

receptor genes can be rescued from T cell clones shown to be effective and safe in therapy and inserted into T cells from other patients with tumors that express the same tumor antigen and MHC-restricting allele, overcoming the need to isolate tumor-reactive effector cells in each individual patient. Survival of transferred cells can also be enhanced by introducing chimeric cytokine receptors that use cytokines such as GM-CSF that are produced by effector CD8 T cells after target recognition as regulated autocrine growth signals (44).

An alternative genetic strategy to introducing new structures or functions to T cells is to disrupt signaling pathways that normally serve to dampen responses such as those through Cbl-b, an adapter protein that negatively regulates T cell receptor signal strength (45). Preliminary studies in which dominant-negative Cbl-b proteins are expressed or Cbl-b expression is reduced through small interfering RNA approaches suggest that increasing signal strength can both reduce the threshold for T cell activation and restore regulated IL-2 production to effector CD8 T cells. Many other targets for these approaches have been identified by studies in knockout mice, suggesting the possibility of designing T cells capable of circumventing many of the obstacles posed by tumors.

Future Directions

It was not long ago that most scientists questioned whether the human immune system was capable of recognizing spontaneously arising tumors and whether immune therapy could ever become a meaningful treatment for human malignancy. The answers are a resounding and unequivocal "Yes!" The administration of cytokines and mAbs

have already become components of some standard cancer treatment regimens. Many vaccines have advanced through preliminary testing to efficacy trials, and T cell therapy is being explored with new sophistication in many disease settings. As our understanding increases of the requirements for immune cell activation, homing, and accumulation at tumor sites, and for disrupting the regulatory mechanisms that limit responses, the ability to direct a coordinated and effective attack against tumors engaging multiple components of the immune system should evolve in parallel. Clinical trials of passive transfer of large numbers of tumor-reactive T cells or mAbs should not only help define the nature and magnitude of responses that will be necessary to achieve by stimulating endogenous responses, but will offer the possibility to genetically or chemically engineer immune responses with functional capacities beyond what can be elicited from the normal immune system. Despite Niels Bohr's caution that "prediction is very difficult, especially about the future," we confidently predict that immunotherapy will become an increasingly essential component of future cancer therapies.

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VIEWPOINT

Therapeutic Vaccines for Chronic Infections

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Therapeutic vaccines aim to prevent severe complications of a chronic infection by reinforcing host defenses when some immune control, albeit insufficient, can already be demonstrated and when a conventional antimicrobial therapy either is not available or has limited efficacy. We focus on the rationale and challenges behind this still controversial strategy and provide examples from three major chronic infectious diseases—human immunodeficiency virus, hepatitis B virus, and human papillomavirus—for which the efficacy of therapeutic vaccines is currently being evaluated.

The term "vaccine" was first coined by Edward Jenner in 1796 after his successful prevention of infection by the smallpox virus. Louis Pasteur later extended the concept to other pathogens and sought to cure humans of rabies, declaring to the French Academy of Sciences, "I have developed a method that will be generally applicable to all animals and to humans" (1). By inocu-

lating a boy bitten by a rabid dog with his vaccine, he was able to prevent the onset of the symptoms of rabies. This procedure, known as postexposure prophylaxis, remains the only cure for this otherwise fatal disease, and the equivalent strategy is now an integral part of the pharmacopeia in preventing severe disease after acute infections such as tetanus and diphtheria.

The efficacy of therapeutic immunization in rabies, in which symptoms can appear after several months or years, raised the question of whether the concept could be extended to other chronic infections. Although there is no doubt that prophylactic vaccines have been heralded as a medical success story (Fig. 1A), the concept of therapeutic vaccines remains controversial. Among the many questions is whether there is a sound rationale for using vaccines

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when antibiotics and antiviral agents have become the standard of care? Can a vaccine be effective once an infection is established, in light of the conventional wisdom that fighting against a persistent infection is far more difficult than eliminating the relatively minute numbers of pathogens when they first enter the body? What are the proofs of concept, if any? Here, we focus on these questions and on examples taken from three major chronic infectious diseases for which the ability of therapeutic vaccines to ultimately prevent pathology is currently being evaluated.

Therapeutic Immunization: Rationale and Challenges

Therapeutic vaccines aim to prevent severe complications of a chronic infection by reinforcing or broadening defenses when specific immune responses are unable to do so during the natural course of the disease and when a conventional antimicrobial therapy is not sufficient (Fig. 1, B and C). The rationale for this objective stems from the notion that the ultimate complications of a chronic infection—including severe immune deficiency caused by the human immunodeficiency virus (HIV); chronic hepatitis, cirrhosis, and hepatocarcinoma induced by the hepatitis B virus (HBV); and cancer induced by the human papillomavirus (HPV)—result from a lack of immune control or an inappropriate state of immune tolerance. Thus, vaccines appear to represent a valuable therapeutic strategy when the following conditions are met: (i) No specific treatment is available or efficacious against the pathogen or the disease, antimicrobial agents cannot eradicate the pathogen and thus select for resistance, or antimicrobial agents are too toxic to be administered over long periods. (ii) Some degree of immune control can be demonstrated during the infection's natural course, as shown by a clearance after the primary infection in some cases of HBV or HPV infections or by an accelerated progression of the disease as seen with HBV or HPV-related diseases in immunocompromised patients. The existence of a prophylactic vaccine capable of inducing sterilizing immunity and preventing both infection and its complications, as for HBV or HPV, is also a major indicator of the potential of the immune system to deal with a specific pathogen. (iii) A chronic carrier status with low pathogen burden precedes the onset of severe life-threatening symptoms, reflecting pathogen proliferation, chronic inflammation, or malignant transformation of the pathogen-induced lesions.

The first challenge of generating efficient therapeutic vaccines will be to improve our understanding of relevant im-

mune correlates of protection against chronic infections. Importantly, specific immune defenses against continuous replication in tissues may differ from those that operate at the time of pathogen entry. For example, whereas antibodies are key in preventing pathogen entry, T cells may be preferentially used for destroying infected cells as a disease progresses. Consequently, antigens targeted by therapeutic and prophylactic vaccines will also differ, meaning that success in prophylactic vaccination will not necessarily guarantee success against chronic infection, even by the same pathogen.

The concept of immune memory, a cornerstone of preventative vaccines, might also be challenged. Harnessing immune memory makes sense in cases of the vaccination of uninfected naïve individuals or after acute infection. Memory cells survive after the initial burst of immune effector cells in response to the vaccine, offering a means of rapidly deploying new effectors when the body is rechallenged by the pathogen itself (2). In persistent infections, the stage of T cell differentiation reflects the extended duration of exposure to the pathogen (3). The goal of therapeutic vaccines, therefore, will be to trigger immune cells with immediate effector capabilities as well as cells that possess an ability to survive and proliferate, thus providing both immediate and durable protection.

The second challenge deals with levels and timing. Continuous immune stimulation by persistent pathogens can eventually lead to immune exhaustion. On the other hand, chronic antigen presentation by infected cells lacking the appropriate costimulatory molecules may induce inadequate stimulation and T cell anergy. Thus, vaccine stimulation might only serve to contribute to these dwindling responses. In addition, to compete with chronic pathogen production, therapeutic vaccines need to generate proportionally more vigorous immune reactivity than would normally be needed for preventative vaccines. Here, again, antigen doses provided by a vaccine might face an obstacle: They may be tiny relative to those present in an established infection. Finally, presence of preexisting antigen-experienced T cells might limit amplification of new T cell clones, which may require distinct routes of antigen presentation.

The third challenge will be to overcome immune evasion strategies used by persistent pathogens. Variability in the dominant epitopes, inhibition of major histocompatibility complex molecule expression, integration of the virus genome in host DNA, latency, and "hiding" in the sanctuary subcellular compartments or tissues are several mechanisms used by pathogens. These obstacles must be faced by both prophylactic and therapeutic vaccines.

Finally, chronic infections induce immunopathological events mediated by both adaptive and innate immune responses and these contribute to the severity of the chronic disease state, as seen in the progressive immune deficiency caused by HIV and chronic hepatitis induced by HBV. Reinforcing specific immunity may thus be futile or even harmful in such advanced stages.

Such challenges have so far limited the development and efficacy of therapeutic vaccines, and ignoring them will guarantee failure. We propose the following three key points to optimize the strategy of therapeutic vaccines: First, therapeutic vaccination should be developed only when pathogen burden remains limited, far before onset of severe symptoms. When available, antimicrobial agents should be administered first to decrease pathogen burden and inflammatory events down to a level that would allow the immune system to restore its capacity to respond. Second, the addition of a therapeutic vaccine during this phase of treatment should provide, amplify, and broaden repertoires of immediately competent and long-lived immune cells. Third, at a point when immune responses reach a peak, treatment can be interrupted if it becomes overtly toxic. As a consequence, the immune responses developing in these types of therapeutic settings should encounter bursts of pathogens similar to those faced by memory cells after a prophylactic vaccination and should help prevent disease (Fig. 1C).

Vaccines as Therapeutic Tools

Candidate vaccines need to elicit strong CD4 T help and CD8 T cell responses. To do so, attenuated pathogens have traditionally been the choice for preventative vaccines, but these expose potentially uncontrolled risks. Instead, live attenuated genetically engineered recombinant viral vectors, such as poxviruses or adenoviruses, are now favored, because they are generally safe and provide a demonstrably superior adjuvant effect in eliciting T cell immunity than naked DNA alone. Indeed, such "live" vectors mimic the "danger signals" normally expressed by bona fide pathogens and trigger both innate and adaptive arms of the immune response (4). A vaccine against a chronically infecting pathogen might, however, require several inoculations, and its efficacy will be limited by the undesired immunity directed at the vector that accompanies the desired immunity to the pathogen itself. To avoid this complication, we need inert vectors that can repeatedly trigger potent pathogen-specific immunity. To achieve this, combinations of recombinant viral vectors with inactivated viruses, pseudoparticles, proteins, peptides, polynucleoti-

des, or RNA-based alphavirus vaccines should act synergistically to promote stronger pathogen-specific immune responses, while limiting vector-specific immunity.

The selection of the appropriate adjuvant is equally important, and improved adjuvants are urgently needed to mimic the efficacy of live pathogens. To this end, a variety of physiological immune ligands are now being identified (5–7). Cytokines and chemokines could also be used as adjuvants to regulate, modulate, or enhance effector T cell function and memory T cell maintenance. Plasmid DNAs coding for interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-12, IL-15, and IL-7 show such promising features. For example, IL-2 and GM-CSF have shown encouraging results in macaque models of HIV infection (6, 7), although the safety of these growth factors in humans remains to be evaluated. Chemokines, such as macrophage inflammatory protein 1- α , macrophage chemoattractant protein (CCL-2) (MCP-1), RANTES, IL-8, and CC chemokine receptor (CCR7) ligands that augment T helper 1 (Th1) and cytotoxic T lymphocyte (CTL) responses to HIV-1 and herpes simplex virus-2, might also improve vaccine efficacy, but are still at early steps of development (7).

Therapeutic Vaccines Against Chronic HBV Infection

With 200 million chronic carriers worldwide, HBV is still the most common cause of chronic liver disease. Despite the success of preventative vaccines, it may take several decades to reduce HBV morbidity (8). The virus persists in about two-thirds of the cases of infection; some patients remain healthy carriers and develop a low or late immune response, whereas others have a weak, narrowly focused CD8⁺ T cell response and develop chronic active HBV hepatitis and subsequent cirrhosis with a high

risk for hepatocarcinoma development. Chronic hepatitis in infants born to infected mothers remains a public health issue in many countries. Termination of the carrier state and of chronic hepatitis itself may avert these risks. The recent introduction of antiviral treatment inhibits formation of new viruses but does not eradicate existing infec-

during chronic hepatitis is proposed as one means of overcoming tolerance and boosting suboptimal immune responses to help viral clearance in chronically infected individuals. Several strategies are being tested, including vaccines that incorporate T cell epitopes in presurface (pre-S) and S antigens that should help eliminate HBV-infected hepatocytes. In

addition, DNA vaccines and traditional existing HBV vaccine, alone or complexed to anti-HBV immunoglobulins (HBIG), are being evaluated.

A strategy similar to postexposure prophylaxis, with vaccination alone or with HBIG, prevents the development of chronic hepatitis in 85% of infected infants born to carrier mothers. A pioneering therapeutic immunization study in adults with chronic hepatitis has shown that a pre-S2/S or S vaccine was immunogenic and significantly decreased HBV production to undetectable levels, although for less than a year (9). However, limitations of the various studies include the short duration of T cell immunity or the absence of enhanced anti-HBV levels in the presence of preexisting antibodies (10). Preliminary data from one study combining vaccine, antiviral agent, and IL-2 suggest that potent antiviral immune responses could indeed be induced that led to viral elimination (11).

More effective strategies will require increased doses and numbers of immunizations in combination with antiviral agents and immune modulators. Better selection of the stage of the chronic HBV infection should also help to improve these promising early results.

HPV Therapeutic Vaccines in Clinical Trials

Genital papillomavirus infections are widespread among sexually active adults (12). The continued expression of HPV proteins drives the development of cervical dysplasia and cancer, which can be prevented by early detection and treatment of preinvasive cervical

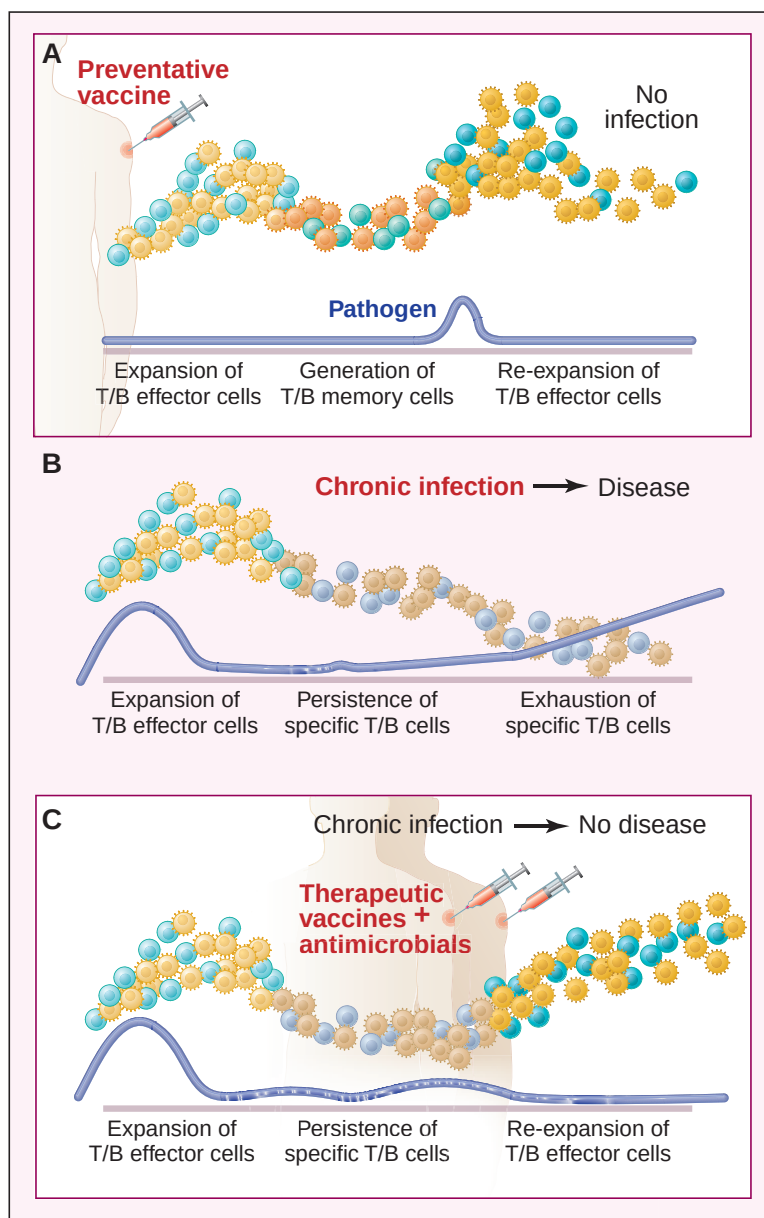


Fig. 1. (A) Prevention of infection when a prophylactic vaccine induces T (light blue) and B (gold) effector and memory cells before exposure to the pathogen (dark blue line). (B) Natural course of a chronic infection in which continuous pathogen production exhausts immune responses and leads to a failure to prevent disease. (C) Therapeutic vaccines added to antimicrobials in chronic infection might restore immune control and prevent disease.

tion. Similar to anti-HIV treatment, it suspends rather than cures disease, leading to the emergence of resistance, or to HBV relapses after drug administration is terminated.

Therapeutic immunization against HBV

disease (13). Prophylactic vaccines that use virus-like particles to induce neutralizing antibodies against HPV (14) prevent primary HPV infection and subsequent development of HPV-induced cervical intraepithelial cell-mediated immunity mainly triggered by the HPV-early protein 6 (E6) and E7 proteins. These vaccines may control virus-induced cervical lesions (15). Most attempts using therapeutic vaccines have focused on eliciting CTLs that are directed against these oncoproteins. However, such studies have also evaluated efficacy of HPV vaccines after the oncogenic transformation of the HPV cervical infection occurred. Peptide-based vaccines have revealed some T cell immunogenicity (16) but so far have yielded only limited clinical responses. Full-length E6 and/or E7 proteins (17) and recombinant vaccinia viruses expressing HPV-16/18 have proven immunogenic in 60% of cases, with significant clinical improvement in 83% of the women (18). These results, although still modest, raise expectations that a better clinical management of earlier premalignant lesions and prevention of cervical cancer will be possible long before prophylactic vaccines have eradicated HPV infections.

Therapeutic Vaccines Against HIV Infection and AIDS

Twenty years after the first cases were identified, the HIV-1 pandemic is still growing exponentially, causing more than 42 million cases of individuals living with HIV worldwide. Continuous virus replication in CD4 T lymphocytes induces progressive immune defects and ultimately, after 6 to 10 years, acquired immunodeficiency syndrome (AIDS) and death. The course of the HIV infection has changed markedly with new antiretroviral regimens that combine inhibitors of reverse transcription, virus protein cleavage, or even virus entry. They reduce viral burden and immune damage caused by HIV (19) but cannot eradicate the virus (20). Thus, lifelong therapy is required to transform this otherwise lethal disease into a chronic, continuously treated infection by preventing the progression to AIDS. However, the drugs' efficacy is limited by severe drug-related adverse effects and drug resistance, and the drugs are not affordable for the vast majority of patients worldwide. Because no therapeutic breakthrough is likely to appear that would soon eradicate HIV or limit side effects, additional therapeutic strategies must be found to durably prevent the onset of AIDS.

One such strategy might be to combine antiretroviral treatment with immune responses to HIV. Some immune control of HIV is apparent from the temporal association of virus reduction and outgrowth of HIV-specific T cells (21), whereas anti-HIV neutralizing antibodies appear too late to play a key role. Nevertheless, HIV-specific CD4 T helper cells become rapidly exhausted (22), and although CD8 T cells partly control chronic infection, HIV eventually escapes host immunity (23). In some individuals, so-called long-term nonprogressors, immune control of the

virus can be maintained for up to 25 years (24), but such individuals account for no more than 2% of the infected population. Even so, such cases raise the hope that immune control of HIV is realistic.

Antiretroviral therapies, despite their relative effectiveness, do not restore immunity to HIV (19). Early treatment of acute HIV infection preserves HIV-specific CD4 T helper cells (22) but limits the development of CD8 responses (25). Treatment in chronic phases of the disease does not restore anti-HIV CD4 T cells (19, 22), and anti-HIV CD8 effector T cells decay with virus (26). These limitations reflect antigen-driven homeostasis of virus-specific lymphocytes; the production of HIV antigens during treatment maintains a threshold of viral production below that needed to efficiently stimulate effector T cells (27). Immune memory to HIV persists nonetheless, as indicated by the transient restoration of immune responses following virus relapses when treatment is discontinued (28).

With these issues in mind, a new strategy has been proposed to first treat patients with antiretroviral therapies and restore immune competence and then to subsequently treat with therapeutic vaccines to boost the rested immune responses to HIV before interrupting treatment. In theory, this should enhance the immune control of the virus, help attenuate disease progression during treatment interruptions, and limit further usage of antiretroviral drugs, thus minimizing their toxicity and cost (29).

Although anti-HIV vaccines have yet to successfully prevent infection (30), several vaccines are currently evaluated as adjuncts to antiretroviral therapy and their efficacy is generally assessed on the duration of treatment interruption they permit. In addition, results already obtained in primate models appear promising (31), and pilot trials of naked DNA and inactivated vaccine have shown some immunogenicity in chronically infected patients (32). In acutely infected treated patients, an HIV-recombinant canarypox virus, either alone or combined with an inactivated vaccine, induced a significant increase of HIV-specific CD4 and CD8 T cells. However, this could not be clearly correlated with viral control after treatment discontinuation (33). A similar canarypox vaccine, alone or combined with lipopeptides and IL-2, tested in chronically infected treated patients, also significantly enhanced and broadened specific CD4 and CD8 T cells with encouraging correlations between immunogenicity and a prolongation of treatment interruption (34). Thus, no clear benefit was apparent in these studies from targeting acute infections versus chronic stages of disease, provided immune function was first restored with treatment. These modest results may reflect the relatively low immunogenicity of the vaccines tested so far, although there is hope that this will be improved with the planned testing of new therapeutic vaccine regimes over the next 5 years.

Conclusions

Therapeutic vaccines are proposed as a strategy for preventing severe complications of chronic infections including but not limited to HIV, HBV, and HPV, although definitive proof of concept for clinically relevant, long-term efficacy remains to be demonstrated. The success of the current preventative vaccines against HBV and HPV contrasts with the promising but still modest results from therapeutic vaccines against complications of these diseases. Despite ongoing uncertainty about the efficacy of an anti-HIV vaccine for prevention of infection by the virus, the concept of therapeutic vaccines against this and other chronic infections remains. Indeed, the successes of antiretroviral drugs, despite their limitations, make it possible to reduce viral burden and thus facilitate the therapeutic vaccine's task. The exceptional knowledge accumulated about the biological and clinical aspects of chronic HIV, HBV, and HPV infections provides excellent models for evaluating therapeutic vaccines and opens up new perspectives for vaccines.

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