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# Modulating host immune responses to fight invasive fungal infections

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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 antifungal 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.

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## Introduction

Invasive fungal infections (IFI) are an increasing global health problem, resulting in significant morbidity and mortality among individuals with impaired immunity [1,2,3•]. Despite recent advances in the care of patients with IFI, conventional therapeutic options 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 *Talaromyces (Penicillium) 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

**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**

| | Aspergillus | Candida | Cryptococcus |
|---|---|---|---|
| **G-CSF** | 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]. | |
| **GM-CSF** | 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] |
| **M-CSF** | Enhanced protection in neutropenic animal models [39] | | |
| **IFN- γ** | Enhanced protection and antifungal response in animal models [47,48]. | Increased susceptibility and mortality in knockout mice [41]. | Increased susceptibility in IFN- γ deficienty/inhibition [42,46]. Exogenous IFN- γ results in reduced mortality in animal models [51] and faster clearance in human trials [53]. |
| **PD-1 blockade** | | Improved T cell responses and survival in mice [71] | |
| **mAb** | 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] |
| **Granulocyte transfusion** | Animal model demonstrate benefits of posaconazole-loaded leukocytes transfusion[61] | Better than expected outcome in human pilot studies [58]. | |
| **T cell transfusion** | Prolonged survival in animal models [65,69]. No complications in human pilot studies [66] | | |
| **Vaccination** | Improved survival with dendritic cell vaccine in mice [89] | New vaccines confer protection in animal models [84,90], and are immunogenic and safe in humans; clinical trials have recently completed enrolment [91,92]. | Glycoprotein and glucan particle vaccine provide protection in animal models [85,87]. |

haematopoietic stem cell transplantation (HSCT), there are now efforts to explore novel conditioning strategies using haematopoetic 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 [32,33,34••]. 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