CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Immunotherapy for HIV Infection

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The provision of immunotherapy through antibody infusion has a venerable and valuable record in the treatment of infectious disease. In 1901, the first Nobel Prize in Physiology or Medicine was awarded to Emil von Behring for "serum therapy, especially its application against diphtheria," and more recently, postexposure prophylaxis against rabies has combined antibody treatment with active immunization. Although immunotherapy for chronic, persistent infections is more problematic, new studies by Barouch et al.[1] and Shingai et al.[2] on the treatment of rhesus macaques indicate that monoclonal antibodies show much promise in clearing infection with a hybrid form of the simian immunodeficiency virus (SIV) that bears the envelope antigens of the human immunodeficiency virus type 1 (HIV-1) and SIV, referred to as SHIV.

During the past few years, several novel monoclonal antibodies that have been derived from cells from HIV-infected persons combine extraordinarily high potency with breadth in neutralizing diverse strains of HIV-1. The impetus for this work has come from vaccine research that is based on the premise that a better understanding of how these monoclonal antibodies bind to the HIV envelope will lead to the design of protective immunogens. This important goal has yet to be realized, but the new studies indicate that the same monoclonal antibodies can be used therapeutically. A rapid and profound clearance of virus from the peripheral blood of infected macaques after the infusion of one or more monoclonal antibodies was observed by both Barouch et al.[1] and Shingai et al.[2] Although the virus eventually reappeared as levels of monoclonal antibodies waned over time, in several animals viral levels did not rebound to their pretreatment level, indicating that the set point of the viral load was permanently reduced.

The exact mechanism through which monoclonal antibodies work remains to be elucidated. Their effectiveness as potent neutralizers of infectious HIV particles has been established, but it is also thought that they may reduce the number of virus-producing cells. Such destruction of the factories of virus production (Fig. 1) may be mediated through antibody-dependent cellular cytotoxicity or through cell lysis by complement. The number of cells infected with viral DNA in lymph nodes and mucosa also diminished, according to analysis of biopsy specimens; one antibody in particular was effective in reducing viral load and the number of infected cells.[1] A different therapeutic immunization strategy was recently reported by Hansen et al.,[3] who infected

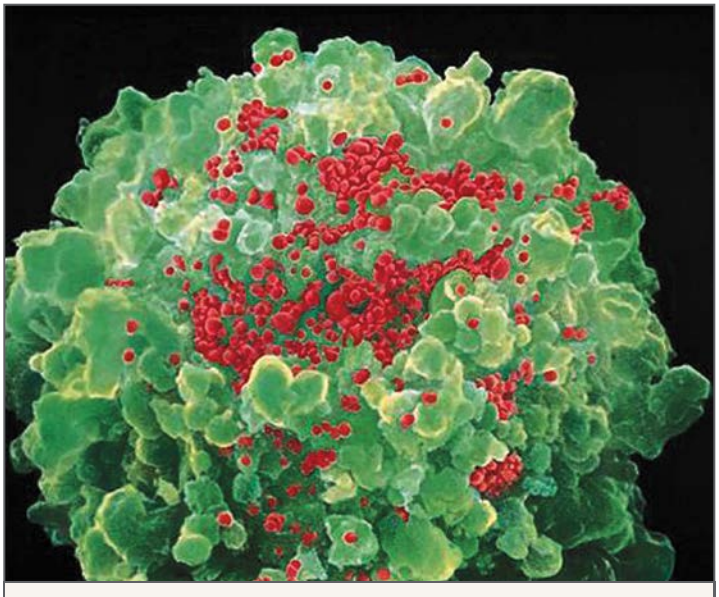

Figure 1. A CD4+ T Lymphocyte Infected with HIV.

The host cell (green) is infected by and produces HIV particles (red). Recent studies indicate that potent monoclonal antibodies not only neutralize released virus but may help to destroy infected cells.[1,2] The scanning electron micrograph was obtained by Dr. David Hockley from an infected culture provided by Dr. Weiss.

macaques with a modified simian cytomegalovirus expressing SIV antigens and then observed clearance of SIV after stimulating specific memory T cells. Thus, antibodies and cell-mediated immunity may have synergistic therapeutic potential.

Given the effectiveness of oral antiretroviral treatment, what advantage might be proffered by inoculation with monoclonal antibodies? The answer may be a long-term effect and an alternative treatment for those in whom antiretroviral treatment has failed. Moreover, a combination of conventional drugs and immunotherapy may be better than either alone. One of the problems with antibody therapy is the need for repeated injections of the monoclonal antibody in order to maintain levels sufficient to control the virus. An alternative is to deliver the genes encoding the heavy and light chains of the monoclonal antibody so that the patient can generate it internally. Balazs et al.[4] have studied this approach. Using a mouse model containing human lymphoid tissue, they observed that the genetic delivery of a neutralizing monoclonal antibody through a viral vector blocked HIV-1 infection. Moreover, a single intramuscular injection induced lifelong expression of the monoclonal antibody at high plasma levels, suggesting that this approach could be considered for immunotherapy as well as immunoprophylaxis.

Potent neutralization of anti-HIV monoclonal antibodies can also prevent new infection when locally administered before a mucosal SHIV challenge. It is often assumed that mucosal immunity requires secretory IgA responses, although we know that protection against cervical cancer through human papillomavirus vaccines is mainly achieved through IgG. Watkins et al.[5] recently reported that the use of passive monoclonal antibody protection with dimeric IgA1 (which captures virus particles and prevents their transcytosis across mucosal cells) was more effective than direct neutralization of SHIV, whereas the nontranscytotic dimeric IgA2 isotype of the same monoclonal antibody offered poor protection. This observation should be borne in mind if monoclonal antibodies are to be developed as vaginal microbicides for the prevention of HIV-1 transmission.

Monoclonal antibodies already have a well-established role in immunotherapy for cancer and autoimmune disease. There is no reason to hesitate to explore their clinical potential for use in the control of chronic infection with viruses such as HIV-1, especially given the recent data on the effects of treatment with highly potent, broadly neutralizing monoclonal antibodies.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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