HIV Vaccine Strategies - an Update

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MJAfI 2004; 60 : 157-164

Key Words : Candidate vaccine trials; HIV vaccines; Specific immunity

Introduction

Acquired immunodeficiency syndrome (AIDS) has a significant impact on mankind. Worldwide, it is the fourth leading cause of death. At the end of 2002 an estimated 42 million were living with HIV/AIDS globally. The first reported case of HIV/AIDS in India was detected in Chennai in 1986. Since then HIV infections have been reported in all states and union territories. In 2001, National AIDS Control Organisation's (NACO) national estimate of HIV prevalence in India was 3.97 million. With a population of more than one billion, about half in the 15-49 years age group, the HIV/AIDS epidemic in India will have a major impact on the overall spread of HIV/AIDS in Asia and the Pacific, as well as globally. The best strategy for controlling the HIV epidemic remains the development of an efficacious prophylactic vaccine based on Indian subtype "C", the most prevalent subtype in India [1].

Principles of HIV-Specific Immunity

The goal for a preventive HIV vaccine is to generate both humoral and cellular immunity against HIV in the host before exposure to the virus. Following initial exposure to HIV, the generation of cellular immune responses against HIV may take a while to develop, and therefore neutralizing antibodies against free virus are important to dampen initial viral spread. Subsequently, generation of HIV-specific T-helper lymphocytes (THL) and cytotoxic T lymphocyte (CTL) responses become important in removing HIV-infected cells from the host and in controlling further activation and spread of the virus once established in the host. Thus, both arms of the immune system are important in the immunologic control of HIV infection [2].

Humoral immunity involves neutralizing antibodies directed at various epitopes on the viral surface. Cellular responses, particularly the CTLs, are targeted at the epitopes present on an HIV infected host cell. The CTL response is triggered by HIV specific THLs and generation of various cytokines. The HIV specific THLs

are recruited when CD4⁺ cells are activated. Antigen presenting cells (APCs) such as dendritic cells and macrophages engulf the infecting virus, break it down into smaller epitopes and present this to the CD4⁺ cells, thus activating it.

However, in most cases of HIV infection, the rapid loss of HIV-specific THLs and functional abnormalities in a variety of other immune cells ultimately leads to the establishment of chronic infection with high viral load, which, if untreated over time, results in further progressive loss of immune function. Moreover, the neutralizing antibodies have a limited ability to bind to gp 120, as it is heavily glycosylated [3].

Identifying epitopes of HIV that are most critical in establishing infection or, conversely, which epitopes should be targeted for the development of cell mediated and humoral immune responses to control HIV, is a major concern in vaccine development. HIV vaccine can be either preventive vaccine, which can be given to healthy individuals who are HIV negative, or it can be therapeutic vaccine, which can be given to people who are already ill with the goal of curing them or improving their health [4].

The goals for an HIV vaccine should include (a) protection against HIV infection i.e. against all routes of transmission, against intravenous transmission only, against mucosal transmission only (b) protection against progression to disease i.e. reduction of the viral load (c) reduction of transmission i.e. vaccines likely to have lower viral load or lower transmission rate.

An ideal HIV vaccine

The ideal characteristic of an AIDS vaccine would include (i) efficacy in preventing transmission by the mucosal and parenteral route (ii) excellent safety profile, (iii) single dose administration (iv) long lived effect resulting in protection many years after vaccination (v) low cost (vi) stability under field conditions (vii) ease of transportation and administration and (viii) ability to induce protection against infection with diverse viral isolates preventing the need for many isolate specific

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vaccines. Although the overall strategy is to achieve sterilizing immunity, a more realistic goal is to develop a vaccine, which could control viral replication, delay the onset of the disease and reduce viral transmission [5].

Barriers to HIV vaccine development

Obstacles to the development of an effective HIV vaccine include factors related to the biology of HIV-1 infection and practical realities of developing and testing an HIV vaccine (Table 1).

Table 1

Obstacles to the development of HIV vaccine

- Antigenic diversity and hyper-variability of the virus
- Transmission of disease by mucosal route
- Integration of the viral genome into the host cell chromosome
- Transmission of the virus by the infected cell
- Latency of the viral infection
- Sequestration of the virus in the CNS
- Progressive dysfunction and destruction of the immune system of the host
- No spontaneous recovery from natural infection in spite of high level immune responses of the host

Sequence variation

The rapid replication of HIV-1 in vivo produces 10^{10} new virions /day which facilitates rapid generation of sequence variants. Because a significant proportion of HIV specific neutralizing antibodies and CTL are subtype specific, this sequence diversity has fostered efforts to induce broadly reactive immune responses or to utilize multivalent HIV vaccine [6].

Protective immunity

Another fundamental barrier is the lack of information regarding the type of immune responses that may protect against HIV infection. CTL responses may be important to induce vaccine mediated protective immunity. HIV vaccine should be able to induce both HIV specific CTL and neutralizing antibody responses [7].

Latency

Like other retroviruses, HIV integrates into the host genome where it can remain in a latent form that does not express HIV structural proteins and is thus less likely to be eliminated by the host cellular and humoral immune responses [8].

Transmission

HIV-1 is predominantly transmitted by mucosal route. Yet our knowledge of the event occurring during mucosal infection and immune responses responsible for defending against mucosal infection are quite limited. In addition, HIV transmission may occur by both cell free and cell associated virus particles. Cell associated virus is thought to be resistant to neutralizing antibodies

and will not be recognized by the host CTL responses, unless there is a fortuitous match between the HLA molecules of the host and the donor [9].

HIV vaccine concepts

Several different HIV vaccine concepts (Fig 1) have been used in the animal model to elicit HIV specific immune response as follows :-

Recombinant subunit vaccine : A vaccine produced by genetic engineering simulating a part of the outer surface envelope or other part of HIV gp 120 is the most well studied candidate HIV-1 vaccine. VaxGen, a San Francisco - based company, initiated the first phase III - efficacy trial of an HIV vaccine in 1998 using its gp 120 subunit vaccine known as AIDSVAX. The vaccine is safe and it elicits a strong serological response with homologous virus neutralizing antibodies. However, it fails to generate measurable CTL responses, as subunit vaccines do not induce endogenous synthesis of viral proteins in antigen presenting cells (APCs) [10]. However on 24th February 2003 in New York, VaxGen Inc. announced that its investigational AIDS vaccine, AIDSVAX, although safe, did not prove effective in human trials in North America and Europe. In the trial, 3330 volunteers received AIDSVAX and 1679 received a placebo. The percentage of volunteers who received AIDSVAX and became infected with HIV was statistically equal to the percentage of volunteers who received the placebo and became infected with HIV. This proved that the vaccine was not protective. AIDSVAX is the first AIDS vaccine ever fully tested in humans (<http://iavi.org/press/2003/n20030224.htm>).

Synthetic peptide vaccines : Synthetic peptides of HIV are small epitopes of HIV proteins. Peptide based approaches offer the advantage of targeting specific epitopes that lie within the conserved area of the virus. Most peptide vaccines have been based on the peptide sequence of the V3 loop, the most hyper variable region of the virus. Extensive basic research has shown that the immune system will mount a response to very short

Fig. 1 : HIV vaccines approaches

peptide secretions of a protein antigen when presented appropriately to the immune system. However, they run the risk of eliciting immune responses that are too narrowly directed. Peptides administered without an adjuvant are unlikely to be immunogenic. Synthetic peptides can be linked to lipid molecules (eg. lipopeptides) to facilitate induction of cellular immune responses such as CTLs. Finally the peptide can be combined as a multi-peptide vaccine in a strategy to include diverse subtypes so as to increase the breadth of the vaccine induced response [11].

Virus like particles (VLP) and Pseudovirions : These are non-infectious particles resembling HIV that has one or more HIV proteins. Pseudovirions are replication incompetent viruses produced in mammalian cell cultures that contain all the viral proteins required for viral assembly, but do not contain the RNA genome, thus making it non-infectious. Particulate antigens provide immunological advantages in presentation of multiple epitopes to the immune system, and provide safety advantages since they can be engineered to exclude the genes of the pathogens. For example, core particles of hepatitis B virus have been engineered and evaluated preclinically to present HIV antigens. The gag precursor proteins of HIV and SIV can form virus like particles when expressed in a variety of systems. The only construct that have entered human trials, however have been expressed in yeast cells. The Ty transposon found in yeast (*Saccharomyces cerevisiae*) encodes the protein p1. When the p17 or p24 gag proteins are fused to the carboxy termini of the p1 proteins, the resulting fusion proteins assemble in to 50 nm virus particles that can be purified and used as an antigen. Testing of these constructs has begun in sero-negative volunteers as well as in HIV-1 infected individuals as a potential therapeutic vaccine [12].

Live vector vaccine : A live bacteria or a virus that is harmless to humans and is used to transport a gene that makes HIV proteins. These include live attenuated bacterial vectors such as *Bacille Calmette-Guerin* (BCG) and *Salmonella*. These vectors are safe and can establish infection via a mucosal route and can elicit strong mucosal immune responses. *Salmonella-HIV gp 120* candidate vaccine is presently in Phase 1 trial (AVEG 029). New virus vector system includes improved poxvirus vectors such as canarypox vectors and modified vaccinia Ankara (MVA). NYVAC is an attenuated vaccinia strain. Canarypox vectors (eg. ALVAC) are unable to complete their replicative cycle in human cells but are able to synthesize foreign proteins. The limited replicative ability of these virus strains enhances their safety. A viral vector vaccine, Venezuelan equine encephalitis virus (VEE) has been recently developed

by Alpha Vax. MVA vaccine in non-human primates can elicit potent CTL responses [13]. CTL responses are also enhanced when MVA vectored vaccines primed with a DNA vaccine, are used to boost immune responses [13]. Canarypox vectored vaccines presently in human clinical trials include recombinant vector Vcp205 which expresses HIV gag, env and protease. Other live vectors expressing HIV antigens that are in development include adenovirus, poliovirus, influenza virus, and Semliki Forest virus. Live attenuated poliovirus vaccines also have the potential to induce both mucosal and systemic immune responses [14].

Whole killed or inactivated vaccine : In this, the entire virus particle is presented to the immune system but it cannot infect or replicate and is thus safer. However, production issues of whole inactivated vaccines in which the integrity of the virus particle is maintained in the face of chemical and physical inactivation modalities has thus far limited the development of this vaccine. Also, the method of inactivation could disrupt the structures of potentially neutralizing epitope [15].

Live-attenuated vaccines : Live attenuated virus vaccines have been successfully used to protect against a great number of diseases including polio and measles. Nef-deleted strains of simian immunodeficiency viruses (SIV) have shown promising immune protection from challenge with infectious SIV. Safety is a serious concern with this vaccine as the chance of reverting to a more virulent HIV strain is quite high [16].

DNA immunization (Naked DNA or nucleic acid vaccine) : One of the newest technologies for vaccine design offer significant advantages in ease of manufacturing. Pieces of HIV DNA are incorporated into harmless plasmid DNA from bacteria. These bacterial plasmids that have been genetically engineered to contain viral genes are injected into the muscle or skin. HIV DNA vaccines have been developed using HIV antigen from the *env* and core region of the virus. The immune system will recognize HIV proteins and mount immune responses against expressed viral proteins. Several innovative strategies for presentation of DNA vaccines (eg. within attenuated strains of bacteria) offer the potential for oral administration of such vaccines [17].

Prime Boost Protocols / Combination vaccines : Recognizing that protection from HIV may require a broad spectrum of immune responses including humoral, cellular and mucosal immunity, scientists have designed combination regimens in an attempt to elicit such broad-spectrum immunity. Prime boost refers to a vaccination regimen involving a primary vaccination with one vaccine generating CMI response followed by a boost

with another vaccine, often a subunit protein to elicit humoral response. Combination vaccine approaches elicit the most potent immune responses in non-human primates and in humans. These include Phase I/II trials of Vcp205, followed by a gp120 subunit boost or a p24 subunit boost. Other combinations include a vaccinia virus prime plus protein (gp 120)- boost strategy, a Salmonella recombinant-prime plus protein boost strategy and a DNA-prime plus protein or canarypox-boost [18].

Complex vaccines : In contrast to developing vaccine, which target HIV specific proteins, some groups have focused on development of HIV vaccine by directing immune responses against human host cell receptors, which HIV utilizes as a port of entry for initial infection. Vaccines directed against the common host cell receptors such as CD4 and CCR5 are often referred to as “host cell complex” or “complex vaccines” [19].

Therapeutic HIV vaccine

The rationale for therapeutic vaccine is to vaccinate immunocompetent, aviremic individuals under HAART to restore and broaden HIV specific cell mediated immunity, contain viral replication and delay viral rebound. Therapeutic vaccine studies have a significant advantage over prophylactic vaccine trial. A limited number of HAART treated patients are required to conduct efficacy trials and end points based on viral rebound can be obtained within a relatively short period of time. Several Phase I clinical trials using various pox vectors, lipopeptides and inactivated virions, either alone or in combination and with or without IL-2 are being conducted in France and USA. The HIV transactivating factor Tat is another promising antigen for inclusion in a therapeutic vaccine [17].

HIV vaccine Trials

The first Phase I trial of an HIV candidate vaccine was conducted in the USA in 1987, using a gp 160 candidate vaccine. Subsequently, more than 30 HIV candidate vaccines have been tested in 60 Phase I or Phase II trials, involving more than 10,000 healthy volunteers. Most of the trials have been conducted in USA and Europe, although some have also been conducted in developing countries including Brazil, China, Cuba, Haiti, Kenya, Thailand and Uganda (Table-3). Other countries are preparing for clinical trials including India and South Africa.

The leading HIV candidate vaccines designed to induce cell mediated immunity are live recombinant vectors expressing several HIV genes such as canarypox. Modified vaccinia Ankara (MVA, the Indian vaccine candidate), alpha viruses, bacteria, or combination of these vectors in “prime-boost” regimens with gp 120, DNA or other vectors.

The first phase III trial of an HIV candidate vaccine began in June 1998 in USA (with “sites” in Canada and Netherlands), using a bivalent BB (i.e. based on two different subtype B stains) gp 120 candidate vaccine (VaxGen, Brisbane, CA, USA). This candidate vaccine is being tested in 5400 human volunteers, the majority of whom are homosexually active men. The second Phase III trials, started in March 1999 in Thailand, is designed to assess a bivalent BE gp 120 candidate vaccine (also from VaxGen) in 2500 volunteers recruited among recovering injecting drug users in Bangkok. Result from these trials will be available by the end of 2004. Another prime-boost Phase III trial using the prime-boost approach with canarypox (Aventis Pasteur, Marcy l'Etoile, France) and gp 120 (VaxGen) candidate vaccines based on the sub type E of the virus is also being planned in Thailand. Efficacy results from these trials will be available around 2006 at the earliest, and would represent a second chance of identifying an effective vaccine. Thailand has played and is still playing a major role of leadership in South-East Asia, but also among developing countries worldwide for HIV prevention and care and HIV vaccine development (Table 2 & 3).

Table 2

HIV vaccine candidates in clinical trials

Product	Company	HIV subtype	Phase
Peptide			
C4-V3 peptide	Wyeth	B	1
V3 peptide	CIBG	B	1
p17	Cel-Sci	B	1
Recombinant subunit			
Bivalent rgp 120	VaxGen	B+E	3
Bivalent rgp 120	VaxGen	B	3
Oligomeric gp 140	Aventis	E	1
rgp 120	Chiron	E	1
p24	Chiron	B	1
DNA			
gag	Merck	B	1
env-rev	Wyeth	B	1
Live viral vector			
Vaccinia - env-gag-pol	Therion	B	1
Canarypox - env-gag-pr	Aventis	B	1
Live bacterial vector			
Salmonella -env	Univ Md.	B	1
Combinations (Vector prime + subunit boost)			
Canarypox - env-gag-pr, nef, pol	Aventis	E	2
• rgp 120	Chiron	E	
• rgp 120	Vaxgen	B+E	
Canarypox - env-gag-pr	Aventis	B	2
Salmonella - env	Univ. Med	B	1
(DNA prime+vector boost)			
DNA-gag, pol	Wyeth	B	1
• Canarypox-env, Gag-pr	Aventis	B	1
DNA-env-rev	Wyeth	B	1

Table 3**HIV vaccine candidates in clinical trials Developing World**

Product	Company	HIV subtype	Phase	Site
Peptide				
V3 peptide	CIBG	B	1	Cuba
Recombinant subunit				
Bivalent rpg 120	VaxGen	B+E	3	Thailand
Live viral vector				
Canary pox - env-gag-pr	Aventis	B	1	Uganda
Live bacterial vector				
Salmonella - env	Univ. Md.	B	1	
Combinations (Vector prime + subunit boost)				
Canary pox - env-gag-pr,	Aventis	E	2	Thailand
• Nef, pol rpg 120	Chiron	E		
• rpg 120	VaxGen	B+E		
Canary pox - env gag-pr	Aventis	B	2	Haiti, Trinidad, Brazil

Recently vaccines designed to stimulate CD8+ and CD4+ T-cell immunity have protected macaques from challenge with the aggressive strain SHIV 89.6 P, which causes a rapid decline in the CD4+ T cell numbers and fatal immunodeficiency. Barouch [20] has shown that this SHIV strain can escape vaccine induced immune control by the mutation of a single amino acid - a process that is facilitated by the focus of the T cell response on a dominant epitope.

Several HIV vaccines have entered Phase 1 and 2 clinical trials in uninfected volunteers in the United States, Europe, Uganda and Kenya (Table 4). So far the immune responses have been small as compared with responses in macaques to the same vaccines, possibly because the doses used are lower and the assays are different. Combination of these vaccines in prime-boost approaches may show additive effects. It is too early to say how broad and long-lasting the T-cell responses are in these early trials, but such data will undoubtedly

Table 4**Prophylactic HIV vaccines in clinical trials**

Vaccine	Immunogen	Clade	Sponsor	Country	Phase
AIDSVAX B/E	gp 120	B, E	VaxGen	Thailand	3
AIDSVAX B/B	gp 120	B	VaxGen	USA	3
ALVAC Vcp 1452	Env-Gag-Pol-CTL	B	NIAID	USA	2b
ADISVAX B/B	gp 120	B			
ALVAC Vcp 1452	Env-Gag-Pol CTL	B	NIAID	Brazil, Haiti Peru Trinidad, Tobago	2b
AIDSVAX B/B	gp 120	B	IAVI/MRC	UK Uganda	2a
DNA.HIVA	Gag-CTL	A			
MVA.HIVA	Gag-CTL	A			
ALVAC vCP205 Or vCP 1452	Env-Gag-Pol CTL	B	NIAID	USA	2a
AIDSVAX B/B	gp 120	B			
ALVAC vCP 205	Env-Gag-Pol	B	WRAIR	USA	1
ALVAC vCP 1452	Env-Gag-Pol CTL	B	NIAID	USA	1
DNA. HIVA	Gag-CTL	A	IAVI/MRC	Kenya	1
MVA. HIVA	Gag-CTL	A			
MRKAd5	Gag	B	Merck	USA	1
Poly-env 1 vaccinia	Env	A,B,C,D,E	St Jude's	USA	1
VCR-HIVDNA 009-99-VP	Env Gag-Pol-Nef	A,B,C B	NIAID/VRC	USA	1
GTU-Nef DNA	Nef	B	FIT Biotech	Finland	1
VCR 4302 DNA	Gag-Pol	B	NIAID/VRC	USA	1
Gag DNA	Gag	B	Merck	USA	1
PGA2/JS2DNA	Gag,R,Env Tat,Rev, Vpu	B	NIAID	USA	1
NefTat Fusion/gp 120	Nef-Tat,gp 120	B	NIAID	USA	1
Lipo-4T lipopeptide	Gag-Pol-Nef-TT-CD4	B	ANRS	France	1
ALVAC vCP1452	Env-Gag-Pol CTL	B			
LIPO-5T or LIPO-6T lipopeptide	Gag-Pol-Nef-TT-CD4	B	ANRS/Aventis	France	1

Table 5**HIV vaccines currently in clinical trials (2002-03)**

Vaccine Sponsor	Trial ID	Vaccine type	Description
Phase III			
VaxGen	Vax 004	AIDSVAX B/B	Gp 120 protein vaccine, clade B, being tested in Thailand
Phase II			
NIAID/Aventhyis/VaxGen	HVTN 203	ALVAC vCP 1452	Canarypox vaccine (expressing <i>gag</i> , <i>env</i> and <i>pol</i>) with or without AIDSVAX B/B gp 120 boost)
Phase I/II			
NIAID/Aventhyis/VaxGen	PACTG 326/ACTG 326	ALVAC vCP 1452	Canarypox vaccine with or without gp 120 boost in babies of HIV positive mothers
Phase I			
ANRS/AVANTIS	VAC 12	LP HIV 1	Lipopeptide (LIPO-4T) express in <i>gag</i> , <i>pol</i> and <i>nef</i> -also includes a CD4 epitope
ANRS/AVANTIS	VAC 10	ALVAC-vCP 1452 +/- lipopeptide	Canarypox and lipopeptides (LIPO-5T, LIPO-6T) separately and in combination
FIT Biotech	NA*	GTU-Nef DNA	HIV-1 <i>nef</i> gene expressed in DNA plasmid vaccine
IAVI/KAVI/DT	IAVI 004	MVA-HIVA	Recombinant vaccinia viral vector, clade A, single dose Kenya
IAVI/MRC	IAVI 005	MVA-HIVA	Recombinant, vaccinia viral boost to volunteers previously vaccinated with DNA prime in IAVI 001
IAVI/MRC/Cobra	IAVI 001	P THr-HIVA	HIV-1 clade A, DNA vaccine, dose response United Kingdom
IAVI/MRC/IDT	IAVI 003	MVA, HIVA	Single dose of recombinant vaccinia viral vector. Clade A- United Kingdom
KAVI/IAVI Cobra	IAVI 002	P THr-HIVA	HIV-1 clade A, DNA vaccine, dose response Kenya
Merck	NA	DNA	Dose response study of <i>gag</i> DNA, clade B
Merck	NA	MRKAd 5	None applying adenovirus vector, clade B, expressing <i>gag</i>
NIAID/Aventis	HVTN 093	ALVAC vCP 1452	Dose response study of canarypox vector, clade B
NIAID/Aventis/VaxGen	AVEG 038	ALVAC vCP 205	Canarypox vaccine boost (expressing <i>gag</i> , <i>pol</i> <i>env</i>) in volunteers who already received pox virus based vaccine
NIAID/Glaxo Smith Kline	AVEG 027	ALVAC vCP 205	Canarypox vaccine with or without VaxGen's gp 120, delivery method also evaluated
NIAID/Glaxo Smith Kline	HVTN 041	Nef-Tat-gp 120 +	Protein vaccine with ASO2A adjuvant (clade B)
WRAIR/Aventis	RV 138	ALVAC vCP 205	Canarypox vaccine delivered either in skin, muscle or dendritic cells in HIV-negative volunteers

be obtained over the next year (Table 5).

The assays used to measure immune responses also need research. Currently, enzyme-linked immunospot assays, in which the T-cells that make interferon- γ on peptide challenge, are counted [21-23]. Although the assay is robust and reliable, it may have limitations when used to measure relatively weak acute T-cell responses. Most of the validation for this assay has been done on well-established, large T-cell response to EBV, cytomegalovirus or HIV in chronically infected people [24,25], whereas early vaccine-induced responses are likely to be weaker or more fragile. As results start coming in, it will be possible to validate the assays on vaccine-induced responses and improve them. Interferon- γ may not be the best cytokine to measure, given that it has little anti HIV effect. The use of flow cytometry to measure intracellular cytokine production in T-cell stimulated with peptide or antigen in vitro might

be a better option [26]. This is potentially more sensitive, and additional data on phenotypes of T-cells can be gained.

The most important measurement will be to quantify long-term memory T-cells, especially their proliferative and functional potential because most exposure to HIV in vaccine recipients will occur many months after vaccination [27,28]. The duration of such memory is important. Experiments in mice indicate that memory can be maintained without further antigenic stimulation [29,30].

Indian Scenario (HIV Vaccines)

Live recombinant vaccinia vector based vaccine, Modified Vaccinia Ankara (MVA) a joint collaborative project of International AIDS vaccine initiative (IAVI), NACO, Govt. of India and ICMR. The vaccine is jointly being developed by US based Therion Biotech, National

AIDS Research Institute (NARI) Pune, and National Institute of Cholera and Enteric Diseases (NICED, ICMR) Kolkata. The Phase I trial of this vaccine on HIV seronegative healthy human volunteers is likely to commence in Pune in early part of the year 2004. Seth et al. at All India Institute of Medical Sciences (AIIMS), New Delhi, are actively carrying out work on DNA vaccines based on *gag*.

Challenges ahead

There are three main challenges to developing an HIV vaccine. The first is to find a vaccine that can stimulate the equivalents of the five known monoclonal neutralizing antibodies in high titer in most or all individuals who are immunized and this may require conceptual breakthrough in protein engineering. The second challenge is to find a way to optimize the T-cell-inducing vaccines so that some of them can be taken into Phase 2 and Phase 3 trials in high-risk volunteers. Combination in prime-boost regimes should increase the T cell responses and stimulate a long-term memory.

The third challenge is to increase the capacity to carry out Phase 3 trials in developing countries. These trials will need to be designed so that viral infection, or sero conversion, is the primary endpoint and reduced viral load is the secondary end point. A major step forward might be the combination of T-cell vaccine and a good antibody-stimulating vaccine.

Conclusion

In spite of the difficulties and complexity associated with the development of HIV vaccine, there is reason for optimism. The development of antibody-based vaccine against transmissible viruses remains a formidable challenge, but the chances to improve vaccines based on cell-mediated immunity are reasonable. The best marker of vaccine efficacy remains protection in man. The choice of when and how to proceed to Phase III trials remains a complex decision, but it is likely that only through such trials knowledge will be gained to advance this important effort towards the development of a safe and effective vaccine. Information gained from therapeutic trials may help accelerate the development of prophylactic vaccine.

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MEDICAL PHILATELY

Dr. B C Roy

Dr Bidhan Chandra Roy, one of the great builders of modern India, is the source of inspiration for us even today. He was born in Patna in the year 1882. His father, Prakash Chandra was an Excise Inspector. His simplicity, discipline and sense of service to needy people made the foundation of Bidhan Chandra's character. He joined Calcutta Medical College in 1901. After his father's retirement, due to financial hardship, Bidhan had to fend for himself through scholarship and borrowed books. In 1909, he sailed to England for higher studies and completed both FRCS and MRCP simultaneously within only two years and three months. Dr Roy believed that independence is of no real use, unless the people are strong in body and mind. He established numerous hospitals and medical colleges. He served as Vice-Chancellor of Calcutta University, member Legislative Council and member of Congress Working Committee. In 1948, he became the Chief Minister of West Bengal. He was conferred Doctor of Science and Bharat Ratna. On July 01, 1962, after treating his patients, discharging affairs of the State, he sang a piece of "Brahmo Geet" and eleven hours later he left for heavenly abode. BC Roy National award was instituted in 1976 for work in the areas of Medicine, Politics, Science, Philosophy, Literature and Arts. Since then, this coveted award was bestowed to AMC on a number of occasions, including Padamshree Lt Col GW Bird, Maj Gen RS Hoon PVSM, AVSM, Artificial Limb Centre, Dr VR Mysorekar, to name a few. We must carry on the unfinished work of Dr Bidhan Chandra Roy, with a sense of service to the poor and needy. Only then we will be able to do real justice to the memory of the great son of India.

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