Development of a Vaccine for Invasive Aspergillosis

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(See the viewpoint by Stevens on pages 1131–6)

Invasive aspergillosis (IA) remains one of the most feared infectious complications in immunocompromised patients. Despite the introduction of new antifungal compounds, the mortality rate associated with this disease remains ≥50% [1–3]. The incidence of IA has increased over the past several decades, and advances in transplantation and in the treatment of immunocompromised patients are likely to continue to increase the size of the at-risk population in the future [4, 5]. Therefore, it is easy to build a compelling case for an urgent clinical need for the development of an Aspergillus vaccine, as has been done by Stevens [6] in the comprehensive review found in this issue of Clinical Infectious Diseases.

Although this clinical need is beyond question, significant hurdles remain that must be overcome before such a vaccine can become reality. As Dr. Stevens notes [6], the development of a vaccine designed to work exclusively in an immunocompromised host is a new and challenging paradigm in vaccinology, paralleling the challenges for the development of vaccines to be used in patients infected with HIV. However, what is perhaps a greater hurdle facing the development of an IA vaccine is the fact that the patient groups at risk for IA—and the underlying defects in immunity that predispose them to IA—have become increasingly heterogeneous. Although classic IA (experienced during neutropenia caused by cytotoxic chemotherapy or related to corticosteroid-induced T cell and macrophage dysfunction) remains a major clinical problem, new at-risk populations have been identified. A chronic form of IA is associated with the T cell deficiency that accompanies HIV infection [7]. Cases of IA acquired in the late post–bone marrow transplantation period are an increasing problem and are likely related to T cell dysfunction in patients with clinical or subclinical graft-versus-host disease (GVHD) or cytomegalovirus infection [8]. Most recently, the use of new TNF inhibitors for the treatment of rheumatoid disease, GVHD, or Crohn disease has been linked to an increased incidence of IA [9–11]. The diversity of these populations and of their underlying immune defects will provide not only a scientific challenge to the induction of an efficient immune response, but also a real-world challenge in the design of clinical trials and the development of immunization guidelines.

In addition to the challenges involved in enhancing the efficacy of an Aspergillus vaccine, there is also the potential for safety issues. A wide range of allergic diseases are associated with sensitivity to Aspergillus antigens in subsets of the population. The potential for adverse immune reactions to an Aspergillus vaccine is real and may prove problematic.

Despite these challenges, Dr. Stevens [6] has identified several reasons for optimism. The populations that are at risk are easily identifiable clinically, and they provide an excellent opportunity for targeted vaccination. The period of risk is predictable and is often self-limited, allowing for strategic timing of interventions. Indeed, full protection may not be necessary in many cases, because simply slowing disease progression long enough to allow recovery of the native immune response may be quite sufficient for many patients. Scientifically, several studies have elicited protection with crude Aspergillus fumigatus vaccines [12, 13]. Most encouragingly, in murine models, this protection has been shown to persist in immunosuppressed animals, although each of these vaccines has been tested for efficacy in a single immunodeficiency state. It remains unclear if protection can be elicited across a range of immunological defects, such as those resulting from corticosteroid therapy, neutropenia, T cell dysfunction, and anti-TNF therapy.

Given all of these considerations, what type of vaccine is likely to be the most effective in preventing IA? Current efforts have focused on the development of active
immunization protocols that use either crude antigen preparations [12, 13] or individual \textit{A. fumigatus} antigens [14]. Although these efforts are beginning to bear fruit, there remain some fundamental concerns about efficacy across a wide range of immunological deficiency states. Novel adjuvants, including cytokines and other immunomodulators, may help to circumvent this problem.

In contrast, passive immunization approaches have been neglected, because humoral immunity seems to play little role in natural defense against IA [15, 16]. This finding does not mean, however, that experimentally derived monoclonal or polyclonal antibodies directed at novel antigens will be unable to provide protection. Furthermore, passive immunization is less dependent on host immunity and, therefore, could potentially be effective across a wider range of immunological defects in the host. Indeed, in addition to functioning as opsonins, antibodies may act directly on the organism to slow growth, block adherence to host tissues, or interfere with morphogenesis, all in the absence of other immune cells. For example, Moragues et al. [17] have described a monoclonal antibody directed against a hyphal mannoprotein of \textit{Candida albicans} that directly inhibits growth, adherence, and germination in vitro in the absence of any immune effector cells. It is of interest that this antibody also inhibits the growth of \textit{A. fumigatus} in vitro, a finding that needs to be investigated further. The most compelling evidence that passive immunization may prove to be a successful strategy comes from the studies of Cenci et al. [18]. This group used a killer anti-idiotypic monoclonal antibody to protect mice from a lethal \textit{A. fumigatus} challenge during experimental bone marrow transplantation. This antibody also directly inhibited \textit{A. fumigatus} growth in vitro, suggesting a role for direct effects on the fungus.

A final approach combines active and passive immunization through the use of adoptive transfer of previously immunized cells. Bozza et al. [19] have demonstrated that transfer of dendritic cells exposed to \textit{A. fumigatus} can protect mice that have received allogeneic bone marrow transplants from subsequent fungal challenge. Considerable work will be necessary to determine how practical this and similar strategies will be.

Thus, although the clinical need for a vaccine against \textit{A. fumigatus} is indisputable, there remain several important hurdles to overcome, both practical and scientific. In particular, the heterogenous nature of the patient population susceptible to \textit{A. fumigatus} will make the development and testing of an \textit{A. fumigatus} vaccine a challenge. However, the encouraging preliminary results of successful vaccination in animal models and the availability of new molecular tools, adjuvants, and immunomodulators create considerable enthusiasm for the pursuit of vaccine strategies for control of this ever-increasing problem in immunocompromised hosts.

References