HIV: Terror of our Times

by Terry Ng

"The AIDS epidemic claimed more than 3 million lives in 2002, and an estimated 5 million people acquired the human immunodeficiency virus (HIV) in 2002—bringing to 42 million the number of people globally living with the virus."

— UNAIDS/WHO AIDS Epidemic Update 2002

Last year, the National Institute of Health, poured over 1.7 billion dollars into researching the causes, manifestations and treatments of HIV/AIDS in order to put an end to HIV's terror. Since the 1980s, there has been an increasing need to find some method to prevent the spread of HIV infection among individuals and populations.

Currently, the main form of HIV treatment employs a combination of drugs to target different stages of HIV infection. This therapy, known as Highly Active Antiretroviral Therapy (HAART), slows HIV spread by reducing a victim's "viral burden" to very low or undetectable levels. (Kimball 2000, NIAID 2001). However, they are only temporary solutions. HAART and such therapies are costly, and are inaccessible to most people living in developing nations – which comprise approximately 90 percent of HIV-infected individuals worldwide (UNAIDS, 2002). This is why researchers are still in search of the ideal vaccine that is safe, inexpensive, easy to store and administer, would elicit strong immune responses that confer long-lasting protection against HIV infection by exposure to infected blood and by sexual contact, and would also protect against exposure to many different strains of HIV.

Before delving into the intricacies involved in HIV vaccine development, one must have a basic understanding of the nature of HIV. It is a retrovirus that infects immune cells of the body, causing either death or dysfunction of these cells. Most accept that HIV is the cause of AIDS. Once HIV depletes the body's immune system, the body's immune system awaits death helplessly at the mercy of minor infections that previously had no effect on a healthy body (Clark et al., 1991; Cooper et al., 1985; Daar, Moudgil, Meyer, and Ho, 1991; Pantaleo, Graziosi, and Fauci, 1993; Tindall and Cooper, 1991).

The virus is mainly spread through sexual intercourse, contaminated needles used for intravenous drug delivery, and therapeutic use of infected blood or blood products. In occasional instances, an infected mother can also transmit the virus to her baby at birth or through breast milk feeding (Janeway, Travers, Walport, and Shlomchik, 2001). An individual 13 years or older is diagnosed with acquired immunodeficiency syndrome (AIDS) if they present one or more of the 25 AIDS-indicating conditions (such as Kaposi's sarcoma or any mycobacterial disease) if they are HIV-positive and if they have a CD4+ T cell count less than 200 cells per cubic millimeter (mm^3) of blood (CDC, 1987a; CDC, 1992). AIDS diagnosis for children under 13 also includes lymphoid interstitial pneumonitis and recurrent bacterial infections (CDC, 1987b).

The CD4+ T cells that define AIDS diagnoses are immune cells (known as lymphocytes) that mature in the thymus gland (hence "T" cells), and have CD4 molecules that can act as cell-surface receptors for HIV. The HIV virion (the virus particle itself) is surrounded by an outer coat known as the viral envelope. Freshly assembled in the cell, the HIV virion carries with it some of the cell's lipid bi-layer membrane as it exits the cell. Protruding through the actual virus particle (virion) and the envelope are approximately 70 copies of a complex HIV protein known as env proteins, which consists of a cap made of three molecules called glycoprotein (gp) 120 and a stem consisting of three gp41 molecules that anchor the glycoprotein structure in the viral envelope. The gp120 molecules are the active sites that have high affinity for and bind to the CD4 molecule(s), which as previously mentioned, characterize the cell's surface (Dalgleish et al., 1984; Klatzmann et al., 1984; McDougal et al., 1985, McDougal et al., 1986). This binding results in a conformational change in the gp120 molecule, allowing it to bind to a second molecule on the cell surface known as a coreceptor. (Fig. 1) The envelope of the virus and the cell membrane then fuse and allow the virus to enter the cell (Janeway et al., 2001; NIAID, 2001).

In the cytoplasm of the host cell, an enzyme, found in HIV, known as reverse transcriptase, converts viral genomic ribonucleic acid (RNA) into deoxyribonucleic acid (DNA) so that another enzyme, known as integrase, can incorporate or splice the viral DNA into the host cell's DNA. This newly integrated viral DNA is now called a provirus. For a provirus to produce new viruses, transcription must occur to convert the provirus into messenger RNA (mRNA). After HIV mRNA is processed in the cell's nucleus, it is transported to the cytoplasm. In the cytoplasm, the viral mRNA works with the cell's protein-making machinery - including structures called ribosomes - to make long chains of viral proteins and enzymes by acting as a template for translation into different proteins. Newly made HIV core proteins, enzymes and genomic RNA gather just inside the cell's membrane to form a new HIV virion, while the viral envelope proteins aggregate within the membrane. Proteins encoded by the env gene from the provirus become the viral envelope, which includes the protruding gp120 molecules. The gag and pol genes encode one single protein molecule. (fig. 2)Protease then cleaves it into the capsid proteins that form the RNA-containing capsule, reverse transcriptase, integrase, and protease itself, thus forming another mature and infectious HIV molecule (Janeway et al., 2001; Kimball, 2000; NIAID, 2001).

Once inside the body, HIV infects a large number of CD4+ cells and replicates rapidly, causing the blood to spread the viral particles into various organs, particularly lymphoid organs, which store and produce lymphocytes. The initial infection, approximately two to four weeks after exposure to the virus, results in an abrupt

Organization of the HIV-1 Virion

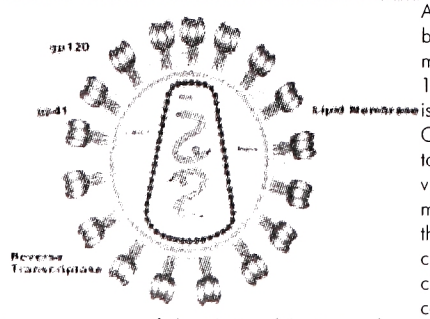

Image courtesy of the National Institute of Allergy & Infectious Diseases, National Institutes of Health (2001)

Figure 1

A pictorial diagram of the basic organization of the main components of the HIV-1 virus. The protein gp120 is the active site that binds CD4 molecules and is the target of many current HIV-1 vaccines. The lipid membrane is derived from the host cell in which it was created. Reverse transcriptase is responsible for conversion of viral RNA into viral DNA, which is also known as provirus.

decline in the number of lymphocytes. Up to 70 percent of HIV-infected individuals suffer flu-like symptoms during this period.

The body's immune system soon fights back with its soldiers, which mainly consist of killer or cytotoxic T cells (CD8+ T cells) and B cells (or B lymphocytes). Each T cell or B cell "knows" that a specific invader has breached into the immune system because it presents a specific antigen or epitope at its surface that marks it as "foreign". B cells secrete Y-shaped antibodies, which are molecules that attach to free floating viruses in the bloodstream and prevent them from infecting other cells. T cells consist mainly of helper T cells and killer T cells. Helper T cells, which comprise CD4+ T cells, orchestrate the immune response by bringing in other immune defense cells. Killer T cells or cytotoxic T lymphocytes (CTLs) (also known as CD8+ T cells) directly or indirectly kill actual cells that have been infected by viruses. These adaptive immune preventative measures dramatically reduce HIV levels. The number of CD4+ T cells in an infected individual may rebound and even approach its original number. Because of the activated immune system, the individual may remain free of symptoms for many years.

Unfortunately, some of the HIV invariably escapes by hiding in the lymphocytes themselves. Inside the host lymphocyte, latent HIV provirus replicates whenever the lymphocytes themselves replicate to fight those invading molecules, including HIV, that remain in other parts of the body (NIAID, 2001). To illustrate this manifestation in a different way, HIV "terrorists" hide, feed, and grow in numbers inside the lymphocyte camp, while the lymphocyte soldiers are fighting other HIV terrorists that seem to persist no matter how many they kill. Eventually, the lymphocyte soldiers become exhausted and are no longer able to suppress the number of HIV terrorists. The terrorists then take over, and completely destroy the body's immune system, which leads to the inevitable result of AIDS.

HIV takes the upper hand even when faced against lymphocytes because it has all the time to grow strong in numbers while it is hidden and under protection inside the host cell. Meanwhile, lymphocytes have to expend themselves continually to hunt down the remaining "visible" HIV molecules. Eventually, the lymphocyte army weakens so much that they soon become helpless when faced with even the most common of intruders that would not have a single effect on the body normally.

The chances of finding a way to stop this do not look too optimistic. However, while there are lymphocytes designed to attack, other cloned B or T cells remain in the body as memory cells so that a more rapid and more powerful immune response may occur on subsequent encounters with the same antigen (Janeway et al., 2001; Keeton and Gould, 1986; Kimball, 2002; NIAID, 2001). Therefore, there is a good chance that by administering a vaccine that presents the antigenic properties of a weakened or killed virus to the body, the body's immune system will be more prepared to attack or kill the virus before it can spread or do any damage to the body.

There are many reasons that make HIV vaccine development uniquely challenging for researchers. As discussed previously, HIV is shielded from the T lymphocytes and B-cell antibodies by existing as a provirus within the cell. The resultant proliferation of proviral DNA that happens during lymphocyte proliferation results in more cells with proviral HIV and therefore increased HIV replication. HIV also leads to chronic immune system activation of B cells (NIAID, 2001). The exhaustion of these cells impairs their ability to synthesize antibodies against other pathogens (Kimball, 2000; NIAID, 2001). Furthermore, HIV

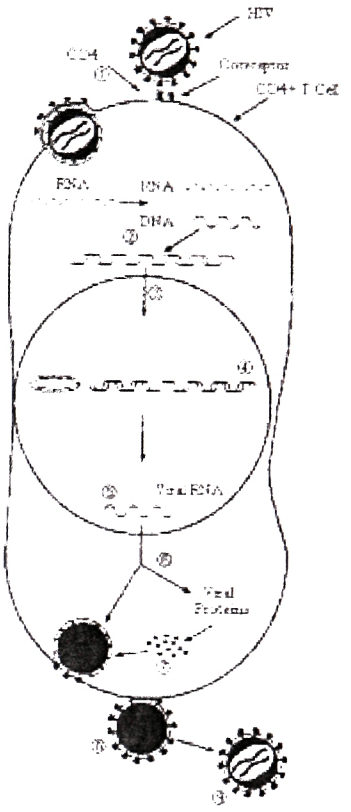

Figure 2

HIV enters the cell by binding the CD4 molecule and coreceptor at the cell surface. Once in the cell cytoplasm, the membrane proteins disintegrate. The viral RNA, which has been released is transcribed into DNA by reverse transcriptase. Splicing into the host cell's DNA is then mediated by integrase enzymes. The viral DNA can then have a chance to synthesize new HIV molecules during protein synthesis from the infected host cell's "new" DNA.

Image courtesy of the National Institute of Allergy and Infectious Diseases, National Institutes of Health (2001)

impairs CD4+ T cell function, which is crucial to coordinating the combat against HIV (NIAID, 2001).

Although the normal immune response is usually sufficient to clear most viral infections, it is unable to do so for HIV because T cells and B-cell secreted antibodies are antigen-specific. A high rate of mutations occurs during the process of HIV replication (Connor and Ho, 1994; Kimball, 2000; Richman and Bozzette, 1994). Consequently, the immune system cannot produce enough lymphocytes to combat the rapidly evolving strains of HIV. Because HIV can exist as a free virus or as integrated DNA in host cells, vaccines must be able to induce not only antibody-mediated immunity (or B cell-mediated immunity), but also cell-mediated immunity, which comprises the action of CD8+ T cells destroying HIV infected cells.

In addition to the complications related to HIV, vaccine testing is also a drawn out process. Vaccine trials must first be tested on animals because of undue risk to humans. For example, animals can be inoculated with an experimental vaccine and then exposed to a virus to test the vaccine's effectiveness – a study that would be unethical to conduct in humans. Each candidate vaccine must undergo extensive pre-clinical evaluation in the laboratory, in small animal models, and in non-human primates before it is tested in humans. There are three phases of clinical (i.e. human) testing, which can take at least 8-10 years to complete.

Some of the most recent vaccine trials use a prime-boost combination, which consists of an antigen and an adjuvant, which can stimulate a strong cellular immune response, including persistent killer CD8+ T cells, as well as antibodies that neutralize the virus (NIAID, 1998). This type of vaccine is being developed in Kenneth Rosenthal's research lab at McMaster University (Meducator Issue #1 – *A Vaccine for HIV*). Rosenthal and his team showed that administering a gp120 depleted, whole-killed HIV-1 virus with a short DNA strand adjuvant known as CpG oligodeoxynucleotide at the mucosal surface of mice

can significantly increase HIV-specific mucosal antibodies and T cells, allowing protection from genital infection (Dumais, Patrick, Moss, Davis, and Rosenthal, 2002). The vaccine is significant because it has a high potential of preventing infection at the mucosal surface, especially the genital mucosa which is the first target following sexual transmission of HIV. The mucosal surfaces are thin and permeable barriers to the interior of the body because of their function in gas exchange in the lungs, food absorption in the gut, sensory activities in the eyes, nose, mouth, and throat, and reproduction in the uterus and vagina (Janeway et al., 2001). Thus, the necessary permeability of the mucosal surface lining these sites creates obvious vulnerability to infection.

The vaccine preparation or combination of vaccine preparations that best protect the mice from infection will go on to a small phase I clinical trial to test in humans. If successful, the same preparations will proceed to larger phase II and phase III clinical trials in Canada and Africa to further confirm their safety and effectiveness (CANVAC, 2002). Needless to say, vaccine development is an expensive and long drawn process with many unclear paths ahead. It is especially difficult to design a vaccine that, to be effective, needs to activate the very cells that the virus infects. Although there may not be a complete preventative measure for HIV/AIDS at present time, it is the hope of many researchers that a vaccination that stays true will arise by the end of this decade. ■

Greetings from the Executive

Missing

Karen Ho
Zain Kassam