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## Modulating host immune responses to fight invasive fungal infections

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### Abstract

Modulation of host immunity in invasive fungal infection is an appealing but as yet mostly elusive treatment strategy. Animal studies in invasive candidiasis and aspergillosis have demonstrated beneficial effects of colony stimulating factors, interferon-gamma and monoclonal antibodies. More recent studies transfusing leukocytes pre-loaded with lipophilic anti-fungal drugs, or modulated T-cells, along with novel vaccination strategies show great promise. The translation of immune therapies into clinical studies has been limited to date but this is changing and the results of new *Candida* vaccine trials are eagerly awaited. Immune modulation in HIV-associated mycoses remains complicated by the risk of immune reconstitution inflammatory syndrome and although exogenous interferon-gamma therapy may be beneficial in cryptococcal meningitis, early initiation of anti-retroviral therapy leads to increased mortality. Further study is required to better target protective immune responses.

### INTRODUCTION

Invasive fungal infections (IFI) are an increasing global health problem, resulting in significant morbidity and mortality among individuals with impaired immunity [1–3]. Despite recent advances in the care of patients with IFI, conventional therapeutic options

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#### Conflicts

The authors have no conflicts to report

remain limited, and outcomes poor. A potential strategy to improve this is to reverse underlying immune deficits, or modify and enhance host immune responses using immunomodulatory treatments. However, immune responses against fungal pathogens are diverse, and detailed understanding of the underlying immunology is essential to enable effective interventions. Here we review recent advances in immunomodulatory therapies for treatment and prevention of invasive fungal infections. A summary of the main findings is given in Table 1.

## REMOVAL OR REVERSAL OF UNDERLYING IMMUNE SUPPRESSION

Clinical practice guidelines strongly recommend reduction or elimination of immune suppression in patients with invasive aspergillosis (IA) and disseminated candidiasis [4,5]. These recommendations are based on observational data and an understanding of the epidemiology and immunopathogenesis of invasive fungal disease [6]. However, in some patients with fungal infection this strategy may not be feasible and may also result in paradoxical clinical worsening. The best example of this is HIV-associated cryptococcal meningitis immune reconstitution inflammatory syndrome (CM-IRIS), where patients develop worsening meningitis following initiation of anti-retroviral therapy (ART) [7]. The main predisposing factor for CM-IRIS is a lack of cerebrospinal fluid (CSF) inflammation and increased fungal burden prior to ART initiation [8,9]. Following ART initiation, excess CSF antigen triggers chemokine-mediated cell trafficking, macrophage activation, and marked inflammation [10,11]. After two randomised controlled trials demonstrated increased mortality with early ART [12,13], treatment guidelines now recommend delaying initiation of ART until at least four weeks of antifungal treatment have been completed to minimise the risk of CM-IRIS [14]. IRIS is also reported among individuals with HIV associated *Pneumocystis jirovecii*, *Histoplasma capsulatum*, and *Taralomyces marneffei* infections [15]. Similar clinical deteriorations have also been observed in solid organ transplant recipients with cryptococcal meningitis who undergo rapid reductions in immune suppressive medications [16], and in patients with chronic disseminated candidiasis following neutrophil recovery [17]. Given the problems with infection following haematopoietic stem cell transplantation (HSCT), there are now efforts to explore novel conditioning strategies using haematopoietic cell-specific immunotoxins that avoid such profound immune suppression [18].

## CYTOKINE THERAPY

A variety of pro-inflammatory cytokines have been studied to determine whether their administration may improve host immune response against IFIs. Given the clear association between neutropenia and IFIs much of this focus has been on colony stimulating factors. The prophylactic use of granulocyte colony stimulating factor (G-CSF) in patients with chemotherapy-associated neutropenia is well established and reduces overall incidence of infections and febrile neutropenia by almost half [19]. G-CSF stimulates neutrophil production, maturation, phagocytic activity and oxidative burst metabolism [20], and enhances protection against disseminated *Aspergillus* and *Candida* in animal models [21–23]. In clinical practice, prophylactic G-CSF has not convincingly been shown to reduce the incidence of IFIs [24]. However, two small studies demonstrate a potential benefit of G-CSF

when used alongside anti-fungal therapy as an adjunctive treatment leading to faster resolution of infection compared to antifungal therapy alone [25,26].

Granulocyte-macrophage colony stimulating factor (GM-CSF) is also licenced for treatment of chemotherapy-associated neutropenia. It promotes the production, maturation, activation, and migration of neutrophils, monocytes, macrophages and lymphocytes [27], and has potential advantages over G-CSF due to its wider effects on the immune response [28]. Animal and cell culture models suggest GM-CSF is important in the host response against *Aspergillus* and *Cryptococcus* [29,30], and individuals with anti-GM-CSF auto-antibodies have been found to be at increased risk of infection with *C. gattii* [31]. In patients receiving chemotherapy for acute myeloid leukaemia and allogeneic haematological stem cell transplantation (HSCT), prophylactic GM-CSF results in faster neutrophil recovery, lower all-cause mortality, lower transplantation-related mortality, and lower invasive fungal disease-associated mortality [32–34]. Case reports and case series suggest GM-CSF may be beneficial when used alongside antifungal treatments in treating a variety of IFI, including candidiasis, aspergillosis, and zygomycosis [35–37].

Macrophage colony-stimulating factor (M-CSF) also rapidly increases myeloid differentiation of hematopoietic stem cells via activation of the myeloid regulator PU.1 [38]. Data from animal models suggest that M-CSF may also play a role in controlling invasive fungal infections [39]. However, it has never been tested in humans and unlike G-CSF and GM-CSF, there is no pharmaceutical product available.

Interferon-gamma (IFN- $\gamma$ ) is produced by NK cells and T lymphocytes and promotes classical activation of macrophages resulting in increased phagocytosis, production of reactive oxygen species and reactive nitrogen intermediates; it is a vital component of the host immune response against intracellular pathogens [40]. IFN- $\gamma$  knockout mice and people with impaired IFN- $\gamma$  signalling (IFN- $\gamma$  receptor 1 deficiency or anti-IFN- $\gamma$  autoantibodies) are at significantly increased risk of severe infection with *C. albicans*, *C. neoformans*, *H. capsulatum* and *Coccidioides immitis* [41–46]. In animal models of invasive aspergillosis, IFN- $\gamma$  enhances neutrophil function augments the response to anti-fungal therapy resulting in significantly improved survival [47,48]. Improvements in neutrophil function resulting in significant reductions in serious infections have also been observed in patients with chronic granulomatous disease (CGD) treated with prophylactic IFN- $\gamma$  [49].

In HIV-infected individuals with cryptococcal meningitis, low CSF concentrations of IFN- $\gamma$  are associated with higher fungal burden, slower clearance of *Cryptococcus*, and increased mortality [50]. Animal models have demonstrated significantly improved survival when IFN- $\gamma$  was used as an adjunctive treatment alongside amphotericin B [51], prompting two phase II trials of adjunctive IFN- $\gamma$  in AIDS patients with cryptococcal meningitis [52,53]. The first showed a non-significant trend towards better CSF sterilization; the second showed significantly faster clearance of infection when IFN- $\gamma$  was added to antifungal treatment. IFN- $\gamma$  has also been used to augment the host immune response in cases of HIV-negative patients with cryptococcal meningitis, invasive aspergillosis, invasive candidiasis and disseminated *H. capsulatum* infection [54–56].

## LEUKOCYTE TRANSFUSIONS

Infusion of donor granulocytes is an experimental technique to improve survival from invasive fungal infections in the setting of profound neutropenia and requires harvesting of granulocytes from an ABO matched donor using leukapheresis. Case reports and retrospective case-control studies suggest granulocyte transfusions are feasible, safe and associated with better than expected survival rates [57–59]. However, clinical benefit has yet to be clearly demonstrated, and the single randomised controlled trial conducted to date showed no survival benefit in the setting of neutropenic sepsis [60]. In a mouse model of invasive aspergillosis, significant improvement in outcome was observed when granulocytes were loaded with the lipophilic triazole posaconazole [61].

Adoptive transfer of pathogen-specific T cells is another promising treatment strategy. Prolonged lymphopenia is a major risk factor for post-engraftment invasive aspergillosis following HSCT, and the presence of *Aspergillus*-specific Th1 cells is associated with successful resolution of infection [62–64]. Murine studies have demonstrated that adoptive transfer of *Aspergillus*-specific Th1 memory CD4 T cells (generated through exposure to *Aspergillus* culture filtrate antigens) results in prolonged survival in experimentally infected mice [65]. This strategy was replicated in a single small human study involving ten HSCT patients with pulmonary aspergillosis; reductions in serum galactomannan and a trend towards improved survival were seen [66].

To expedite clonal expansion, co-stimulatory molecules (CD137 and CD154) can be used to select antigen-specific T cells. This technique has been used to generate *Aspergillus*-specific T cells, with *in vitro* activity against a wide range of fungal isolates [67]. In a further refinement, adoptive transfer of chimeric antigen receptor (CAR) T cells targeting tumor antigens has been adapted to target fungal pathogens [68]. This involves fusing the extracellular domain of Dectin-1 to a CAR cassette and transferring into human T cells resulting in a modified  $\beta$ -1,3-glucan-specific T lymphocyte. Such cells have been shown to inhibit germinating *Aspergillus* spores *in vitro*, and improve outcome in experimentally infected mice [69]. These two techniques are clarified further in Figure 1.

An alternative approach to improving T cell responses is the use of immune checkpoint inhibitors targeting the inhibitory T cell co-receptors, including programmed death 1 (PD-1) [70]. Although mostly studied in cancer, in a murine model of *Candida* blood stream infection, PD-1 blockade improved T cell responses and survival when combined with fluconazole [71]. A trial of PD-1 blockade was also used successfully in a patient with refractory mucormycosis in combination with IFN- $\gamma$  and anti-fungal therapy [72].

## MONOCLONAL ANTIBODY THERAPY

Administration of monoclonal antibodies reactive with fungal cell surface components protects animals in models of candidiasis, aspergillosis, cryptococcosis and histoplasmosis [73–76]. Human trials of monoclonal antibodies directed against *C. albicans* heat shock protein 90 resulted in faster clearance of infection, and pilot studies of anti-*C. neoformans* capsule antibodies showed temporary reductions in antigen titres [77,78]. Efforts to develop

a monoclonal antibody with pan-fungal efficacy have shown some promise with monoclonal antibodies directed against  $\beta$ -glucans [79] and  $\beta$ -1,6-poly-N-acetyl-D-glucosamine [80].

## VACCINATION

No fungal vaccine has been licensed for human use, and special challenges arise in developing vaccines for diseases that almost exclusively affect immune compromised individuals. While some live attenuated fungal strains induce protective immunity in mice [81], caution needs to be exercised that such strains are sufficiently attenuated so as not to cause disease in persons with impaired immunity. Killed strains obviate this concern but autoimmune and inflammatory reactions to vaccine components need to be carefully monitored. For example, a formalin-killed *Coccidioides* spherule whole cell vaccine targeting individuals at risk for the endemic mycosis coccidioidomycosis showed a trend towards protection but was poorly tolerated [82].

One strategy for fungal vaccines is utilization of conserved fungal cell wall components to stimulate adaptive immunity. This strategy has the potential for eliciting protective antibodies against multiple genera of fungi. While cell wall glycans are poorly immunogenic, glycan conjugate vaccines effectively induce adaptive responses [83]. A glycoconjugate vaccine consisting of brown algae  $\beta$ -glucan covalently linked to diphtheria toxin protects against challenge with multiple fungi in animal models [84], and similar approaches have been used to develop protective antibodies against capsular components of *C. neoformans* [85].

Due to their capacity to be innately recognized by the host immune system, fungal cell wall glycans ( $\beta$ -glucans, mannans and chitosan) have been utilized as antigen delivery systems and adjuvants [83]. The benefits of this technique have been demonstrated in murine experiments where encapsulation of antigen in  $\beta$ -glucan particles resulted in durable antigen-specific Th1 and Th17 T-cell and antibody responses [86,87]. Dendritic cell (DC) vaccination is another potentially beneficial approach and in murine models of HSCT associated aspergillosis, this resulted in improved antigen-specific Th1 responses, accelerated lymphoid and myeloid cell recovery, and improved survival following infective challenge [88].

An active area of investigation is the identification of immunoreactive fungal antigens that can be used in subunit vaccines. Although many antigens are species- or genus-specific and would elicit protective responses against only a narrow range of fungal pathogens, this approach may have merit in targeted at-risk populations. For example, a vaccine consisting of a recombinant N-terminus of Als3 protein (required by *Candida* for endothelial adherence) has been shown to induce antigen-specific antibody, Th1 and Th17 T-lymphocyte responses, and reduce fungal burden in hematogenously challenged mice [89].

Phase I trials have shown it to be safe and immunogenic in healthy adults [90], and a clinical trial of this vaccine in women with recurrent vulvovaginal candidiasis recently completed enrolment [91].

## IMMUNE SUPPRESSIVE THERAPY

Finally, although the majority of evidence for immune modulation in IFI favours techniques that stimulate the immune response, in some fungal infections inhibition of an overly exuberant response may be preferential. In patients with HIV-associated *Pneumocystis jirovecii* pneumonia (PCP), adjunctive corticosteroids reduce IL-8 driven neutrophil pulmonary infiltration and decrease patient mortality in severe disease [92,93]. Corticosteroids may also reduce the incidence of cerebrovascular events in *Coccidioides immitis* meningitis [94] and beneficial effects have been reported in individual patients with chronic disseminated (hepatosplenic) candidiasis and in cryptococcal meningitis-IRIS [7,17]. However, the use of corticosteroids in patients with HIV-associated cryptococcal meningitis who do not have IRIS is not recommended after a clinical trial demonstrated slower clearance of infection and worse clinical outcome [95]. This is consistent with immunological studies that demonstrate an association between a poor inflammatory response in the CSF and blood, and increased disease severity and mortality [96,97].

## FUTURE DIRECTIONS

The pathogenesis of fungal infections is intrinsically linked to host immune response. Given the recent advances in immune therapy against cancer, the prospect of modulating the host immune response in fungal infections is appealing but thus far elusive. Many techniques have shown great promise *in vitro* and in animal models but very few have been tested, much less proven to work, in patients. Future research should concentrate on translating promising ideas such as adoptive T cell transfer and adjunctive IFN- $\gamma$  therapy to the clinic and developing immune assays to identify groups of patients likely to benefit.

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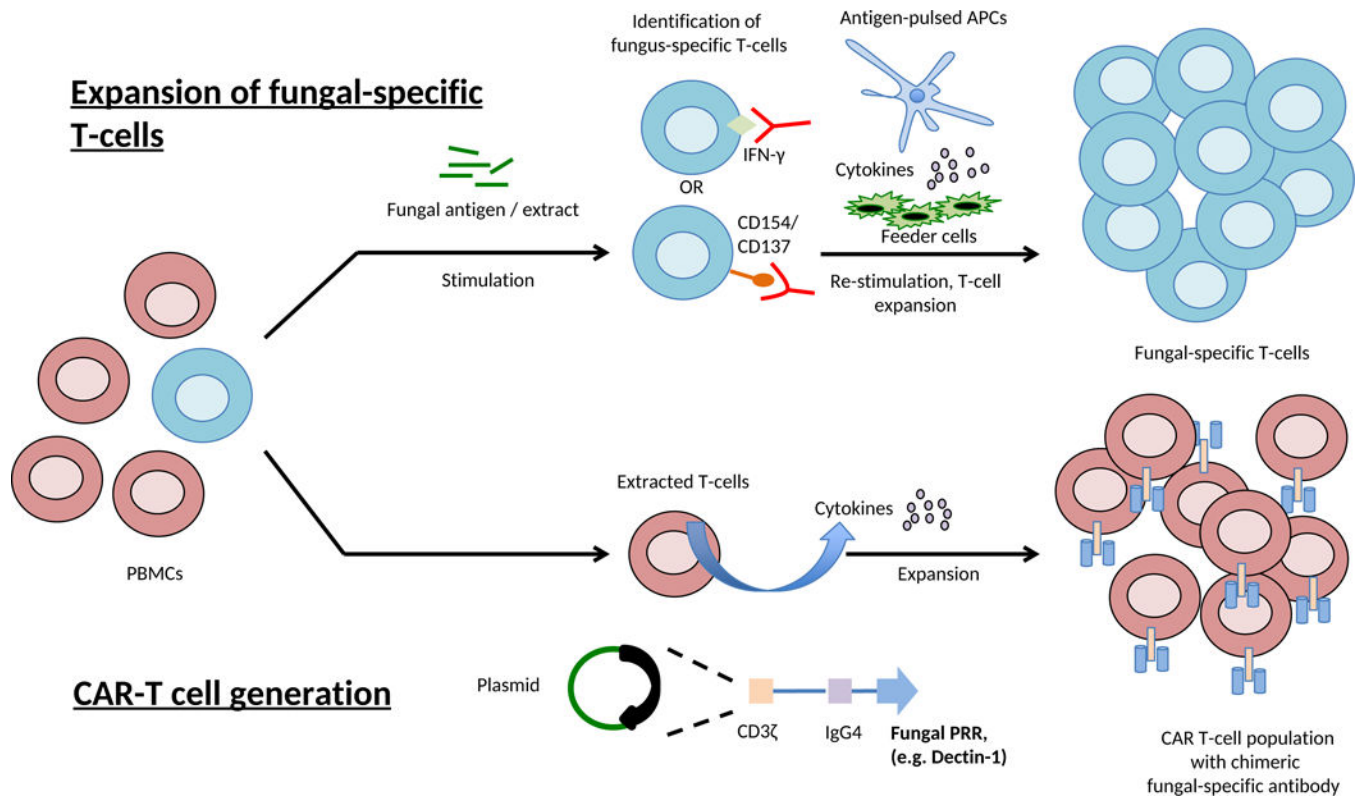


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**HIGHLIGHTS**

- Pro-inflammatory cytokine therapy confers benefit in animal models of mycoses
- Translation of pre-clinical findings into patient therapy is limited to date
- IFN-gamma therapy in humans results in faster clearance of *Cryptococcus*
- Antigen-specific T cell therapies are promising but technically challenging
- Results of anti-*Candida* vaccine trials are awaited





**Figure 1. Mechanisms of adoptive T-cell generation**

Therapeutic fungal-specific T-cells can be generated through PBMC exposure to fungal antigen, identification of fungal-specific T-cells (e.g. immunomagnetic sorting), and T-cell expansion or through generation of CAR T-cells with expression of antibodies containing extracellular fungal recognition component (e.g. Dectin-1). CAR– chimeric antigen receptor; PBMC – peripheral blood mononuclear cells; PRR – pattern recognition receptor

**Table 1**  
**A summary of evidence supporting different immunomodulatory strategies in three main invasive fungal infections**

Shading indicates level of evidence: green – cell culture or animal experiments; orange – animal models and exploratory human studies; red – animal models and human clinical trials.

	<b>Aspergillus</b>	<b>Candida</b>	<b>Cryptococcus</b>
<b>G-CSF</b>	Enhanced protection & antifungal response in animal models [22,23]	Enhanced protection and antifungal response in animal models [21]. Faster resolution of infection in human trials [25].	
<b>GM-CSF</b>	Reduction in tissue burden in experimental infection [29]	Resolution of fluconazole-refractory oropharyngeal candidiasis in 7 out of 11 AIDS patients [35]	Enhanced response to antifungal therapy in cell culture models [30]. Persons with anti-GM-CSF autoantibodies at risk of infection [31]
<b>M-CSF</b>	Enhanced protection in neutropenic animal models [39]		
<b>IFN-<math>\gamma</math></b>	Enhanced protection and antifungal response in animal models [47,48].	Increased susceptibility and mortality in knockout mice [41].	Increased susceptibility in IFN- $\gamma$ deficient/inhibition [42,46]. Exogenous IFN- $\gamma$ results in reduced mortality in animal models [51] and faster clearance in human trials [53].
<b>PD-1 blockade</b>		Improved T cell responses and survival in mice [71]	
<b>mAb</b>	Improves protection in animal model [75].	mAb to hsp-90 protect mice from infection [74] and associated with faster clearance in clinical trials [77]	Enhanced protection and animal fungal response in animal models [73,79]. Reduction in antigen titre in human pilot studies [78]
<b>Granulocyte transfusion</b>	Animal model demonstrate benefits of posaconazole-loaded leukocytes transfusion [61]	Better than expected outcome in human pilot studies [58].	
<b>T cell transfusion</b>	Prolonged survival in animal models [65,69]. No complications in human pilot studies [66]		
<b>Vaccination</b>	Improved survival with dendritic cell vaccine in mice [88]	New vaccines confer protection in animal models [84,89], and are immunogenic and safe in humans; clinical trials have recently completed enrolment [90,91].	Glycoprotein and glucan particle vaccine provide protection in animal models [85,87].