

Editorial

Development of a vaccine against AIDS: state of the art

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After the identification of human immunodeficiency virus (HIV-1) as the primary cause of AIDS and related diseases in man by Luc Montagnier and Robert Gallo in 1983, it was speculated by many specialists in the field, that the newly discovered disease could be controlled within the next few years by the use of a preventive vaccine, which would soon be developed. However, today, more than seven years later, there is still no vaccine available and the tools to combat the infection are little more than epidemiological measures based on the identification of seropositive individuals, and limited therapeutic possibilities that prolong the survival time without really curing the patients. In the meantime HIV-1 is spreading epidemically, infecting millions of people all over the world.

That an HIV-1 vaccine is not yet available is partly due to the insidious character of the infection and partly to a number of specific problems concerning the interaction between HIV-1 and the immune system. First HIV-1 is a lentivirus (family Retroviridae, subfamily Lentivirinae). Retroviruses possess the enzyme reverse transcriptase that enables them to incorporate a DNA copy of their RNA genome into the host cell DNA. In this way infected cells do not, or only at a very low level, express viral proteins and can remain largely

undetected and unaffected by the host immune system. Such persistently infected cells may constitute a permanent source of infection. Unlike the situation in most other virus infections, the virus is predominantly transmitted from one person to another through direct transfer of infected cells present in blood or semen. A mechanism of cell fusion by which the virus is directly transmitted from one cell to another, without the need of any extracellular presence of the virus, makes the spreading of the virus through the body little accessible to virus neutralizing antibodies. Furthermore it has become clear that the major target for HIV-1 neutralizing antibodies, is a loop structure on the viral glycoprotein. This loop proved to be highly variable, implying that virus variants, which constantly arise and even occur within one individual, may escape from newly produced specific virus neutralizing antibodies.

The major site of virus infection and replication in the human body is the T lymphocyte carrying the CD_4 molecule, which serves as the specific receptor for the virus. This CD_4^+ T lymphocyte plays a central role in the functioning of the immune system and directs or helps many of its effector mechanisms, like the production of antibodies by B cells and the cytotoxicity of T cells towards antigen carrying cells. This is one of the major reasons why infection with HIV-1 exhibits its characteristic immunosuppressive effects. Perhaps one of the most fundamental problems for the development of a vaccine is that it is not clear which immune mechanisms may be responsible

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for the protection of man after infection with HIV-1 and if under natural circumstances effective immune mediated protection against this infection does occur. Most of the research in this area has focussed on the immune response of individuals who were already infected and would eventually prove to develop AIDS. These studies on protective immune responses had to be focussed largely on studies in humans, since apart from chimpanzees and gibbons, no animal species seem to be susceptible to infection with HIV-1. However, recently a number of closely related lentiviruses has been found in different animal species, which may also cause AIDS-like syndromes in these animals. The newly discovered HIV-2, a virus closely related to HIV-1 that has also been identified as an important cause of AIDS in man, was shown to replicate in macaques. HIV-2 was shown to belong to a cluster of simian immunodeficiency viruses (SIV), that also occur in macaques and may under certain conditions cause AIDS in these monkeys. Recently, a lentivirus was also isolated from cats (feline immunodeficiency virus – FIV) with an AIDS-like syndrome.

The strategies that are explored at present for the development of a safe and efficacious vaccine against HIV infection, still include all the classical and modern approaches for virus vaccine development (Table 1). This also indicates that the final solution for HIV vaccine development has not yet

been found. The use of attenuated live viruses which has proven so successful in the global eradication of smallpox, should be excluded for retroviruses for safety reasons. This may also hold true for inactivated whole virus preparations, which approach is e.g. presently used for the eradication of poliovirus. Therefore, the use of nucleic acid free "subunit" vaccines, containing only those elements of the virus which are responsible for the induction of protection should be preferred. In this light it is interesting to realize that an intensive search for antigenic determinants on HIV-1 proteins responsible for the induction of B and T cell responses and the variability of these determinants is going on. These determinants should eventually be incorporated in a vaccine preparation. Therefore, they have to be produced on a large scale either by the production of whole virus particles, from which they can be purified, or by recombinant DNA techniques. Also the direct synthesis of relevant peptide structures is possible at present. The use of live recombinant viruses like e.g. vaccinia virus containing foreign DNA coding for HIV-1 proteins has been considered too, and even tried albeit with little success in experiments in chimpanzees and humans.

One of the problems concerning the use of subunits for immunization is that isolated monomeric structures are usually poorly immunogenic. New adjuvants (e.g. MDP derivates) and systems

TABLE 1

Strategies for the development of a vaccine against HIV.

Type of vaccine	Advantages	Disadvantages
Attenuated live virus	Good immune response (B and T cell)	Not safe
Inactivated whole virus	All viral antigens present	Safety? Insufficient immune response (lack of cytotoxic T cell response)?
Viral subunits (from whole virus, recombinant, organisms or synthetic peptides)	Safe	Little immunogenic, adjuvant systems needed (iscoms, MDP, etc.)
Live recombinant virus or bacteria (e.g. vaccinia virus, <i>Salmonella</i> strains)	Carrier determined immune response, topical application possible	Low efficacy? Booster immunizations possible?
Virus chimeras (e.g. poliovirus, Hep B virus)	Carrier determined immune response	Limited coding capacity
Anti-idiotypes	Host components	Little immunogenic

for multimeric antigenic presentation are therefore explored. The use of iscoms (immune stimulating complexes), a novel way of multimeric antigen presentation in the context of a built-in adjuvant molecule [1], has recently shown promising results: Not only superior B and T helper cell responses, but also cytotoxic T cell responses that can usually not be induced with "non live" preparations, could be induced with iscoms containing the glycoprotein of HIV-1 [2]. An iscom sub-unit vaccine proved to be protective against feline leukemia virus (FeLV) infection, a retrovirus that may cause an AIDS-like syndrome in the cat [3].

Although until recently all the experiments carried out with the above mentioned candidate HIV-1 vaccines in chimpanzees have failed to show the induction of protective immunity, a number of experiments in the SIV and in the FIV model systems and recently also in the HIV-1 chimpanzee model proved to be successful. Several groups in the USA, the UK and Sweden have shown that a certain degree of protection against SIV infection or disease can be induced in macaques by immunization with inactivated whole virus or with live HIV-2 [4-6]. In all these cases, challenge infection was carried out with a very low dose of cell free SIV via the intravenous route and in most cases it concerned a homologous challenge shortly after vaccination. However, protection against heterologous SIV strains from a different origin also seems to be possible. Similar experiments in the FIV system using a homologous challenge are being conducted at different places and also seem to be successful. These data clearly indicate that the induction of protective immunity against lentivirus infections causing AIDS in animals is not impossible. It should however be stressed that all experiments using similar protocols with HIV-1 in the chimpanzee, with the exception of one or two experiments in which a recombinant HIV-1 glycoprotein was used [7], have failed so far. Collaborative studies in the U.S.A. and in Europe are carried out in the SIV macaque model system

now, to determine if the use of different adjuvant or antigen presentation systems and/or immunization schedules may enhance the protective responses induced in macaques with these experimental vaccines. The results of these studies may form the basis for immunization studies with candidate HIV vaccines in chimpanzees and subsequently in humans. The limited availability of chimpanzees has led to a special evaluatory procedure for this purpose within the EC.

It is not clear if indeed the successful results in the animal model systems justify expectations for the development of a safe and efficacious vaccine against HIV infections in man and if such a vaccine would provide the range of protection required against the virus strains circulating in a certain area. It is however clear, that a vaccine against HIV will not become available and licensed for general use within the next few years.

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