challenging, may be invaluable in the context of actively vaccinating people with HIV/AIDS who might otherwise not be able to mount a sufficient response to *H. capsulatum* infection due to low CD4+ T cells counts [34].

Passive Immunization Strategies

The natural humoral response to histoplasmosis is not well understood. However, that does not preclude the use of antibodies against *H. capsulatum* as a therapeutic tool to control histoplasmosis. *H. capsulatum* infection in murine models induces the production of polyclonal antibodies against a variety of *H. capsulatum* antigens. Nonetheless, passive immunization with polyclonal serum from mice immune to *H. capsulatum* does not protect naïve mice from lethal *H. capsulatum* infection [35]. This may be due to the need of cellular components for an effective response against *H. capsulatum*, but also to the differential composition of polyclonal serum, which has been found to include both protective and non-protective (infection enhancing) antibodies. A few *H. capsulatum*-specific mAbs, however, have been shown to confer protection against histoplasmosis, and are currently being studied as potential passive immunization strategies [36].

IgM against Histone 2B (H2B)

Immunization of mice with heat inactivated *H. capsulatum* yeast cells elicits the production of IgM mAbs against H2B, a protein exposed on the cell surface of *H. capsulatum* [37]. Pre-treatment with these mAbs prior to *H. capsulatum* infection reduces the overall severity of the disease and increases survival in mouse models of histoplasmosis [37,38]. This protective effect is enhanced with the addition of sub-therapeutic concentrations of amphotericin B; however, even with the addition of amphotericin B, the protection is incomplete with only about 40% survival at 45 days after lethal *H. capsulatum* infection [37]. The treatment of histoplasmosis with IgM is limited by nature due to the large pentameric structure of the immunoglobulin, which impedes its ability to easily move from the bloodstream to the alveolar space. However, when preincubated with *H. capsulatum* prior to intranasal challenge, the IgM mAb to H2B not only enhances survival, but it also decreases the fungal burden and tissue damage in experimental infections [34].

IgG against rHSP60

Protective IgG mAbs against rHsp60 have been raised and are currently under study [39]. Intraperitoneally (IP) administered IgG1 and IgG2a mAbs against rHsp60 have been shown to significantly prolong the survival of mice challenged with a lethal intranasal inoculum of *H. capsulatum* yeast cells. However, the efficacy of these mAbs is limited. IP administered IgG1 and IgG2a mAbs conferred protection in only about 60% of the recipients. Surprisingly, an IgG2b mAb does not confer protection against lethal *H. capsulatum* challenge in murine models, even though it was demonstrated to bind to the same epitope on rHsp60 as one of the protective IgG1 mAbs. The pre-treatment of mice with the anti-Hsp60 IgG2b has no effect on mice survival after a lethal challenge with *H. capsulatum*, but incubation of the fungus with this mAb prior to infection leads to a 30% survival of infected mice. The pre-incubation of *H. capsulatum* with this IgG2b mAb has no effect on the rate of phagocytosis by macrophages, but the mAb significantly enhances the intracellular growth of the yeast [36]. Currently, research is underway to determine whether the agglutination properties [40], isotype or other fine specificity issues mediate this differential protective effect.

Pan-Fungal Therapeutic Antibodies

An ever-expanding armamentarium of mAbs is being generated against a diverse set of pan-fungal antigens. Most recently, a lectin (wheat germ agglutinin - WGA) was fused with the Fc domain of an IgG2a generating the chimera WGA-Fc. WGA has high affinity to chitin oligomers, a product generated by chitin degradation, a main fungal cell wall constituent [41]. Not only does WGA-Fc directly inhibit fungal growth in culture, it also enhances phagocytosis of diverse fungal species by macrophages *in vitro* [42]. Opsonization of *H. capsulatum* with WGA-Fc prior to co-culture with macrophages decreases the rates of intracellular growth and most importantly, pretreatment of mice with WGA-Fc completely protects mice against subsequent lethal challenge with an intranasal inoculum of *H. capsulatum* [42]. Additional examples of pan-anti-fungal mAbs include but are not limited to an IgG2b against 1,3 β-glucan, IgM against the fungal surface antigen glucosylceramide, and an IgM against melanin. These mAbs are not necessarily *H. capsulatum*-specific but

they may be useful down the road in combination therapy to treat histoplasmosis [43–48]. Pan-fungal antibodies represent a novel strategy to control diverse mycoses, including histoplasmosis. Therapeutic antibodies may end up being the most effective way to treat mycoses such as histoplasmosis in immunocompromised patients who might otherwise not benefit from active immunization strategies. Certainly, more research into the safety and efficacy of these antibodies in a variety of experimental models is indicated.

Immune System Modulation

Recently, immune system based therapeutic approaches to treating cancer are being investigated as new potential tools for treating fungal infections. One new strategy takes advantage of the PD-1 peripheral immunologic tolerance pathway. Binding of PD-1 ligand (PD-L1) to its receptor (PD-1) on T cells activates inhibitory pathways leading to T cell anergy and immunosuppression [49]. *H. capsulatum* infection in mice induces the upregulation of both PD-L1 and PD-L2 on the surface of macrophages and dendritic cells as well as T cells, promoting disease progression. PD-1 knockout mice survive challenge with a lethal inoculum of *H. capsulatum* yeast cells; moreover, 70% of mice treated with mAb against PD-1 survive lethal *H. capsulatum* infection. Although the selective blockade of the PD-L1 – PD-1 interaction does not represent a passive immunization strategy, it constitutes a promising use of antibodies to treat histoplasmosis by blocking inhibitory immunologic checkpoints [50].

CAR T cells that target 1,3 β-glucan, using the extracellular domain of Dectin-1, have been made and tested in experimental models of murine aspergillosis. Mice treated with the modified T cells showed reduction in hyphal expansion of *Aspergillus fumigatus* compared to mice that did not receive the modified T cells [51]. Although this therapy has not been tested in experimental histoplasmosis, the use of CAR T cells to target pan-fungal antigens represents a potentially powerful tool in the armamentarium of the clinician to treat advanced mycoses as access to these biotechnologies becomes more widely available.

Conclusion

There are numerous candidate preventative and therapeutic vaccines against histoplasmosis described in the literature. Additional epidemiologic data will be needed to evaluate who should be vaccinated and when it would it feasible and reasonable to do so. Determining the utility of vaccination in the setting of variable incidences of disease, particularly with an endemic pathogen in and outside of the high incidence regions, and in different settings of immune competency or suppression will be essential for optimal implementation of vaccine strategies against *H. capsulatum*. Additionally, specific work testing efficacy in the absence of different components of the immune system in animal models can aid in predicting which individuals may benefit most from different immunization approaches. Nevertheless, these epidemiological questions should not preclude the much-needed transition from pre-clinical laboratory research to clinical trials. Numerous lives could be saved, and ultimately healthcare costs may be reduced.

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References:

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1. Antinori S Histoplasma capsulatum: More widespread than previously thought. Am J Trop Med Hyg. 2014;90:982–3. [PubMed: 24778192]
2. Deepe GS. Outbreaks of histoplasmosis: The spores set sail. PLoS Pathog. 2018;14:1–5.
3. Bahr NC, Antinori S, Wheat LJ, Sarosi GA. Histoplasmosis Infections Worldwide: Thinking Outside of the Ohio River Valley. Curr Trop Med Reports. 2015;2:70–80.
4. Chu JH, Feudtner C, Heydon K, Walsh TJ, Zaoutis TE. Hospitalizations for endemic mycoses: a population-based national study. Clin Infect Dis. 2006;42:822–5. [PubMed: 16477560]
5. Manos NE, Ferebee SH, Kerschbaum WF. Geographic variation in the prevalence of histoplasmin sensitivity. Dis Chest. United States; 1956;29:649–68.
6. Armstrong PA, Jackson BR, Haselow D, Fields V, Ireland M, Austin C, et al. Multistate Epidemiology of Histoplasmosis, United States, 2011–2014. 2018;24:425–31.
7. Wheat J, Marichal P, Bossche HV, Monte AL, Connolly PA. Hypothesis on the Mechanism of Resistance to Fluconazole in Histoplasma capsulatum. 1997;41:410–4.
8. Deepe GS, Gibbons RS, Smulian AG. Histoplasma capsulatum manifests preferential invasion of phagocytic subpopulations in murine lungs. J Leukoc Biol [Internet]. 2008;84:669–78. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18577715
9. Ray SC, Rappleye CA. Flying under the radar: Histoplasma capsulatum avoidance of innate immune recognition. Semin Cell Dev Biol. England; 2018;pii: S1084–9521(17)30206–9.
10. Newman SL, Gootee L, Gabay JE, Selsted ME. Identification of constituents of human neutrophil azurophil granules that mediate fungistasis against Histoplasma capsulatum. Infect Immun. 2000;68:5668–72. [PubMed: 10992469]
11. Horwath MC, Fecher RA, Deepe G. Histoplasma capsulatum, lung infection and immunity. Future Microbiol. 2015;967–75. [PubMed: 26059620]
12. Thind SK, Taborda CP, Nosanchuk JD. Dendritic cell interactions with Histoplasma and Paracoccidioides. Virulence. 2015;6:424–32. [PubMed: 25933034]
13. Wood KL, Hage CA, Knox KS, Kleiman MB, Sannuti A, Day RB, et al. Histoplasmosis after treatment with anti-tumor necrosis factor-α therapy. Am J Respir Crit Care Med. 2003;167:1279–82. [PubMed: 12615627]
14. Deepe GS Jr, Nosanchuk JD. Fungal Vaccine Development Mol Princ Fungal Pathog [Internet]. American Society of Microbiology; 2006 [cited 2018 Aug 10]. p. 565–81. Available from: http://www.asmscience.org/content/book/10.1128/9781555815776.ch38
15. Deepe GS. Modulation of infection with Histoplasma capsulatum by inhibition of tumor necrosis factor-alpha activity. Clin Infect Dis [Internet]. 2005;41 Suppl 3:S204–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15983901
16. Limaye AP, Connolly PA, Sagar M, Fritsche TR, Cookson BT, Wheat LJ, et al. Transmission of Histoplasma capsulatum by Organ Transplantation. 2000;343:1163–6.
17. Gomez AM, Rhodes JC, Deepe Jr. GS. Antigenicity and Immunogenicity of an Extract from the Cell Wall and Cell Membrane of Histoplasma capsulatum Yeast Cells. Infect Immun. 1991;59:330–6. [PubMed: 1987047]

18. Gomez FJ, Gomez AM, Deepe, Jr. GS. Protective Efficacy of a 62-Kilodalton Antigen, HIS-62, from the Cell Wall and Cell Membrane of Histoplasma capsulatum Yeast Cells. Infect Immun. 1991;59:4459–64. [PubMed: 1937804]
19. Gomez FJ, Gomez AM, Deepe GS. An 80-Kilodalton Antigen from Histoplasma capsulatum That Has Homology to Heat Shock Protein 70 Induces Cell- Mediated Immune Responses and Protection in Mice. Infect Immun. 1992;60:2565–71. [PubMed: 1612726]
20. Gomez FJ, Allendoerfer R, Deepe GS Jr. Vaccination with Recombinant Heat Shock Protein 60 from Histoplasma capsulatum Protects Mice against Pulmonary Histoplasmosis. Infect Immun [Internet]. 1995;63:2587–95. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=7911197207696073954related:4mTJ8PE3ym0J%5Cnhttp://www.ncbi.nlm.nih.gov/pmc/articles/PMC173347/pdf/632587.pdf
21. Deepe G, Gibbons R, Brunner GD, Gomez FJ. A Protective Domain of Heat-Shock Protein 60 from Histoplasma capsulatum. 1996;174:828–34.
22. Clemons KV, Darbonne WC, Curnutte JT, Sobel RA, Stevens DA. Experimental histoplasmosis in mice treated with anti-murine interferon- γ antibody and in interferon-γ gene knockout mice. Microbes Infect. 2000;2:997–1001. [PubMed: 10967280]
23. Allendoerfer R, Deepe GS. Intrapulmonary Response to Histoplasma capsulatum in Gamma Interferon Knockout Mice. Infect Immun. 1997;65:2564–9. [PubMed: 9199420]
24. Zhou P, Miller G, Seder RA. Factors Involved in Regulating Primary and Secondary Immunity to Infection with Histoplasma capsulatum: TNF-α Plays a Critical Role in Maintaining Secondary Immunity in the Absence of IFN-γ. J Immunol. 1998;160:1359–68. [PubMed: 9570555]
25. Deepe GS, Gibbons RS. Cellular and Molecular Regulation of Vaccination with Heat Shock Protein 60 from Histoplasma capsulatum Infect Immun [Internet]. American Society for Microbiology; 2002 [cited 2018 Jun 14];70:3759–67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12065519
26. Scheckelhoff M, Deepe GS. The Protective Immune Response to Heat Shock Protein 60 of Histoplasma capsulatum Is Mediated by a Subset of Vβ8.1/8.2+ T Cells. J Immunol [Internet]. 2002;169:5818–26. Available from: http://www.jimmunol.org/cgi/doi/10.4049/jimmunol.169.10.5818
27. Purcell AW, McCluskey J, Rossjohn J. More than one reason to rethink the use of peptides in vaccine design Nat Rev Drug Discov [Internet]. Nature Publishing Group; 2007;6:404–14. Available from: 10.1038/nrd2224
28. Guimarães AJ, de Cerqueira MD, Nosanchuk JD. Surface architecture of Histoplasma capsulatum. Front Microbiol. 2011;2:1–14. [PubMed: 21716958]
29. Reeves MW, Pine L, Bradley G. Characterization and evaluation of a soluble antigen complex prepared from the yeast phase of Histoplasma capsulatum. Infect Immun. 1974;9:1033–44. [PubMed: 4208527]
30. Zancopé-Oliveira RM, Bragg SL, Reiss E, Peralta JM. Immunochemical analysis of the H and M glycoproteins from Histoplasma capsulatum. Clin Diagn Lab Immunol [Internet]. 1994;1:563–8. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=368339&tool=pmcentrez&rendertype=abstract
31. Pine L, Malcolm GB, Gross H, Gray SB. Evaluation of purified H and M antigens of histoplasmin as reagents in the complement fixation test. Sabouraudia [Internet]. 1978;16:257–69. Available from: 10.1080/00362177885380361
32. Deepe GS, Durose GG. Immunobiological Activity of Recombinant H Antigen from Histoplasma capsulatum. Infect Immun. 1995;63:3151–7. [PubMed: 7622243]
33. Deepe J, Gibbons R. Protective Efficacy of H antigen from Histoplasma capsulatum in a Murine Model of Pulmonary Histoplasmosis. Infect Immun. 2001;69:3128–34. [PubMed: 11292732]
34. Hsieh SH, Lin JS, Huang JH, Wu SY, Chu CL, Kung JT, et al. Immunization with Apoptotic Phagocytes Containing Histoplasma capsulatum Activates Functional CD8 + T cells to Protect against Histoplasmosis. Infect Immun. 2011;79:4493–502. [PubMed: 21911464] -This paper demonstrated the efficacy of cross-priming a CD8+ T cell reponse against histoplasmosis. This is significant in that it represents a possible active vaccination strategy for those with compromised immune systems, specifically those suffering from unmanaged HIV infection or AIDS.

35. Tewari RP, Sharma D, Solotorovsky M, Lafemina R, Balint J. Adoptive Transfer of Immunity from Mice Immunized with Ribosomes or Live Yeast Cells of Histoplasma capsulatum. 1977;15:789–95. [PubMed: 870432]
36. Nosanchuk JD, Zancopé-Oliveira RM, Hamilton AJ, Guimarães AJ. Antibody therapy for histoplasmosis. Front Microbiol. 2012;3:1–7. [PubMed: 22275914]
37. Nosanchuk JD, Steenbergen JN, Shi L, Deepe GS, Casadevall A. Antibodies to a cell surface histone-like protein protect against Histoplasma capsulatum. J Clin Invest. 2003;112:1164–75. [PubMed: 14561701]
38. Shi L, Albuquerque PC, Lazar-Molnar E, Wang X, Santambrogio L, Gacser A, et al. A Monoclonal Antibody to Histoplasma capsulatum Alters the Intracellular Fate of the Fungus in Murine Macrophages. 2008;7:1109–17.
39. Guimarães AJ, Frases S, Gomez FJ, Zancopé-Oliveira RM, Nosanchuk JD. Monoclonal Antibodies to Heat Shock Protein 60 Alter the Pathogenesis of Histoplasma capsulatum Infect Immun [Internet]. American Society for Microbiology; 2009 [cited 2018 Jun 11];77:1357–67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19179416
40. Guimaraes AJ, Frases S, Pontes B, de Cerqueira MD, Rodrigues ML, Viana NB, et al. Agglutination of Histoplasma capsulatum by IgG Monoclonal Antibodies against Hsp60 Impacts Macrophage Effector Functions. 2011;79:918–27.
41. Rodrigues ML, Alvarez M, Fonseca FL, Casadevall A. Binding of the wheat germ lectin to Cryptococcus neoformans suggests an association of chitinlike structures with yeast budding and capsular glucuronoxylomannan. Eukaryot Cell. 2008;7:602–9. [PubMed: 18039942]
42. Liedke SC, Miranda DZ, Gomes KX, Gonçalves JLS, Frases S, Nosanchuk JD, et al. Characterization of the antifungal functions of a WGA-Fc (IgG2a) fusion protein binding to cell wall chitin oligomers. Sci Rep. 2017;7:1–17. [PubMed: 28127051] -This paper is significant in that WGA-Fc (IgG2a) represents a potentially powerful passive vaccination strategy against diverse mycoses.
43. Bryan RA, Guimarães AJ, Hopcraft S, Jiang Z, Bonilla K, Morgenstern A, et al. Toward Developing a Universal Treatment for Fungal Disease Using Radioimmunotherapy Targeting Common Fungal Antigens. Mycopathologia. 2012;173:463–71. [PubMed: 22048869] -This paper is significant because it demonstates that it is possible to develop radio-immunotherapuetics against diverse mycoses. Here, the efficacy of the mAb is not necessarily dependent on cellular immunity and thus it represents a way of passively vaccinating those with immunedeficiencies in antibody dependent cellular cytotoxicity.
44. Qureshi A, Wray D, Rhome R, Barry W, Poeta M Del. Detection of Antibody against Fungal Glucosylceramide in Immunocompromised Patients: A Potential New Diagnostic Approach for Cryptococcosis. Mycopathologia. 2012;173:419–25. [PubMed: 21971701]
45. Mor V, Farnoud AM, Singh A, Rella A, Tanno H, Ishii K, et al. Glucosylceramide Administration as a Vaccination Strategy in Mouse Models of Cryptococcosis. 2016;1–15.
46. Rodrigues ML, Shi L, Barreto-Bergter E, Nimrichter L, Farias SE, Rodrigues EG, et al. Monoclonal Antibody to Fungal Glucosylceramide Protects Mice against Lethal Cryptococcus neoformans Infection. Clin Vaccine Immunol. 2007;14:1372–6. [PubMed: 17715331]
47. Rhome R, Singh A, Kechichian T, Drago M, Morace G, Luberto C, et al. Surface Localization of Glucosylceramide during Cryptococcus neoformans Infection Allows Targeting as a Potential Antifungal. PLoS One. 2011;6:e15572. [PubMed: 21283686]
48. Rhome R, Mcquiston T, Kechichian T, Bielawska A, Hennig M, Drago M, et al. Biosynthesis and Immunogenicity of Glucosylceramide in Cryptococcus neoformans and Other Human Pathogens. 2007;6:1715–26.
49. Dermani FK, Samadi P, Rahmani G, Kohlan AK, Najafi R. PD-1/PD-L1 immune checkpoint: Potential target for cancer therapy. J Cell Physiol. 2018;
50. Lazar-Molnar E, Gacser A, Freeman GJ, Almo SC, Nathenson SG, Nosanchuk JD. The PD-1/PD-L costimulatory pathway critically affects host resistance to the pathogenic fungus Histoplasma capsulatum. Proc Natl Acad Sci [Internet]. 2008;105:2658–63. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.0711918105-This paper is significant in that it represents a new potential indication for PD-1R mAb.

51. Kumaresan PR, Manuri PR, Albert ND, Maiti S, Singh H, Mi T, et al. Bioengineering T cells to target carbohydrate to treat opportunistic fungal infection. Proc Natl Acad Sci [Internet]. 2014;111:10660–5. Available from: http://www.pnas.org/cgi/doi/10.1073/pnas.1312789111-This paper is significant because it provided evidence that cytotoxic CD8+ T cells could be raised in-vitro against diverse fungi. This engineered specific immunity is invaluable to those with various immunodeficiencies as well to those for whom standard vaccination stategies may not work.