HIV Vaccine Development at Duke University Medical Center

Abstract
With the AIDS epidemic continuing to spread throughout the world, development of a safe, practical, and effective HIV vaccine is a national priority. HIV vaccine research efforts are currently targeted towards design of HIV immunogens that induce both cellular and humoral immunity. This brief review summarizes ongoing work at the Duke University School of Medicine on HIV vaccine development.

Key Words
HIV vaccines global health

Introduction
With 15,000 new HIV-1 infections per day, 12,000,000 infections within the last 2 yr, and 95% of the new infections occurring in developing countries with no access to antiretroviral therapy, the need for an effective HIV vaccine remains a high international priority (1). AIDS is devastating the African continent and parts of Southeast Asia, and there are no longer any countries within which what happens to a country is of no interest to other countries (2). Thus, with near unlimited resources in the United States, we have a moral imperative to continue to work diligently to develop an effective, safe, and practical HIV vaccine, and as well to ensure that any successful vaccine is available as soon as possible for use in developing countries. In particular, the Sub-Saharan areas of Africa as well as Thailand and the Far East are in desperate need of a vaccine. For example, in recent years, the life expectancy in Sub-Saharan Africa has fallen by 20 years (1). In this paper we will briefly review HIV vaccine development at Duke University and discuss some of the important current issues that are critical for development of an effective HIV vaccine.

Where We Have Been
Initial Work on T Cell Line-Adapted (TCLA) HIV Strains
In 1982, Robert Gallo at the National Cancer Institute at the NIH organized an HIV working group to study the new immunodeficiency
disease that was affecting gay men and hemophiliacs in the US. Dani Bolognesi and Barton Haynes joined that group and began meeting at the NIH with Gallo and other NIH investigators. Haynes’ task was to screen hemophilic sera for antiretroviral antibodies and to send to the Gallo laboratory patient samples for cultures and identification of new infectious agents. Working with Gil White in the Hemophilia Center of the University of North Carolina, this was accomplished, resulting in HIV isolates from patients ET and SN, which were among the first series of HIV isolates in the US (3).

In 1985, Dani Bolognesi, Tom Matthews, Kent Weinhold, Tom Palker, and Bart Haynes joined together and received a program project grant on HIV vaccine development, and this grant was the first NIH extramural money spent on development of a vaccine for AIDS. Soon thereafter, Bolognesi, Matthews, and colleagues showed that the gp120 outer envelope protein of HIV could induce neutralizing antibodies for T cell line adapted (TCLA) HIV in animals (4). Tom Palker and Bart Haynes, using peptides of gp120, and Matthews and Bolognesi with Scott Putney at Repligen, independently identified the third variable region of gp120 called the V3 loop as the principal neutralizing determinant of gp120 (5,6). Palker and Haynes developed a general peptide design that was highly immunogenic, termed Th-CTL, where Th is an MHC Class II restricted T helper epitope and CTL is a MHC Class II-restricted CTL epitope (7). An early epitope identified by Berzofsky et al. was in the fourth constant (C4) gp120 region, termed T1 (8). By synthesizing the T1 sequence N-terminal to the V3 peptide, termed SP-10, a series of “C4-V3” peptides were made with V3 sequences from different HIV isolates (9,10). Later it was realized that the V3 loop also contained potent MHC Class I-restricted CTL epitopes restricted in humans by HLA-B7 and in mice by MHC Dd (reviewed in 10). These peptide constructs induced high levels of neutralizing antibodies for TCLA HIV in mice, goats, rhesus monkeys, and chimpanzees (11), and induced anti-HIV MHC Class I-restricted CTL in mice (12) and in rhesus monkeys (13).

**The First C4-V3 Clinical Trials, DATRI 010 and AVEG 020**

For proof of concept for immunogenicity in humans, and to determine if humans could respond to multiple variant sequences of one CTL epitope, four C4-V3 peptides were designed reflecting sequences from the disparate HIV isolates HIVMN, HIVRF, HIVEV91, and HIVCan0A (Table 1). Spicer et al. at Duke solved the structures of these four V3 loops and showed HIVMN, EV91, and Can0A to be similar in secondary structure, whereas the secondary structure of HIVRF was markedly different from the other three V3 loops (14,15). The first human clinical trial with this immunogen was DATRI 010 in HIV seropositive subjects with CD4+ T cell counts of \( \geq 500 / \text{mm}^3 \) (10). We found that the C4-V3 immunogen when formulated in mannose mannoleate plus mineral oil (also known as incomplete Freund’s adjuvant or IFA) was safe and highly immunogenic with regard to induction of anti-HIV T helper and neutralizing antibody responses (10). Because of pre-existing anti-HIV CTL levels, CTL could not be definitively evaluated in this study in HIV seropositive patients.

In a trial in HIV seronegative subjects the C4-V3 experimental immunogen (AVEG020) was again found to be highly immunogenic with induction of neutralizing antibodies in approx 75% of subjects and MHC Class I-restricted CTL to one or more HIV strains in approx 30%—both after only two injec-