NEW APPROACHES FOR THE DESIGN OF AIDS VACCINES

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Introduction

Although several AIDS vaccine candidates in clinical trials such as synthetic peptides, recombinant subunit, live vector and combination vaccines have been shown to induce HIV specific antibodies and CTL responses in non-human primate models and humans, major obstacles facing the development of AIDS vaccine still remain. These include the induction of long-lasting protective immunity, identification of the correlates of immune protection, cross-protection against diverse natural isolates, protection against infection with cell-associated virus end efficacy against mucosal transmission. Recently, plasmid DNA vaccines for genetic immunization have induced high titers of neutralizing antibodies and strong cytotoxic T lymphocyte responses. Immunization with multiple doses of an HIV-1 env DNA vaccine and HIV-1 env protein preparation have protected monkeys from intravenous infection with an SIV virus expressing the HIV-1 envelope glycoprotein.

Our research goal is the development of a therapeutic AIDS vaccine through the SIV in rhesus macaques animal model system. We believe that both humoral (strong neutralizing antibodies) and cellular (cytotoxic T Cell lymphocyte) responses are necessary for an effective therapeutic or preventive vaccine. One of the major challenges to the development of an HIV vaccine is the antigenic variability which results in overwhelming diversity. The main obstacle to achieve this goal continues to be the lack of a viable approach to account for epitope glycoprotein variability by immunization. Most of the antigenic variability is found at specific regions of the envelope glycoprotein (gp120). This protein is important for attachment and entry into the target cells and is critical for eliciting broad humoral responses, including neutralizing antibodies. Therefore, we have designed and prepared a vaccine component consisting of a cocktail of peptides representing the accumulation of the in vivo variability seen in the envelope glycoprotein. This construct is also designed to overcome MHC restriction limitations in vaccines against variable pathogens which are intended for outbred populations such as humans. This Hypervariable Epitope Construct (HEC) induced a broad humoral immune response in rabbits and rhesus macaques. As a direct result of immunization with this construct we also demonstrated clear capacity to overcome MHC restriction in mice. Following initial proof of concept in the SIV model, we are pursuing this vaccination concept in HIV-1. A previous study involving rhesus macaques immunized with HIV-1 envelope peptide miniproteins from three HIV-1 strains was determined to be safe and immunogenic at the dose of vaccine to be used in humans. Following demonstration of lack of toxicity in monkeys, this HIV-1 synthetic vaccine candidate was approved for clinical trials.

A second generation, more complex synthetic HIV-1 immunogen has been designed and prepared in our laboratory. This new vaccine construct is recognized by antibodies from HIV-1 positive individuals representing HIV-1 subtypes A, B, C, D, E, F as well as HIV-2 strains. Immunization of rabbits and rhesus macaques resulted in the induction of high titers of HIV-1 antibodies, T Cell proliferative response and delayed-type hypersensitivity (DTH) reactions. Our collective data suggest that this preparation is a promising component of an AIDS vaccine. In addition, our concept constitutes a new class of custom-made vaccine that can be prepared to be effective against all antigenically variable pathogens. In addition to the Induction of broad humoral responses with our peptide constructs, a strong CTL response might also be required for an effective vaccine. Therefore, we have designed a combination vaccine using a recombinant vector to express SIV proteins (gag, pol, env, and nef) and synthetic peptide constructs in rhesus macaques.

Preliminary studies have shown strong CTL, secreted IgA/IgG, high antibody titers, neutralizing antibody responses and broad, cross-reactive overall immunogenicity. This combination vaccine is currently one of the vaccines under a Multicenter Preclinical Trial (NIH Protocol 33) being tested as a potential vaccine for use in humans.

DNA vaccination is being developed as a very promising addition to the battle against infectious diseases. There is data that supports the notion that plasmids expressing viral genes are capable of inducing protective antiviral immune responses in some animal models, it is clear that genetic vaccines directed against lentiviruses which cause fatal immunodeficiency in primates can now be developed and tested in a comprehensive manner. We have prepared an SIV plasmid with a deletion encompassing the coding regions for integrase, vif, vpx and vpr. These deletions were introduced into the SIVmac background where the 5' U3 region of the
LTR was replaced with a CMV promoter. Several rabbits received injections of 300 μg of the plasmid at 0, 13 and 43 weeks using a needleless injection system and were boosted IM at week 60. Antibody responses to gp130 and disrupted SIV were detected in all subjects by ELISA. High levels of T-cell proliferative responses to gag and env peptides, disrupted SIV, and gp130 were also demonstrated. Our lab has also produced whole defective particles for genetic immunization and have tested the immune response to HIV-1 in rabbits and SIVmac in macaques and rabbits. DNA and RNA constructs are designed to express HIV and SIV proteins.

We are now monitoring long term humoral and cellular immune responses in macaques. At the end of this study the government expects the development of a construct suitable for clinical trials. Our new projects also include development of a safe retroviral vector to be specifically directed for expression in antigen specific cells and a complex improved large plasmid to be used for immunization though direct targeting of lymphoid tissues.

Este disco compacto contiene los trabajos presentados—tanto en forma oral como en cartel—en formato de reportes cortos en el Congreso Biotecnología Habana 97 celebrado en los días 1 y 6 de diciembre de 1997. Por medio de un programa, desarrollado en ambiente Windows 95 o Windows NT (para plataformas de 32 bits), el usuario puede acceder rápidamente a la información por palabras claves, título, autor, instituciones, países y temáticas. Posee una interfaz amigable y muy sugerente, y un servicio de ayuda que posibilita que se pueda manipular sin una preparación previa. Los resultados pueden ser salvados o impresos usando el formato tipo RTF (Rich Text Format).

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