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Mini-Review

Simian and feline immunodeficiency viruses: animal lentivirus models for evaluation of AIDS vaccines and antiviral agents

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Summary

Infection of captive macaques with simian immunodeficiency virus (SIV) and domestic cats with feline immunodeficiency virus (FIV), both discovered in the last five years, represent excellent animal models for infection of humans with the human immunodeficiency virus (HIV). Protection against challenge infection and protection against development of simian and feline acquired immunodeficiency syndrome has been achieved in each model by use of inactivated whole virus or virus-cell vaccines. A recombinant SIV envelope peptide vaccine has also proved efficacious. These vaccines have protected against 10–100 animal infectious doses of the homologous cell-free virus given systemically, and, in the simian model, apparently show cross protection against a heterologous strain of SIV. Protected animals appear free of any latent infection although late breakthroughs of infection in a few animals imply that not all vaccinated animals are completely protected The mechanism of protection in the simian model apparently involves envelope antibody but the role of neutralizing antibody remains unclear. Questions remaining to be answered in both SIV and FIV models are. (1) the duration of immunity, (2) the extent of protection against heterologous strains and mucosal infection, (3) protection against infection with cell-associated virus and (4) the role, if any, of cellular immunity in vaccine protection Initial attempts at post-infection immunotherapy with SIV vaccines have not yet been successful. The inactivated whole SIV and FIV vaccines offer a promising start and provide hope that a prophylactic AIDS vaccine will be developed. Use of these animal models for antiviral therapy is just now getting underway. Both models should prove especially useful for stud-

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ies of prophylaxis and therapy, especially during the early stages of infection and for investigations on drug pharmacokinetics or toxicity that can not be done as well in HIV-infected humans The animals will also be ideal for testing the pathogenicity of drug-induced mutant forms of SIV and FIV For these purposes it will be necessary to create self-sustaining specific pathogen-free macaque and cat breeding colonies and provide increased housing facilities for infected animals The future of AIDS research is crucially dependent on the long term availability of these animal models

Simian immunodeficiency virus, Feline immunodeficiency virus, Lentivirus, Vaccine

Introduction

Animal lentivirus infections provide a valuable resource for understanding mechanisms of pathogenesis and for development of effective antiviral drugs and vaccines with direct relevance to HIV and AIDS (Gardner and Luciw, 1989b). The simian and feline lentivirus models of AIDS are particularly relevant Most of the prototype strains of SIV that cause AIDS in macaques (i.e. SIV_{mac}, SIV_{mne}, SIV_{stm}) were derived from macaques that were probably accidentally infected by cross species spread (or possibly by doctors' needles) from the natural host, probably an African monkey species related to the sooty mangabey (Hirsch et al., 1989) in which the virus causes no disease (for summary, see Gardner et al., 1988). Other prototype strains of SIV capable of causing AIDS in macaques were derived from captive sooty mangabeys at U S primate centers and zoos. SIV is not indigenous in macaques. By contrast, FIV is indigenous and highly prevalent in domestic cats in which it causes a naturally occurring and an experimentally transmissible AIDS-like disease. In these animal models as in HIV-infected humans, the lentiviruses are infectious and potentially cytopathic for helper T lymphocytes and macrophages, and disease onset after a relatively long incubation period is heralded by a similar pattern of decreasing CD4 lymphocytes, decreasing immune responsiveness and increasing virus load (Table 1) (Desrosiers, 1990, Pedersen, in press) The prototype strains of SIV derived from macaques or captive sooty mangabeys are the animal viruses most closely related to HIV-1, about 50% homologous to HIV-1 and 80% homologous to HIV-2. A newly described chimpanzee SIV isolate, more closely related to HIV-1 than HIV-2 has not yet been inoculated into macaques (Huet et al., 1989). FIV is genetically quite distinct from other known lentiviruses and is most closely related to visna virus (Talbot et al , 1989). Mechanisms of viral pathogenesis at the cellular level appear alike in macaques and cats based on common features of viral integration, activation and the genome organization of structural and accessory genes and the presence of common host factors that control virus transcription Of course, some variations in these features are also noted between species but the similarities far outweigh the differences. The humoral and

TABLE 1

SIV and FIV animal models attributes similar to HIV and AIDS

1	Lentiviruses, infectious and cytopathic for CD4+ T lymphocytes and macrophages
2	Relatively long incubation period, length depending in part on strength of the antiviral immune response
3	Uniformly fatal, nature of protective immunity unknown
4	Disease heralded by decreasing CD4 lymphocytes, decreasing immune responsiveness and increasing virus load
5	Immunosuppressive and CNS disease manifestations similar including B-cell lymphomas
6	Virus integration, latency and expression in each system determined by similar organization and regulation of structural and nonstructural genes and similar host cell proteins
7	Biologic variation among individual SIV and FIV isolates similar to that among HIV-1 isolates
8	Response to antiviral therapy appears similar in each system

cellular immune responses, in general and virus-specific, over the course of infection, and the tissue distribution, neurotropism, level of virus expression and individual cell tropism are similar in each species. The pathology, opportunistic infections and lymphomas that occur in both SIV and FIV models are also alike The many parallels between HIV-1-infected humans, SIV-infected monkeys and FIV-infected cats illustrate the remarkable unity in nature in the behavior of these lentiviruses and highlight their immense value for preclinical basic investigations. This review will cover the recent (within the last 18 months) application of the simian and feline lentiviral models to AIDS vaccine and drug development. Because this is such a rapidly moving field many of the citations are to recently presented abstracts

Vaccines against SIV experimental infection of macaques

All of the vaccine trials in this model system in which results of challenge infection have been reported so far are summarized in Table 2. Successful vaccine protection against SIV under special laboratory conditions has been reported by five groups using relatively crude, inactivated whole virus, by one group using native envelope glycoproteins and by one group using recombinant envelope peptides (for summary, see Gardner and Stott, 1990). The SIV strains used have been isolated from rhesus (*M mulatta*) or pigtailed (*M nemestrina*) macaques (SIV_{mac} or SIV_{mne}) or from sooty mangabeys (*C atys*) (SIV_{sm}). For experimental transmission of SIV and induction of simian AIDS the host species used have been mainly rhesus macaques or cynomolgus macaques (*M fascicularis*) based on their ready availability in primate facilities. The vaccines have been tested against challenge with the homologous virus given as cell-free inoculations systemically [intramuscularly (IM) or intravenously (IV)] or, in one trial, by nontraumatic application to the genital mucosa (Sutjipto et al., 1990). In all trials 100% of the nonvaccinated control monkeys became persistently infected with the challenge virus starting 2 weeks after inoculation It should therefore be possible to identify in a relatively short time whether or not the candidate vaccine is working and to identify the protective anti-

TABLE 2

Vaccines against SIV

Vaccine	Challenge			Results[g] Nos protected/ challenged	References
	Adjuvant	Route	Dose[a]		
Inactivated whole SIV					
Formalin	MDP	IV[e]	10[p]	0/4	Desrosiers et al , 1989a
Triton	MDP[b]	IM[f]	10^3	1/2	Desrosiers et al , 1989a
Triton	MDP	IM	2×10^2	1/4	Desrosiers et al , 1989a
Formalin	MDP	IV	10	8/9	Murphey-Corb et al , 1989a
Psoralen UV light	MDP	IV	10^2–10^3	0/4	Sutjipto et al 1990
Psoralen UV light	MDP	Genital mucosal	1–10	0/4	Sutjipto et al , 1990
β-propiolactone	MDP	IV	10	3/3	Carlson et al , 1990
	IFA[c]	IV	10	1/2	Carlson et al , 1990
	None	IV	10	1/3	Carlson et al , 1990
Formalin	MDP	IV	10	4/4	Cranage et al , 1990
Glutaraldehyde	'Quil A'[d]	IV	10	8/8	Stott et al , 1990
Modified live virus	–	IV	10^2–10^3	0/3	Marthas et al , 1990
Native subunits					
Env enriched	MDP	IV	10	2/4	Murphey-Corb et al , 1989b
Core enriched	MDP	IV	10	0/4	Murphey-Corb et al 1989b
Vaccinia recombinants					
Env	–	IV	2×10^2	0/3	Desrosiers et al , 1989
Env and gag		IV	2×10^2	0/3	Desrosiers et al , 1989
Recombinant peptides (*E coli* env β gal fusion proteins)	CFA[c]-IFA	IV	10^2	2/3	Shafferman et al 1990

[a]Animal infectious dose, [b]MDP = muramyl dipeptide, [c]IFA = incomplete Freund's adjuvant, CFA = complete Freund's adjuvant, [d]Quil A = iscoms (Morein et al , 1984), [e]IV = intravenous, [f]IM = intramuscular, [g]In each study 100% of the nonvaccinated controls became persistently infected starting 2 weeks after inoculation

gens and the protective host immune responses. This information will then serve as a guide for development of more novel SIV vaccine strategies

Inactivated whole virus vaccines

Five independent trials (3 from the U S A , 2 from the U K.) have shown that inactivated whole, relatively crude, SIV vaccine preparations can protect against systemic challenge with low doses, 10–200 animal infectious doses (ID) of homologous virus given IM or IV (Desrosiers et al , 1989a, Murphey-Corb et al., 1989a; Carlson et al , 1990; Cranage et al , 1990, Stott et al , 1990) Higher chal-

lenge doses (> 10^3 ID) have not been protected against by any SIV vaccine (Desrosiers et al , 1989a; Sutjipto et al., 1990), nor was genital mucosal challenge infection prevented in one vaccine experiment (Sutjipto et al., 1990). Virus for the vaccine was grown in human T-cell lines whereas the live virus for challenge was usually grown in fresh human or rhesus T cells. Successful vaccines were achieved by inactivating the whole virus with formalin (Murphey-Corb et al., 1989a; Cranage et al., 1990), beta propiolactone (Carlson et al., 1990), or detergent (Desrosiers et al., 1989a). The psoralen-UV-inactivated vaccine might have worked just as well if the challenge dose of SIV was not as high (i.e. 10^{2-3} ID) (Sutjipto et al , 1990). Sucrose gradient purification was used in two of the successful inactivated whole virus vaccines (Murphey-Corb et al., 1989a; Carlson et al., 1990) and column chromatography in two other (Desrosiers et al., 1989a; Stott et al., 1990). The amount of virus antigen used to confer protective immunity ranged from 500 μg to 2.8 mg and the schedule of effective immunization consisted of a maximum of 5 inoculations over a 13-month period to a minimum of 4 inoculations over a 4-month interval. Vaccine protection was achieved in two trials with a primary and 3 boosters given over a 4-month period with a 2-month interval between the final 2 boosts (Cranage et al , 1990; Stott et al , 1990). With each vaccine the antibody levels declined rapidly after each boost and challenge was done at the height of the immune response, 1–4 weeks after the final boost. In the vaccine protected monkeys the antibodies soon declined after challenge reaching minimal levels by 4–6 months post challenge. The duration of protective immunity in such animals is thus probably short and has yet to be determined Early results suggest that the protective immunity probably lasts for only a relatively short time after the last boost In one study (Murphey-Corb et al , 1990) 2 of 4 SIV vaccinated monkeys were susceptible to challenge infection with 10 ID of the same virus 8 months after the last boost, and in another study (Stott et al., 1990) one of 4 monkeys was susceptible to infection with the same dose at 4 months after the last boost The adjuvant used in most of the studies was muramyl dipeptide (MDP) (Syntex), although successful vaccines also used incomplete Freund's adjuvant (IFA) or Quil A There was no systemic or local adverse reactions from any of the inactivated whole virus vaccines and none of these vaccine preparations contained residual live virus based on thorough in vitro and in vivo assays done prior to challenge.

Each of the whole virus vaccines contained virus proteins from the core (p55, p25, p17) as well as the outer (gp120) and transmembrane envelope (gp32 or gp41). The transmembrane envelope becomes truncated (gp32) from its native form (gp46) by propagation of the virus in human T-cell lines (Kodama et al., 1989). During virus purification SIV, like other lentiviruses, loses much of its envelope. However, because of ill-defined tissue culture variables some stocks of SIV retain more envelope than others. Perhaps for this reason a significant amount (2.3% and 8.5%) of gp120 was preserved in two vaccine preparations in which it was estimated (Murphey-Corb et al , 1989a, Carlson et al., 1990). The vaccines induced antibody to all the major structural proteins of the virus, and titers, particularly to p27 antigen were similar to those seen after infection. However, the vaccine-induced neutralizing antibody levels were usually 1 or 2 orders of magnitude

less in titer than observed during infection as measured by the classical all-or-none infectivity tests In one study (Carlson et al , 1990) vaccine protected monkeys, before challenge, showed a generally higher titer of envelope antibody as measured by ELISA and Western blot as well as neutralizing antibody as detected by a sensitive syncytial inhibition assay Interestingly, sera from protected monkeys in this experiment also showed a selective binding to a synthetic peptide (SP-1) representing a portion of the SIV_{mac} putative V3 loop However in the other two successful SIV vaccine studies in the U S A (Desrosiers et al , 1989a, Murphey-Corb et al., 1989a) some of the nonprotected animals also had antibody reactivity to SIV SP-1 and neutralizing antibody titers did not correlate as well with antibody reactivity to SIV-SP-1 (Gardner et al , 1991) Whether or not immunization of rhesus monkeys with such synthetic peptides will stimulate sufficient neutralizing antibody to protect rhesus monkeys against SIV challenge infection has yet to be tested However, this strategy was successful in stimulating high-titered anti-HIV-neutralizing antibody in rhesus monkeys (Hart et al , 1990). In summary, although the SIV-V3 region may or may not contain an important neutralizing determinant, it is clear that other neutralizing sites must also participate in protective immunity. In view of the correlation also seen between vaccine protection against HIV-1 in chimpanzees and binding of antibody to the HIV-1 V3 loop (Berman et al., 1990), it seems all the more important that this envelope domain be included as part of any successful AIDS vaccine strategy

Initial results (Murphey-Corb et al , 1990) indicate that vaccine cross protection has been obtained against two strains of SIV (SIV_{mac} and $SIV_{smDelta}$) that differ by about 17% in outer envelope nucleotide sequences and 10% in amino acid sequences (Hirsch et al , 1989) Since these animals were challenged with the homologous live virus before challenge with the non-homologous strain it is conceivable that some of the cross protection could have been attributable to the live virus challenge rather than the vaccine However, in a third laboratory (Cranage et al , 1990), cross protection between these virus strains was demonstrated by immediate, direct challenge with the non-homologous virus following vaccination. The putative V3 loop is nearly homologous in these two strains of SIV which may help account for this cross protection Sequence analysis of proviral DNA amplified from lymphocytes of SIV-infected macaques over the course of infection has revealed a surprising conservation of the V3 loop (Ahmond et al , 1990) The lack of variability in the V3 region between SIV_{mac} and SIV_{sm} and the conservation of this region in vivo suggests that this domain may not have the same significance in macaques as it does in man However, the V3 loop sequences are also strongly conserved in some African isolates of HIV-1 (Oram et al , 1990) and a portion (i.e the tip) of the V3 loop is also conserved among many HIV-1 isolates in the U.S A (LaRosa et al , 1990) It will be of interest to compare the V3 loop sequences of other new SIV isolates from macaques (e g SIV_{stm}) which apparently differ significantly from the existing macaque isolates (Kahn et al , 1990). Cross protection of SIV_{mac}-vaccinated monkeys against challenge infection with HIV-2 (Stott et al , 1990) or of HIV-2-infected monkeys against challenge infection with SIV_{sm} (Putkonen et al , 1990) was not possible, probably because these strains are too diver-

gent. Cellular immunity, as measured by SIV specific T cell proliferation and cytotoxic T lymphocyte (CTL) responses to whole SIV and to SIV gag antigens was induced in cynomolgus macaques after vaccination with SIV_{mac} infected cells (Stott et al., 1990), but the role of this and other mechanisms such as antibody mediated cell cytotoxicity (ADCC) in vaccine protection remains to be determined. Vaccine induction of memory T and B cells and cell mediated immunity including CTL activity may well be required for long lasting immunity and protection against cell associated virus infection (Ada, 1990) No evidence as yet suggests that the current SIV, or FIV vaccines meet this requirement.

The mechanism of vaccine protection in these 5 studies thus remains unsettled. Possibly, neutralizing antibody has reached the minimum level necessary to inactivate the relatively low doses of cell-free challenge virus before any transient or latent infection was established. Other mechanisms such as antibody-mediated complement-dependent virolysis may also be involved. It is not known if these challenge doses of SIV are representative of the amount of virus that humans are exposed to by genital mucosal or IV routes. However, humans are certainly exposed to cell-associated as well as cell-free virus. Although the level of vaccine-induced neutralizing antibody was considerably less than that generally reached during the course of infection, this antibody apparently functions more effectively in preventing the establishment of infection than in eliminating virus once infection is established. The probable absence of any covert infection occurring in most of the vaccine-protected monkeys is supported by the lack, after challenge, of an anamnestic antibody response, by the failure to detect viral nucleic acid in blood or tissues (bone marrow, lymph nodes) by PCR and by the failure to transmit infectious virus to naive monkeys by blood transfusion or lymph node extracts. However, in the first two vaccine studies (Desrosiers et al., 1989a; Murphey-Corb et al , 1989a) breakthroughs of infectious virus occurred in apparently protected monkeys, one at 5 months and the other at 7 months after challenge, both accompanied by an anamnestic antibody response at that time. These two monkeys went on to develop simian AIDS. Clearly, only time will tell whether the other vaccine protected monkeys are completely free of latent virus. These findings contrast with previous successful viral vaccines, including Type C and Type D retrovirus vaccines (For summary, see Gardner et al., 1985, Marx et al , 1986), in which protection could be achieved against much higher challenge doses ($\geq 10^6$ ID), and in which a transient infection and anamnestic antibody response after challenge could usually be demonstrated in the protected animals Nevertheless, these results show that it is possible using inactivated whole SIV vaccines to protect macaques against low dose challenge with homologous virus given IV or IM. It should be noted that an inactivated whole HIV-2 vaccine has also protected macaques against IV challenge infection with approximately 100 ID of live HIV-2 (Putkonen et al., 1991). Important questions still to be answered with regard to the inactivated whole or future subunit SIV (or HIV-2) vaccines in macaques concern the duration of protection and the extent of protection against heterologous virus strains, mucosal infection and cell-associated virus

Several of these studies (Desrosiers et al , 1989a, Carlson et al , 1990, Sutjipto et

al , 1990) showed that, in the few vaccinated monkeys that became infected following challenge, the more acute deaths (3–7 months post challenge) from simian AIDS were prevented This result was correlated with a lesser amount of SIV RNA in the lymph nodes of infected vaccinates compared to infected controls (Desrosiers et al , 1989a) However, the infected vaccinates apparently eventually die of simian AIDS within the same extended time frame (≤ 3 years post infection) as observed in individual SIV-infected macaques that are capable of mounting a spontaneous, strong immune response to the live virus Nevertheless, if extrapolated to HIV-1-infected humans, this prolongation of life and reduction in virus load by prior vaccination would be quite significant By contrast, vaccinated monkeys, infected by the genital mucosal route, died significantly sooner than infected controls, raising the possibility that the vaccine may have induced enhancing antibodies in this group (Sutjipto et al , 1990) However, individual variation in the immune response of these animals and the small number of animals used (4 in each group) may have accounted for this seemingly adverse vaccine effect Complement mediating enhancing antibodies were induced by two of the other SIV vaccines but their titers did not correlate with vaccine success or failure. Thus, vaccine protection against SIV infection was achieved even in the presence of such enhancing antibody (Montefiori et al , 1990) Further study is needed to determine whether or not enhancing antibodies play a role in the pathogenesis of SIV infection or are induced by SIV vaccines

Other vaccine approaches

A modified live virus vaccine was developed from an attenuated molecular clone of SIV_{mac} After a transient productive infection with this virus monkeys probably remained persistently but low-grade-infected, seropositive and healthy for ≥ 2 1/2 years Nevertheless, they became productively superinfected after challenge with a high dose (10^2–10^3 ID) of virulent, parental SIV (Marthas et al., 1990). As noted above in the infected vaccinates, these monkeys also survived longer (≤ 3 years) than most of the infected control monkeys. It will be interesting to see if this attenuated viral vaccine protects against low challenge doses of SIV given systemically or by the genital mucosa.

A lentil-lectin column-purified, glycoprotein-enriched, gp120 vaccine of SIV_{sm} protected 2 of 4 macaques against 10 ID of live virus whereas a core enriched vaccine (lentil-lectin flowthrough) of the same virus failed to protect against this challenge dose (Murphey-Corb et al , 1989b). This finding further supports the importance of the SIV envelope as a protective immunogen.

SIV_{mac} vaccinia recombinants expressing env or env + gag proteins failed to protect against IV challenge with 200 ID of the homologous virus despite inducing higher titers of neutralizing antibody then seen in the animals protected with the inactivated whole virus vaccines (Desrosiers et al , 1989b). This disquieting result is most likely explained by the high challenge dose Also, the monotypic nature of the vaccine DNA as compared to the multitypic DNA in the challenge virus may have contributed to this negative result Future experiments will challenge the ani-

mals with a lower dose of live virus (e.g. 10 ID). It would also be interesting to analyze the virus inoculum for a subpopulation of virions not neutralized by the sera from the vaccinated monkeys.

Inhibition, but not complete protection against SIV infection, was observed in 3 of 3 macaques after immunization with a mixture of 4 recombinant SIV_{mne}, envelope peptides, expressed as β-galactosidase fusion proteins in *E coli* (Shafferman et al., 1991). These peptides were selected based on analogy with immunodominant regions of the HIV-1 envelope (Shafferman et al., 1989), and included 2 peptides from the extracellular gp120 and 2 peptides from the transmembrane gp32. The animal showing the strongest protection had the highest neutralizing antibody titer before challenge. The peptides used in this study were from different regions of the SIV envelope than the putative V3 loop indicating the presence of several other protective, B cell neutralization epitopes in the SIV envelope. Undoubtedly these linear epitopes are but part of a complex conformational pattern of the SIV envelope that will be better understood only when X-ray crystallography of the protein becomes accomplished. This is the only example so far in the SIV model of vaccine protection using recombinant envelope peptides. Vaccine protection was also recently achieved in the HIV-1 chimpanzee system using a recombinant gp120 immunogen and protection correlated best with neutralizing antibodies directed at the HIV-1 V3 loop (Berman et al., 1990). Macaques at U C Davis are now being immunized with SIV_{mac} recombinant gp120 expressed in mammalian (CHO) cells (Haigwood et al , 1990) and plans are made to immunize macaques with a mixture of synthetic peptides representing the putative SIV_{mac} env V3 loop combined with other B and T cell epitopes (Hart et al., 1990). It will be interesting to see how these more novel vaccine approaches compare with the results obtained with inactivated whole virus.

Antiviral agents against SIV

Animal models represent a useful but not necessarily indispensable bridge between test tube and humans for development of antiviral drugs. The principal target of HIV antiviral therapy in humans is the viral reverse transcriptase (RT) enzyme. However, virtually every step in the replication of HIV (or SIV and FIV) could serve as a target for new therapeutic intervention (Mitsuya et al., 1990). Such targets include the CD4 receptor and the viral TAT and protease genes The urgent need to develop and apply AIDS drugs quickly to HIV-infected humans and the discovery of the SIV and FIV models in just the last few years has led to the clinical use of the current antiviral agents, mainly 3′-azido-3′-deoxythymidine (AZT), without preclinical testing in either of these particular animal models. The generic antireverse transcriptase effect of AZT and other dideoxy nucleosides (ddC, ddF, d4T), has indeed been demonstrated by suppression of virus activity in several animal oncoretrovirus models including avian myeloblastosis virus (Votruba et al., 1990), murine leukemia virus (Ruprecht et al., 1990, Balzarini et al., 1990; Votruba et al , 1990; Bashan et al., 1990; Morrey et al., 1990), feline leukemia virus (Tavares et al., 1987, Zeidner et al., 1990), bovine leukemia virus (Burkhardt et al.,

1989) and simian Type D retrovirus (Tsai et al., 1989). Six of these antireverse transcriptase drugs were found to completely inhibit SIV replication in vitro in highly permissive B and T cell lines (Tsai et al., 1990), and the RT of SIV was shown to have the same in vitro kinetics of AZT inhibition as HIV-1 (Wu et al., 1988). Uninfected macaques have been used for pharmacokinetic and toxicity studies with several of the dideoxynucleosides (Good et al., 1990, Patel et al., 1990a, Kaul et al., 1989; Russell et al., 1990, Patel et al., 1990b, Boudinot et al., 1990, Kelly et al., 1987, DeMiranda et al., 1987, Unadkat et al., 1988). The pharmacokinetics and toxicity of these agents was similar in macaques as in humans. AZT was shown to readily cross the placenta but not to accumulate in the fetus when administered to near-term pregnant macaques (Lopez-Anaya et al., 1990). Furthermore, the pharmacokinetics of AZT were not significantly affected by pregnancy in the macaques (Lopez Anaya et al., 1991). A recombinant SIV protease gene has been expressed and characterized (Deckman et al., 1990) and synthetic peptide derivatives directed at this target have inhibited the growth of SIV_{mac} in a human T cell line (Tyms et al., 1990).

Only a few studies, summarized in Table 3, have tested the in vivo prophylactic or therapeutic effect of anti-HIV agents on SIV expression or immune function in SIV infected macaques. First to be tested was recombinant soluble human CD4 which had a transient beneficial effect on virus expression accompanied by an

TABLE 3

Antiviral agents tested in vivo in the SIV macaque model

Agent	Dose and schedule	Result	Reference
CD4	2 mg IM q day × 50 days	Virus suppression, bone marrow function improved	Watanabe et al., 1989
AZT	100 mg/kg/day × 28 days starting 1–72 h after infection	Virus suppression, clinical improvement	Martin et al., 1990
PMEA	5–10 mg/kg/day × 28 days starting 1 day before infection	Virus suppression	Balzarini et al., 1989
Foscarnet	Given q 8 h × 7–9 days starting 8 h before infection	Virus suppression	Lundgren et al., 1989
AZT	Given q 8 h × 7–9 days starting 8 h before infection	No virus suppression	Lundgren et al., 1989
Inactivated whole SIV vaccine	Given × 1 to SIV-infected rhesus macaques at 4 months after infection	No virus suppression, boost in immunity or change in clinical course	Gardner et al. 1989
Inactivated whole cell-SIV vaccine	Given × 1 to SIV-infected cynomolgus macaques at 1,2,3 and 9 months after infection	No virus suppression boost in immunity or change in clinical course	Stott et al., 1990
Inactivated whole SIV vaccine	Given q month × 11 to SIV-infected rhesus macaques starting 1 month after infection	No virus suppression, boost in immunity or change in clinical course	Murphey-Corb et al., 1990

improvement in bone marrow function but only as long as administered (50 days) (Watanabe et al., 1989). In another study (Bugelski et al., 1990), soluble CD4 caused no toxicity at doses of < 40 mg/kg/day but antibodies to it were formed in cynomolgus monkeys Very recently it was reported that rhesus CD4 autoantibodies, stimulated by the antigenically closely-related human CD4, probably accounted for the anti-SIV effect (Letvin et al , 1990). The hazards of bypassing animal models and using only the conventional laboratory adapted virus strains and cell lines for antiviral drug testing has recently been emphasized by the finding that much higher concentration of recombinant soluble CD4 are required to neutralize primary HIV-1 isolates as compared to laboratory strains of HIV-1 (Daar et al , 1990). CD4 immunotoxins such as the CD4-pseudomonas exotoxin hybrid protein (Berger et al., 1989) inhibit SIV and HIV-2 as well as HIV-1 in cell culture and are now being tested in this model AZT, dideoxycytodine (ddC), [9-(2-phosphonylmethoxyethyl adenine] (PMEA) and Foscarnet all have been shown to have a beneficial prophylactic effect on SIV by reducing SIV infectivity levels and delaying disease or decline of CD4 cells if given to SIV-inoculated monkeys before or soon after injection, but little or no effect if given therapeutically after infection was established (Lundgren et al , 1989; Martin et al., 1990) (Gerberding, J., Marx, P., Gardner, M , unpublished data). More specifically, AZT given in a dose of 100 mg/kg/day to rhesus monkeys starting 1 or 8 hours prior to IV challenge with 10–50 ID50 of SIV_{sm} did not prevent infection but did slightly suppress viremia and delay the fall in CD4 cells (Martin et al , 1990) Recent reports indicate that prophylaxis with AZT soon after human exposure to HIV-1 also fails to prevent infection (Lange et al., 1990, Looke and Grove, 1990) However, further experiments are needed to determine if AZT or its analogues or combination of drugs will improve survival in monkeys with either asymptomatic or advanced SIV infection (CD4 T cells ≤ 400/ml) as has been found in HIV-1 infected humans (Volberding et al., 1990; Mulder et al., 1990).

The SIV macaque model should be particularly useful for basic investigations on side effects of antiviral drug action and for testing the pathogenicity of drug resistant mutants of SIV reverse transcriptase (Richman, 1990), protease (Meek et al., 1990) or other viral targets. These kinds of studies are now opportune because of the ability to induce simian AIDS with molecular clones of SIV (Kestler et al , 1990) This model will also aid in the selection of candidate drugs or combination of drugs when the number of HIV-infected individuals available for clinical trials are limited or, possibly, for efforts to block vertical transmission of the virus where questions of possible fetal toxicity impede such studies being done on pregnant women. Since in utero infection with SIV has not as yet been well documented, this model may not be useful for studying therapeutic approaches to prevent maternal-fetal virus transmission However, teratogenicity studies in uninfected pregnant rhesus monkeys are still important for the development of preventive therapy for HIV-1 seropositive pregnant women. The genital mucosal route for experimental transmission of SIV is suitable for antiviral drug testing as illustrated by the partial inhibition of SIV vaginal infection by the spermicide, nonoxynol-9 (Miller et al., 1990). Also useful for rapid testing of antiviral or antilym-

phokine agents will be an acutely lethal variant of SIV_{sm} (PBj14) that causes lymphokine-mediated death from diarrhea in just several weeks (Fultz et al., 1989) As yet the SIV model has not been used for therapy with immunomodulators (e g interferon) or with therapy directed at the opportunistic infections (e g CMV) or lymphomas that develop in infected macaques similar to HIV-infected humans Kaposi's sarcoma, however, does not occur in this model, perhaps because the postulated cofactors (possibly a sexually transmitted agent) are not present in the macaque It is, of course, important that the macaques be free of other infectious pathogens that might cause immunosuppression or lymphomas, e g simian type D retrovirus (SRV) or simian T-lymphotropic virus (STLV), or present a health threat to humans, e g , herpes B For this purpose the NIH is sponsoring the creation of specific pathogen free (SPF) self-sustaining rhesus breeding colonies

Based on Salk's hypothesis (Salk, 1987), several studies have been done in this model to test the efficacy of post-infectious immunotherapy with inactivated SIV vaccines The first study used a gamma-irradiated whole SIV vaccine with IFA adjuvant, given once four months after infection (Gardner et al , 1989a), another study used a glutaraldehyde fixed whole virus infected cell vaccine with Quil A as adjuvant given at 4, 8, 12 and 36 weeks after infection (Stott et al , 1990), and the third used a formalin-inactivated whole SIV vaccine given with MDP every month × 11, starting one month after infection (Murphey-Corb et al., 1990) None of these experiments, the latter of which is still in progress, has shown as yet, any detectable change in virus or immune status or clinical course, even though the inactivated whole cell and whole virus vaccines were successful in protecting naive monkeys against challenge infection Testing of novel SIV immunogens, such as recombinant gp120, perhaps depleted of its CD4 binding site (Van Kuyk et al., 1990) might yet show therapeutic value in this model

Efforts at prophylactic passive immunization in this model using immunoglobulin (Ig) from infected monkeys have not been reported and an attempt is now underway at U C Davis to do passive immunization with Ig from SIV-vaccine-protected monkeys Passive immunization with sera from HIV-2 vaccine-protected monkeys appears to have protected 1 of 4 HIV-2-challenged cynomolgus macaques (Putkonen et al , 1990) The SIV and HIV-2 macaque models are thus providing an excellent opportunity to explore further the feasibility of passive as well as active immunization Perhaps a combination of passive and active immunization would have beneficial prophylactic effect in these models and, by inference, also in HIV-exposed humans. A reduction in HIV-1 viremia and clinical improvement has indeed resulted from passive immunization of patients with AIDS or AIDS-related complex using hyperimmune plasma from healthy HIV-1-infected individuals (Jackson et al , 1988, Karpas et al , 1990)

Vaccines against FIV

Three FIV vaccine studies, two in the U S A , one in the U K., have been carried out so far, these utilized inactivated FIV-infected T-cell lines and inactivated whole virus (Table 4) The development of IL-2-independent feline T-cell lines

TABLE 4

Vaccines against FIV

Vaccine	Challenge			Results Nos protected/ challenged	Reference
	Adjuvant	Route	Dose		
Paraformaldehyde-fixed cells + virus	MDP	IV	5×10^3	0/3	Yamamoto et al , 1990b
Paraformaldehyde-fixed cell + virus	MDP	IP	10	7/9	Yamamoto et al , 1990b
Paraformaldehyde-fixed whole virus	CFA + IFA	IP	10	5/6	Yamamoto et al , 1990b
Detergent disrupted, sucrose gradient purified, envelope depleted virus	Iscoms	IP	20	0/4	Hosie and Jarret, 1990

Iscoms = immune stimulating complexes (Morein et al , 1984), IP = intraperitoneal
For other abbreviations see notes to Table 2

(FL4 and FL6) (Yamamoto et al., 1990) facilitated large-scale production of FIV (Petaluma strain) for inactivated vaccine studies. In the first U S A. study (Yamamoto et al. 1991), nine cats were vaccinated with 1×10^7 FIV-infected FL4 cells, inactivated with paraformaldehyde and combined with MDP (Syntex), at 2 week intervals × 5, and 2 months later were given a final boost. Ten control cats were inoculated with either uninfected cells with adjuvant or adjuvant alone. All of the cats were challenged intraperitoneally (IP) with 10 ID of the homologous virus 2 weeks after the final boost. Vaccination led first to the production of antibodies to the viral core protein p24 and later, after the third or fourth boost, to antibodies including neutralizing antibody to the virus envelope gp100. In contrast to the SIV macaque model, FIV-vaccinated cats made higher titers of neutralizing antibody than seen during natural or experimental infection. By seven weeks following challenge, all 10 control cats became persistently infected, whereas 6 of the 9 vaccinated cats had no evidence of virus infection for ≥ 21 weeks. Two of the vaccinated cats were only transiently infected and apparently cleared the infection and one was persistently infected. An anamnestic humoral immune response to FIV was detected only in the vaccinates that became infected and antibodies persisted only in the single chronically infected cat After FIV challenge 4 of 9 vaccinated cats as compared to 8 of 10 controls developed activation of latent herpes virus infection. The vaccinated cats with activated herpes virus included the 3 in which FIV infection occurred These findings suggest that latent herpes virus may become activated during the acute immune suppression that occurs soon after infection with FIV (Yamamoto et al., 1989). It should be noted that a similar vaccine made from an FIV-infected IL2-dependent cell line had previously failed to protect cats against a high challenge dose (5×10^3 ID) of FIV (J. Yamamoto, personal communication)

In the second U S.A. study (Yamamoto et al., 1991) a paraformaldehyde inacti-

vated whole virus vaccine was made from pelleted cell-free culture fluid of FL4 and FL6 cells Two hundred micrograms of this crude preparation were given every 2 weeks × 4 to 6 specific pathogen-free (SPF) cats in combination with Freund's complete and incomplete adjuvant Two weeks after the final boost cats were challenged with 10 ID of FIV Antibodies to the virus core p24 developed in all cats after the second inoculation and envelope antibodies developed in 5 of the 6 cats after the third shot The 5 cats developing both core and envelope antibodies were apparently completely protected from FIV infection for ≥ 4 months after challenge, whereas the single vaccinated cat failing to make envelope antibodies and 3 of 3 controls became persistently infected by 6 weeks post inoculation

In the U K study (Hosie et al , 1990) cats were immunized with an FIV iscom preparation containing mainly core p24 and p15 but little, if any, envelope The virus had been grown to high titer in an IL-2-dependent feline T-cell and purified by sucrose gradient centrifugation Despite induction of high-titered core antibody, 4 of 4 vaccinated cats were not protected against challenge infection with 20 ID of homologous virus

Taken altogether, these findings indicate that protection of cats can be achieved against low challenge doses (10–20 ID) of homologous FIV using inactivated cell-virus or whole-virus immunogens As with the SIV vaccines the envelope proteins appeared to be the major determinant of protective immunity Also in parallel with the SIV vaccine model, the mechanism of immune protection and the other parameters of humoral and cellular immunity, such as mucosal immunity, duration of immunity, immunity to heterologous FIV strains and to cell associated virus remain to be determined An attempt at passive immunization using Ig from naturally infected cats failed to have an antiviral effect and may even have enhanced infection (Hosie et al , 1990) This experiment has not yet been repeated with Ig from vaccine protected cats This should also be a very useful model for application of more modern vaccine strategies including recombinant viral proteins and synthetic peptides (Jarrett et al , in press). Because FIV infection and associated disease are highly prevalent worldwide (~ 1% of all cats infected, 12–15% of sick cats infected) (Yamamoto et al , 1989), a vaccine against this virus will become a part of standard veterinary practice

Antiviral agents against FIV

This model has just begun being used for the testing of antiviral drugs Alpha interferon has shown a powerful antiviral effect vs FIV in vitro but has not yet been used in vivo (J Yamamoto, personal communication) The RT of FIV and HIV have similar in vitro sensitivities to various RT inhibitors including AZT and PMEA (North et al., 1989). AZT or PMEA treatment of cats naturally-infected with FIV has been reported to suppress virus expression and lead to clinical improvement (Smyth et al , 1990, Egberink et al , 1990) Mutants of FIV resistant to AZT have already been described (Remington et al , in press) but their patho-

genicity in cats has not yet been tested. Because of its practical, economic aspects this FIV model should be increasingly used for AIDS therapy as well as vaccine research

Conclusion

The SIV macaque and FIV cat models of AIDS, both discovered in the last 5 years, are excellent surrogates for HIV infection of humans. They share a similar pathogenesis; what is learned in one system likely applies to all. If antiviral drugs or vaccines work effectively in either one of these animal models, they ought to be equally effective in humans (or vice versa). Drug pharmacokinetics, metabolism and toxicity are, of course, likely to be more human-like in macaques than cats. Nevertheless, both of these models will undoubtedly be increasingly used for AIDS preclinical research (Desrosiers et al., 1989c; Pedersen, in press). They will also serve as excellent models for gene therapy using retroviral vectors (Morgan et al , 1990). HIV-2 infection of macaques is also a useful model although most of the infected monkeys apparently stay healthy, this model seems comparable to HIV-1-infected chimpanzees, but is much more practical. Macaques are easily bred in captivity and the expertise for their proper breeding (including SPF colonies) and management exists at the various NIH-sponsored primate centers (Gardner et al., 1988). These centers are also affiliated with universities and many have links to industry, thus providing the resources and diverse talents for collaborative research on HIV antiviral drug and vaccine development. To promote this interaction the NIAID has sponsored a number of Cooperative Drug Discovery and Vaccine Development Groups that could well utilize both SIV and FIV models. The limiting factors of the SIV model are the high cost (~$1000/monkey for purchase, or ~ $150/month per diem per animal for infectious housing at BL2 biocontainment level), the lack of enough adequate housing for infected animals and difficulties in providing adequate delivery systems for reliable oral or systemic administration of antiviral drugs. However, these are not insurmountable obstacles and the advantages of this model far outweigh its limitations. The FIV model has the advantages of lower costs (~$85/cat for purchase, or ~$80/month per diem per animal), greater availability to the scientific community and more reliable, easier drug delivery systems Again, adequate housing facilities for cats and the need for SPF breeding colonies are a limiting factor, but not as big a problem as it is for monkeys Both of these animal models should be utilized more fully to maximize rapid progress towards the most optimal AIDS vaccines and antiviral therapies.

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