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Immunobiological Correlates of SIV Vaccine Vectors and Macaque Tropism

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ABSTRACT

The field of HIV vaccines received a "boost" with around 30% protection obtained in the RV144 randomized, double-blind, efficacy trial in Thailand. Currently, 560 clinical trials in HIV vaccine development are registered as complete and results are expected from several of these studies. The modest success attained at this time may be attributed to early attempts at identifying an animal model to test vaccine efficacy. Macaque models of HIV-1 infection have revealed viral infection, transmission, pathogenesis, and prevention. Identification of simian immunodeficiency virus (SIV) and its related strains served as the macaque counterpart of HIV and through genetic engineering, enabled chimera development that explored how macaques respond to a human antigen as well. Along with understanding viral infection, it is worth exploring the genetic repertoire of macaques for determining how the major histocompatibility complex and anti-retroviral restriction factors offer barriers to viral replication.

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INTRODUCTION

In spite of vast advances in medical science, there has been no better animal model of HIV than the macaque, which, owing to its immunology, reproductive physiology and anatomy that are highly comparable to humans, best reflects the progress and pathogenesis of HIV. Several aspects of HIV transmission and immunology are best studied in the macaque, even though humanized mouse models of HIV are now being developed [1]. These studies are essential for pre-clinical safety and efficacy testing of candidate vaccines and other therapeutics. While the macaque model of choice for several decades has been the Indian rhesus macaque, efforts to develop other macaque species as HIV models have resulted in the use of the cynomolgus macaque and the pigtail macaque for testing vaccine efficacy. Needless to say, the choice of a particular macaque model is significantly affected by the vaccine being tested both in terms of immunologic response and control of viremia. This review explores immunobiological responses in the macaque to SIV and its related vectors and highlights the impact of host immunogenetics on HIV vaccine development.

The need for developing new macaque models for HIV vaccine studies is compelled by the fact that not all macaques are equally permissive to various vaccine vectors. The two most common macaque species currently used in HIV research are the cynomolgus macaque (Macaca fascicularis) [2] and the rhesus macaque (Macaca mulatta) [3]. Even though they diverge by ~2 million years, cynomolgus and rhesus macaques are 99.6% genetically similar [4], [5]. However, these macaque species have unique region-specific characteristics that have been unravelled by genetic sequencing. This is evident in the case of rhesus macaques, which are of Indian, Chinese and Indian/Chinese hybrid species [6], or cynomolgus macaques, which may be of Mauritian, Filipino or Vietnamese origin or a mix of these depending on the geographic source of the animals. Macaque hybridization between vastly different macaque species and subsequent genomic exchanges is exemplified by the estimation that ~30% of the genome of Vietnamese cynomolgus macaque is of Chinese rhesus macaque origin [7] while their genetic divergence is estimated to be approximately 0.4% [8], [4]. While it is important to acknowledge that animals are inefficient efficacy and safety models, currently available options are our best bet in our search for vaccines, which require better understanding of immunological variability. A recent study [9] profiling immune signalling between and within species of macaques, mice, and healthy humans showed significant differences in the frequencies of many populations of blood cells (Fig. 1). Humans, mice and African green monkeys (AGM) have fewer CD4+- CD8+ T cells compared to macaques; mice have 10-fold lower numbers of neutrophils than all primates; all non-human primates have approximately three-fold more B lymphocytes than humans, and mice have approximately 10-fold more B lymphocytes than humans; humans have a higher ratio of classical to non-classical monocytes than any other species

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examined [9]. These findings indicate that model species should be evaluated based on their relevance to the experiment at hand.

Regardless of gene similarities, cynomolgus macaques are very different from rhesus macaques and this is exemplified by the inability of rhesus macaques to be infected by the human varicella zoster virus (VZV) [10] unlike the cynomolgus macaque [11], which makes the latter an ideal candidate animal model to examine the development of varicella-based vectors against SIV/HIV [11]. Further, a rhesus macaque-derived cytomegalovirus (CMV)-based BAC vector (RhCMV-eGFP) was not able to infect cynomolgus macaque [12], while rhesus macaques were previously shown to be permissive to the same vector [13]. Yet another example is that of a mutant SIVmac239 virus that established infection in both rhesus and pigtail macaques. Viremia was rapidly suppressed in pigtail macaques to levels of <15-50 copies/ml in contrast to rhesus macaques and reflect species-specific differences, with virus control being superior in pigtailed macaques that typically exhibits more rapid disease progression following wild-type SIV infection [14]. Therefore, host species-specificity and tropism have to be considered in earnest while designing vectors, in addition to other factors that influence the outcome of a vaccine trial in macaques.

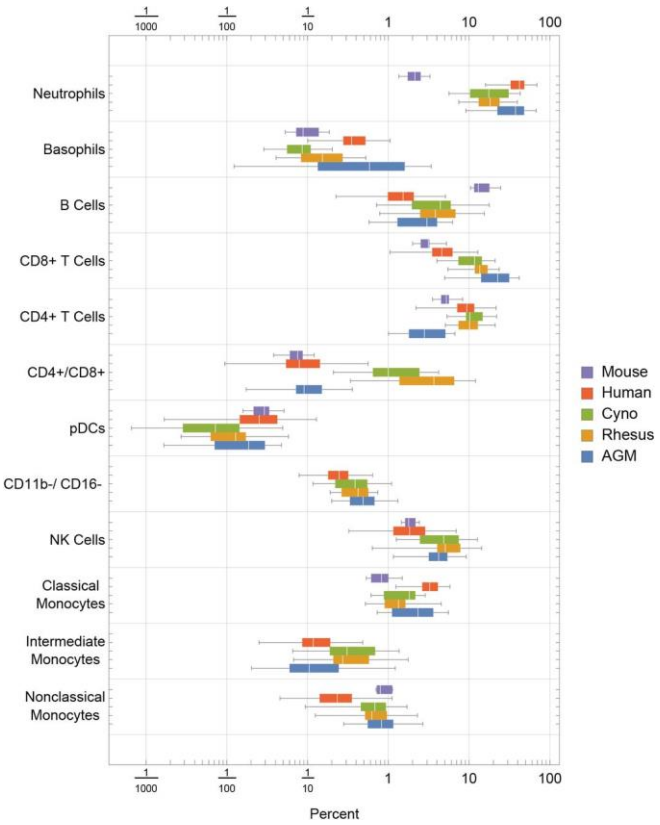


Fig. 1: Percentage of the total number of gated cell types by species [9]

Macaques as HIV Models of Disease Pathogenesis

Macaques belonging to the Cercopithecoidea superfamily are currently being used in AIDS vaccine research and mainly comprise rhesus [3], cynomolgus [2] and to a lesser extent, pigtail macaques (Macaca nemestrina) [3]. Rhesus macaques are mainly of Indian or Chinese origin, though smaller populations of Burmese origin are also used in SIV research [15]. Geographic concordance and phylogenetic analyses corroborate the notion that multiple cross-species transmission events of an SIV strain named SIVcpz from primates to humans gave rise to all known HIV-1 and HIV-2 groups and subtypes [16]. African non-human primates such as the sooty mangabeys, AGMs and mandrills support high burdens of SIV without overt clinical disease manifestations but show lower levels of immune activation than HIV-infected humans or SIV-infected Asian macaques. Rhesus, cynomolgus and pigtail macaques do not harbour SIV in the wild but when inoculated with SIV or SHIV, they exhibit clinical and immunological features of HIV infection in that there is a decline in CD4+ T cells and animals progress to AIDS or SIV-AIDS. The remarkable similarities are reinforced by the utilization by SIV of the same receptor for attachment and entry into cells as HIV.

Morphological Variations Among Macaques that Facilitate Pre-Clinical Testing

Chinese-origin rhesus macaques differ from those of Indian origin in genetics, morphology, behaviour and physiology, which has been reflected in the fact that Chinese rhesus macaques have significantly longer survival times and are less susceptible to infection by pathogenic SIVs/SHIVs than their Indian counterparts. Further, steady state plasma viral load (set point viremia) is significantly lower in Chinese macaques and they strongly respond to viral antigens, with differing patterns of cytokine secretion and expression of CCR5 in CD4+ T cells [17-23].

In terms of viral loads and disease progression, cynomolgus macaques better reflect human HIV infection than rhesus macaques. This obviously has its benefits and disadvantages as well. Due to their smaller size than their rhesus counterparts, cynomolgus macaques might be advantageous from a therapeutic standpoint as lower doses will be required on a body weight basis Further, the basic anatomy, vaginal pH and microbial flora in the vagina and rectum are similar to that of humans [24], thereby facilitating the extrapolation of pre-clinical data, though anatomical features such as a small vaginal vault make colposcopy and vaginal biopsies difficult. Rhesus macaques also share similar aspects of vaginal anatomy, particularly during certain phases of the menstrual cycle, which have made these macaques a popular choice for therapeutic approaches such as microbicides. Pigtail macaques on the other hand, have higher viral loads and more rapid progression to disease than HIV-infected humans. Pigtail macaques also share similar aspects of vaginal and rectal flora with that of humans. A significant advantage with using pigtail macaques is their susceptibility to vaginal exposures of low doses of SIV/SHIV, which resemble that of HIV-infected patient semen viral load, obviating the need for high doses of the virus or application of progestin-based hormones to thin vaginal epithelium to facilitate viral entry [25].

The Mucosa is the Most Important Entry Point for Establishment of Infection

To prevent HIV from gaining a foothold and to determine the kinetics of drug delivery in target areas, it is imperative to establish the paths of viral entry in the mucosa. The mucosal barrier is a dynamic entity that is subject to assaults on a constant basis and a healthy mucosal immune environment inhibits pathogen entry. The vaginal and rectal mucosa are affected by sex hormones and this is important for establishing infections due to the direct effect of sex hormones on the mucosal barrier function. As an example, Indian rhesus macaques treated with a sex hormone (Depot Medroxy Progesterone Acetate, DMPA) had higher levels of the gut homing receptor, α4β7 on CD4+ T cells that are highly

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susceptible to SIV, particularly in the endocervix than in macaques treated with estradiol (E2). However, MAdCAM-1, the α4β7 ligand, was present in higher levels in the vaginal fluids of control and estradiol-treated animals but absent in those from DMPA-treated animals [26].

The female genital tract is thus unique because of its ability to respond to hormones, immune factors, commensal microbes and biochemical processes, all of which contribute to increased rates of heterosexual male-to-female HIV transmission when compared with female-to-male transmission. Therefore, efficacy will be improved if vaccines are able to target the female genital tract and induce local immunity. Human papilloma virus (HPV) naturally infects cervicovaginal keratinocytes and therefore might serve as efficient vectors for HIV vaccines. Plasmid-forming pseudovirions that encapsidate HPV capsid proteins are known to effectively deliver reporter genes to the female genital tract and in addition to transgene expression, also serve as adjuvants, engaging Toll-like receptors and facilitating the activation and maturation of antigen presenting cells. A common feature of vaccines that facilitate expansion and recruitment of T cells is the unwanted effect of recruiting susceptible CD4+ T cells and thereby exacerbating viral replication. However, this was shown to be not true when HPV pseudovirions were used for vaccination against SIVmac251 challenge [27], with virus levels in mucosal tissues inversely correlated with anti-envelope CD4 T cell responses and CD8 T cells playing a role in virus control [28].

Macaque models allow stringent control of virus dose, strain and tropism, timing, mucosal route and status of mucosal tissues [29]. However, the complexity of human sexual practices make it difficult to study sufficiently large numbers of individuals [29], intrarectal or intravaginal routes of challenge reflect human sexual practices only to a certain extent, even though similar to human HIV infection, rhesus macaques carried the lowest risk of SHIV infection, when challenged orally, while the highest permeability was rectal followed by vaginal routes [29]. Nevertheless, primate laboratories working with the SIV model of macaques have not developed a standardized protocol for mucosal inoculation. Standardization of mucosal inoculation is important since it has been demonstrated by genetic analyses that over 78% of typical sexual transmissions originate from a single viral variant from among the diverse quasi-species in the infected donor [30]. Several features such as virus dose, number and frequency of inoculations, volume of inoculum, position of the animal during exposure and duration of the exposure, amount of mucosa exposed to the inoculum and virus dissemination sites as well as draining lymphatic tissues involved in infection are all important aspects to study viral transmission, pathology, prevention and treatment [30]. Intravaginal SIV infection is typically examined in rhesus macaque or pigtail macaque. The vagina is a multi-layered stratified squamous epithelium whose thickness is affected by the menstrual cycle, while the rectum is composed of a single layer of columnar epithelium [31]. The vagina therefore provides a more substantial physical barrier to infection. Due to this, compared to the intravenous route, 10,000 fold more SIV particles are needed to infect 100% of rhesus macaques intravaginally [32]. Compared to rhesus macaques that are seasonal breeders, pigtail macaques breed throughout the year and hence the latter might be preferred for vaginal studies [24]. Pigtail macaques have regular menstrual cycles and in addition to being more susceptible to vaginal chlamydia and trichomonal infection than rhesus macaques, they have higher states of immune activation and different frequencies of memory cells than rhesus macaques, which may lead to an accelerated progression to SIV-AIDS [33].

Vaccine-induced delayed SIVmac251 acquisition in females, but not male rhesus macaques, was attributed to better quality mucosal antibodies that afford better protection compared to males [34]. In a bid to refine current inoculation protocols and to determine where virus entry occurs and how infection disseminates from the mucosal entry sites, dual reporter SIV vector [35] and mucosal inoculations of dyes followed by magnetic resonance imaging were carried out recently [36]. Atraumatic application of one ml of viral inoculum for intrarectal challenges and two ml volume for intravaginal challenges was insufficient for reaching the distal descending colon, and could model rectal exposure in only 50% of the animals. A three ml intrarectal challenge, the volume of a typical macaque ejaculate, would more likely increase the consistency of contact between the mucosa and the inoculum. Nevertheless, other factors such as amount and consistency of feces are variables that can affect this estimation. For vaginal exposure, a two ml volume in sexually mature, nulliparous Indian rhesus macaques resulted in the inoculum contacting the entire vaginal vault but there was no penetration into the cervix. Using a different approach, a dual reporter system containing a non-replicating SIV-based vector preferentially infected the squamous mucosal epithelium and ectocervical barriers of the vaginal vault, along with ovaries and local draining lymph nodes only 48 hours after inoculation with a high dose of virus [35].

Another less frequently described aspect of SIV pathogenesis is the use of SIV/SHIV cell-free viral particles to evaluate preventive approaches. It must be taken into account that infectious HIV is primarily associated with semen, which comprises seminal plasma, spermatozoan cells, germ cells, leukocytes, epithelial cells and commensal microflora; plasma contains inflammatory factors, cytokines, peptides and antibodies. Macaque semen similarly contains leukocytes and SIV host cells. Studies have shown efficient transmission with cell-associated SIV in vaginally exposed progesterone-treated cynomolgus macaques [37] as well as intestinal mucosa to repeated intrarectal exposure to low amounts of SIV-infected peripheral blood mononuclear cells (PBMCs) [38]. This initiated an immune response in the receiver that may confer a protection against infection by the cell-associated virus, thereby resulting in allo-immunization against the major histocompatibility complex (MHC) of the donor, and anti-MHC antibodies generated by vaccines have significant impact on the outcome of SIV/HIV vaccine challenge in macaques [39]. In addition, viral infectivity in the semen is affected by its pH, which in the macaque is slightly basic, ranging from 7 to 9, similar to that of the average human semen (pH 7.7). Compared to semen, the vaginal environment in humans is acidic with a pH ranging from 4 to 6, which can therefore inactivate cell-free HIV. However, pH of the vaginal environment in macaques (rhesus, cynomolgus macaque and pigtails) ranges from 6 to 8, which increases infectivity of cell-free SIV/SHIV in the macaque model [39]. Therefore, factors that regulate the complex microenvironment at portals of HIV entry need to be better understood for testing vaccine efficacy.

Host Immunogenetics

Anti-Retroviral Restriction Factors and Protection in Macaques

The genetic background of the host species, or even subspecies, is important for the purposes of grouping macaques

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for vaccination trials where host immunogenetics profoundly influence immunological responses and virological outcomes [3]. Foremost among these genetic players are the host anti-retroviral restriction factors such as APOBEC3, TRIM5α, SAMHD1 and MHC alleles that influence the progress of disease in macaques infected with SIV. HIV can efficiently enter the cells of old world monkeys but encounters a block before reverse transcription, mediated by TRIM5α, a component of cytoplasmic bodies [40]. TRIM5α targets the capsid protein of incoming lentiviral particles and inhibits subsequent steps of the replication cycle, including inhibition of reverse transcription immediately after viral entry into the cell and therefore is an important mediator of anti-retroviral innate immunity in mammals and confers resistance to HIV-1 infection in old world monkeys [41]. The susceptibility of pigtail macaques to HIV could partly be due to a dysfunctional TRIM5α [42]. The macaque TRIM5α gene displays considerable polymorphism in one of the domains leading to its classification into three classes giving rise to six different genotypes, which have been to shown to display divergent anti-retroviral restriction characteristics. The cynomolgus macaques are positive for TRIM5Q, TRIM5CypA and TRIM5TFP genotypes, while the pigtail macaques are homozygous for TRIM5CypA. Rhesus macaques of Burmese, Chinese and Indian origin possess TRIM5 alleles, but the TRIM5CypA variant is absent in Chinese rhesus macaques, thereby making them less susceptible to SIV infection than the Indian rhesus macaques. Most rhesus macaques are homozygous or heterozygous for the least permissive TRIM5TFP allele. Interestingly, there is no significant effect of TRIM5 polymorphism on the replication of SIVmac251 in Chinese rhesus macaques or SIVmac32H/ixc in Indian rhesus macaques, suggesting that the effects of TRIM5 polymorphism on the evolution of SIV in macaques may be cohort and/or SIV strain specific [43]. Since many host genes dictate immunological responses to vaccines, the role played by the above mentioned restriction factors such as SAMHD1, TRIM5α and MHC alleles that confer protection have to be factored in while designing studies.

MHC Alleles and Protection in Macaques

As CD8+ T cells are an integral component of the immune response against SIV, it is necessary to examine MHC expression in macaques so that CD8+ T cell responses can be monitored during disease progression. The repertoire of MHC alleles and the level of expression of each of these alleles is a critical aspect of an immune response to SIV and the fact that MHC expression varies among distinct leukocyte subsets suggests that SIV tropism can have an impact on the immune response [44]. Characterization of MHC class I alleles allows us to identify the association of cytotoxic T lymphocytes (CTL) response to an immunodominant epitope derived from the SIV Gag region, which may ultimately influence the time of onset of disease in SIV-infected macaques. MHC alleles such as Mane-A1*084:01 (previously named Mane-A*10) control SIV infection by CD8+ T cells [45] and immune escape mutations identified within CTL epitopes restricted by Mane-A1*084 are useful for designing vaccines for use in in pigtail macaques [46]. Indian rhesus macaques are known to have several MHC alleles that confer protection. Expression of Mamu-A1*001 is associated with significantly delayed disease progression in SIV/SHIV infections while Mamu-B*017, Mamu-A*1303 and Mamu-B*008 alleles are associated with favourable disease and control of SIV replication [47]. In the case of cynomolgus macaques, MHC alleles can affect the outcome of vaccine studies similar to that observed in rhesus macaques. Comparison of the MHC region between primates and non-human primates shows that the cynomolgus sequence varied compared to rhesus macaque, human and chimpanzee sequences by 0.48, 4.15 and 4.10% respectively [48], which implies considerable species-specific differences that vaccine design must deal with. MHC alleles in cynomolgus macaques have been described in sufficient detail elsewhere [13].

MHC Alleles and Protection in Humans

MHC class I alleles such as human HLA-B*027 and HLA-B*057 are associated with slow progression of HIV-1 disease [49] while HLA-B*22, HLA-B*35, and HLA-B*44 in humans are associated with shorter survival time [50]. With respect to MHC class II molecules, there is evidence in the RV144 trial for envelope [51]–specific IgA antibodies to be associated with increased risk of HIV acquisition specifically in individuals with DQB1*06. Higher IgG antibody responses to HIV envelope amino acid positions 120 - 204 were associated with decreased risk of acquisition and increased vaccine efficacy only in the presence of DPB1*13. Overall, the underlying genetic findings indicate that HLA class II modulated the quantity, quality, and efficacy of antibody responses in the RV144 trial [52]. Unlike SIV vaccine studies in cynomolgus macaques where MHC/TRIM typing was either not carried out or not reported [2], most studies in rhesus macaques reported these data. It is essential for macaque studies to conduct MHC typing of the animals such that influence of protective alleles in the vaccinated or treated groups could be ruled out as a possible mechanism for the outcome of the study.

Psychosocial Features of Animal Husbandry

An often-neglected aspect of animal housing facilities is the suppression of vaccine efficacy due to neuropsychoimmune effects faced by macaques in a social environment. During competitive encounters, dominance rank is established among macaques, leading to some individuals yielding to others in the group. Low dominance rank in macaque colonies can lead to chronic stress, immune compromise and reproductive dysregulation. Particularly in female rhesus macaques, this can cause alterations in glucocorticoid and sex steroid hormone levels [53], in addition to disruption in serotonergic and dopaminergic signalling [54], and very importantly, in the context of SIV infection and immune response, changes in lymphocyte count and proliferation [55].

Evaluation of Vaccine Efficacy

SIV vaccine efficacy depends on induction of robust and long-lasting antibodies against envelope glycoprotein with potent neutralizing and effector functions to prevent acquisition of infection and induction of cytolytic T cell responses against Gag for controlling viral replication [34]. Frequently, due to lack of systematic vaccination protocols and uniformity in the type of challenge strains, viral doses and macaque species used, there are difficulties in evaluation of vaccine efficacy and identification of correlates of protection associated with vaccination against SIV. On examination of the efficacy of various vaccine vectors in animal trials, most rhesus macaques showed at least 1-2 log lower viremia, even though animals protected were not high (Table 1). A vaccine regimen comparing cellular responses to ALVAC/Env, RepAd/Env, DNA & Env, DNA and Peptide/MVA/ in rhesus macaques

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showed that all vaccine regimes, particularly DNA vaccines (highest frequency of 7.5%), induced antigen-specific CD8+ T cells in the vagina. While only one of three animals was positive with ALVAC, cellular responses were not induced with peptides. IgA and IgG were detected in the mucosa of all vaccines, though IgG was higher than IgA in animals with antigen-specific CD8+ T cell response [56].

With very few exceptions [57], there are no studies where protection has exceeded 50% in SIV-infected rhesus macaques. High seropositivity to adenoviral vectors in the general population might be the greatest challenge in vaccine development as noted with the setbacks associated with replication defective Ad5 vectors in HIV vaccine clinical trials (HVTN505 and STEP). Of many adenoviruses that have been tested, 50% protection was obtained against pathogenic challenge [58], but it seems that Ad26 strain offered the best protection when combined with a robust prime boost strategy [56]. Ad5, Ad6 and Ad7 did not offer significant protection (Table 1). More recently, replicating Ad5hr-recombinants encoding SIV-Gag and/or SIV-nef in addition to SIVenv/rev, boosted with SIVgp120 or polypeptide of CD4 binding site of SIV env, showed 39% of animals protected against intrarectal challenge of SIVmac251 [59]. A similar level of protection against SIVmac251 was afforded by virus-like particles (VLPs) in rhesus macaques [60]. This suggests that a strong immune response is being generated, but with adenoviruses, it seems that the prime boost combination might be working in its favour compared to other vectors that were employed. This was clearly not needed when RhCMV was used, owing to the unique nature of the cytomegaloviruses that exhibit persistent and latent infection, mediating their effects through T effector memory responses [61]. Most studies have used the Indian rhesus macaque though at least one study using Chinese origin rhesus macaques showed lower viremia in immunized animals in the context of adenoviral vectors [62].

SIV Strains Used in Macaque Challenge Experiments

Once the vaccine vector has been validated through *in vitro* studies and macaque model has been identified, the choice of challenge virus gains paramount importance. Pre-clinical macaque vaccine trials use either heterologous or homologous virus challenge, SIVmac251 and SIVmac239 being the principal strains used. SIVmac251 is a swarm whereas SIVmac239 is a clone and this needs to be considered for standardization of vaccine trials. SHIV SF162 and related strains are used in SHIV chimera-based vaccines (Table 1).

SIVmac Strains

SIVmac viruses have only ~55% sequence homology with that of HIV-1 whereas they have ~75% sequence homology with that of HIV-2 and a 54-80% sequence homology with SHIVs. The SIVmac251 virus and SIVsmE660 were isolated from rhesus macaques naturally infected by SIVsm, and SIVmac239 is a derivative of SIVmac251 [63]. Whereas some such as SIVmac239 is highly pathogenic, others have been attenuated due to genetic deletions. SIVmac251-32H-C8 lacks 12 bp in the nef gene, while SIVmac251-J5 displays limited pathogenicity [63]. Most challenge experiments in macaques have been performed using SIVmac251, which is a swarm virus or the pathogenic clone SIVmac239, as well as SIVsmE660, the latter showing low viral loads in the chronic phase, but nevertheless is a swam virus showing considerable variability between animals [63].

SIV-SHIV Chimeras

Among chimeric viruses, SHIV89.6 with HIV-1 env from patient isolate 89.6 and SIVmac239 has been used extensively for vaccine studies in rhesus and cynomolgus macaques [64, 65]. Highly pathogenic SHIVs such as SHIV-89.6P chimeric virus cause a profound depletion of circulating CD4+ T cells within 2-3 weeks of infection and development of AIDS-like disease within a year [66]. SHIV89.6P are either X4-or dual tropic and irreversibly destroy naïve and memory CD4+ T cells rapidly. Even though the HIV-1 env included in SHIV-89.6P was derived from a clone that used both CCR5 and CXCR4 co-receptors for entry into macaque CD4+ T cells, sequential passage in macaques has selected for a SHIV-89.6P clone that is now deemed a pure X4 virus [67]. A relative drawback of SHIVs is the fact that their disease course is not typical of human AIDS in that infected animals become rapidly immunosuppressed immediately with dramatic loss of CD4+ cells and essentially "crash and burn" with almost always gut-related pathology and wasting within the first few weeks. SHIV89.6KB9, a strain derived from Indian rhesus macaque, showed improved pathogenicity when passaged in cynomolgus macaques (resulting in SHIV89.6cy243) due to an 8-amino acid change at the junction between the HIV-1 and SIVmacgp41 cytoplasmic tail gene sequence [66].

As there is an emerging shift in immune correlates of protection from cell-mediated immune response to that of non-neutralizing antibodies to control HIV infection based on the results of the RV144 trial [68], there is a need to develop SHIVs that recapitulate the mechanisms of natural infection and antibody action in macaques. Tier 1 HIV strains are highly neutralization sensitive and SHIVSF162P4 is an example of a chimeric strain, whereas Tier 2 strains, such as R5-tropic SHIVSF162P3, are less sensitive to neutralization, and in non-human primate models both are essential for vaccine discovery. Unless provided at high doses, both these strains are rapidly cleared, but not newer strains such as SHIV-1157 [69].

Challenge Routes

Pigtail macaques inoculated intrarectally with SIVmneE11S clone, showed dramatic increases in total and SIV-specific IgA levels in rectal secretions compared to plasma and non-rectal mucosal samples [70]. A comprehensive study examining different routes of exposure in rhesus and cynomolgus macaques showed that the early plasma viral loads did not differ when administered SIVmac251/32H(1XC), SIVmac251, SIVsmm-3, SHIV89.6P (passaged in rhesus and cynomolgus macaques) orally, intrarectally, intravaginally or intravenous routes, though steady state SIV plasma viral RNA was lower in cynomolgus macaques compared with rhesus macaques [71]. Most studies comparing different routes of vaccine delivery were performed in rhesus macaques, particularly evaluating the bio-distribution and persistence of replication-competent adenovirus vectors expressing SIV transgenes. It is interesting to note that unlike replication-defective vectors that maintain localized anatomic distribution, replication-competent adenovirus vectors are distributed throughout the macaque regardless of immunization route [72]. However, the same group showed that replication-competent Ad5-SIV induced mucosal IgA responses in mucosal (sublingual, rectal, vaginal, or nasal) tissues but the vaginal immunization route was found to generate the highest SIV-specific vaginal T-cell responses [73]. Similarly, live attenuated poxvirus vaccine (NYVAC-SIV) administered intranasally, intramuscularly, or intrarectally induced CD8+ T cells specific

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to the antigen (SIVgpe) in the mucosal tissues of immunized macaques [74]. On the other hand, it has also been noted that cutaneous or intramuscular immunization generates antigen-specific cells that may not migrate to mucosal sites as shown in macaques where mucosal immunization offered better protection than the subcutaneous route following intrarectal challenge with a SHIV strain [75]. Penile immersion in 109 SIVmac251 resulted in higher SIV RNA levels in the genital lymph nodes where virus is initially amplified [76].

Challenge Doses Used in Macaques

HIV is a weak virus with productive infection being a rare event since a minimum of 500 heterosexual contacts are needed to cause one productive infection [77]. HIV/SIV infection is established when a single virus spreads systemically after replication in mucosal tissues. Successful transmission of HIV via a mucosal route is dependent on multiple factors, including the viral dose present in the inoculating fluid (semen, vaginal fluid, breast milk), the integrity of the mucosa, and the number of target cells at the mucosa site. The dose of virus needed to establish infection is crucial to elicit an immune response. Since a majority of infections is initiated by a small number of transmitted viral variants, how the disease course is affected by virus dose and the number of variants in that dose becomes important. Experimental protocols in macaques generally follow one high dose of a SIV clone or a swarm to achieve infection, but this does not recapitulate sexual HIV transmission. High dose infection has the unwanted effect of masking protective effects of an otherwise efficacious vaccine [78]. On the other hand, recent advances in experimental protocols have resulted in a number of studies adopting two low-dose challenge of SIVmac251that imitates natural HIV infection that offered some protection in contrast to a high-dose group in rhesus macaques [78]. In another study, live hyper-attenuated SIV viruses, induced a robust and rapid recall response following multi low-dose SIVmac239 infection in cynomolgus macaques but vaccination failed to induce sterilizing immunity, even though viral loads were dramatically reduced [79]. Vaccines against SIV can provide vaccination-induced immune correlates but multiple low-dose challenges can result in evolving host responses that affect the protective outcome. This is exemplified by a 73% reduction in risk of infection in macaques challenged rectally with SIVmac251, which is attributed to innate antiviral signalling induced by the first challenge followed by vaccine boost-elicited antibody response [80]. Higher diversity of SIV variants was seen in macaques challenged orally with high dose SIV compared to a low-dose challenge, which reflects natural infection by HIV. Interventions applied during the eclipse phase, which is the delay in viral and innate immune responses, is more likely to be successful when oral low-dose SIV inoculations are part of the vaccine trial [81].

However, the low-dose approach is also fraught with problems such as the difficulty in identifying vaccine-induced immune responses from immune responses stemming from repeated exposures to SIV. Also, the timing of infection and tissue sampling procedures that require identification of the precise sequence of challenges that lead to infection will be hard to identify. Challenging animals with a low dose of SIV several times in a short duration (rapid, repeated low-dose) in cynomolgus macaques allow examination of early acute events while using a low-dose challenge. Moreover, because of the nature of the protocol, there is a clearly defined duration between intervention and challenge allowing for studies related to longitudinal efficacy of microbicidal treatments and vaccine trials [82]. In the presence of neutralizing or blocking antibodies, even high doses of highly pathogenic SIVmac239 strain can be controlled [83]. This suggests that a highly efficacious vaccine that induces both cellular and humoral immunity can overcome some of the barriers induced by the viral strain, dose, macaque strain and other variables in a vaccine trial.

CONCLUSION

Despite a ban on export of Indian rhesus macaques from India, primate-breeding facilities in North America have ensured a steady and consistent supply of this species for biomedical research purposes. Therefore, the use and development of other macaque species such as cynomolgus and pigtail macaques, as HIV models is dependent on the tropism and host specificity of SIV strains and of candidate vaccine vectors. Genomic characterization of animals and their allocation in vaccine trials are a necessity when elucidating the protective mechanisms attributed to vaccines in macaques. The ease of genome sequencing in terms of cost and technology has further benefited the macaque biomedical research community in terms of MHC allele databases of various macaques enabling identification of those that confer protection against SIV infection. The species-specific nature of vaccine vectors should complement the immunogenetics and anatomical features of the macaque model being used for that study. Thus, vaccine studies are influenced by host genes as well as immunological correlates of protection specific to vectors employed. Lastly, care must be taken to ensure that animals are well-characterized and obtained from reputed sources.

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Table 1. Evaluation of SIV/SHIV vaccine efficacy in various Rhesus Macaque strains and Pigtail macaques

No	Vector	Macaque	Challenge Route	Challenge Virus	Challenge Virus Dose	Vaccine Dose	Vaccine Type	Prime	Groups	Booster	Vaccine Route	Animals (Total)	Control	Animals Protected	Viremia	MHC exclusion	Trim5	Reference
1	Ad26	Rhesus (India)	IR	SIVmac251	500 TCID	3×10^{10}	SIVsmE543 Env/Gag/Pol antigens	Ad26-Env/Gag/Pol	SIVmac32H Env gp140 protein(Ad/Env; n = 12)	0.25 mg Env gp140 with AS01B Adjuvant	IM	32	Sham; *n* = 8	6 of 12	Negative	*Mamu-A*01, Mamu-B*08*, or *Mamu-B*17*	Trim5	[58]
								Ad26-Env/Gag/Pol	SIVsmE543 Env/Gag/Pol antigens (Ad Alone; n = 12)	Ad35-Env/Gag/Pol								
	Ad26			SHIV-SF162P3	500 TCID		Ad5HVR48-clade C HIV-1 Env/Gag/Pol			0.25 mg HIV-1 clade C C97ZA012 Env gp140 AS01B Adjuvant		20		8 of 20				
										0.25 mg Env gp140 with AS01B at the same six time points (Env Alone; *n* = 8)								
2	AdC6	Rhesus (India)	IR	SIVmac239	300 TCID	10^11	DNA/EP-AdC6-AdC7	Day 0		Wk 16 and Wk 32	IM	6		0	1.6 log lower	All are Mamu-A*01^{+}	N/A	[84]
	AdC7					10^7	VV-AdC6-AdC7				SC	6		0				
	DNA-SIVmac239 Gag-Tat					10^11	DNA/-EP-VV-AdC6				IM	6		0				
	rVV					10^11	DNA/EP-VV-AdC7				IM	6		0				
						10^11	AdHu5-AdHu5-AdHu5				IM	6		0				

Abbreviations
Ad: Adenovirus
BCG: Bacillus Calmette-Guerin
IG: Intragastrical
IM: Intramuscular
IN: intranasal
IO: Intraoral
IR: intra rectal
IT: intratracheal
IV: Intravenous
MHC: Major Histocompatibility Complex
MVA: Modified Vaccinia Virus Ankara
N/A: Not applicable
VSV: Vesicular Stomatitis

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No	Vector	Macaque	Challenge Route	Challenge Virus	Challenge Virus Dose	Vaccine Dose	Vaccine Type	Prime	Groups	Booster	Vaccine Route	Animals (Total)	Control	Animals Protected	Viremia	MHC exclusion	Trim5	Reference
3	Ad6	Rhesus (India)	IR	SHIV-SF162P3	1,000 TCID	10^11	Ad5-HIV-Env gp140 JRFL			Ad6-1-5-2	Vag injection /IM	4		0				[85]
	Ad1										intranasal-preim				Lower	Genotyped after study	N/A	
	Ad5															*Mamu-A01, A02, A08, A11, B01, B03, B04, B08, B17, and B29* alleles		
	Ad2																	
4	AdC7	Rhesus (India)	IR	SIVmac239	300 TCID	10^11	SIVmac239-CO-Gag-Tat	Day 0	n=10 (C6 and C7 switched for boosting)	Wk 24	IM		n=10	2 of 10	Lower	18 MaMu-A*01+ and 12 MaMu-A*01-	N/A	[86]
	AdC6																	
5	Ad5	Rhesus (China)	IR	SIVmac239	500000 TCID	10^11	SIVmac239 Gag-Pol-Env	Ad5		Ad5	IM	4	PBS			negative for Mamu-A1*01	N/A	[87]
	Vaccinia					10^9					IO, IN	8		1 of 8	1.7 log lower			
6	Ad5	Rhesus (China)	IR	SIVmac239	900 TCID	10^10	SIVmac239 Gag-Nef-Pol-gp140			Day 0-14-28-42	SC	15	15	8 of 15 Immunized	Lower	MHC	Trim5	[62]
														2 of 15 control				

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No	Vector	Macaque	Challenge Route	Challenge Virus	Challenge Virus Dose	Vaccine Dose	Vaccine Type	Prime	Groups	Booster	Vaccine Route	Animals (Total)	Control	Animals Protected	Viremia	MHC exclusion	Trim	Reference
7	Ad5	Rhesus (China)	IV	SIVmac239	1000 TCID	10^11	SIVmac239 Gag-Env-Pol		Ad5-SN-PBMC incubated with Ad5-SIVGag		IM	4	4	0	1.1 log lower	negative for Mamu-A1*01	N/A	[88]
									Ad5-SN-Ad5-SIVGag			4						
									Ad5-SP-PBMC incubated with PBMC			6						
									Ad5-SP-Ad5-SIVGag			5						
8	Ad5hr	Rhesus (I/C)	Penile	SIVmac251	100000 TCID	10^10	SIVmac239 Gag-Pol-Nef	Ad5hr pre-im	Ad5 Vx-SIV		Intra tracheal	9	8		Lower	MHC	Trim5	[6]
9	MVA	Rhesus (India)	IV	SHIV-E-P4.1	80 TCID	10^8	SIVmac239 Gag-Pol, HIV E Env				IM	5	5		Lower	Mamu-A1*01	N/A	[89]
10	DNA/ MVA	Rhesus (India)	IR	SIVmac251	100 ul of stock	10^8	SIV239 Gag-Pol, Env, Tat, and Rev	DNA prime		MVA Wk 16, 24	IM	16	8		Lower	*Mamu-A*01*, *Mamu B08*, and *Mamu B17*	N/A	[90]
11	Herpes virus	Rhesus (India)	IV	SIVmac239	10 TCID	10^5	SIV-Gag-Env-Rev-Tat-Nef				IV	5	3		1.85 log Lower	Mamu-A1*01	N/A	[91]
						3x10^5 Control												
12	DNA	Rhesus (India)	IR	SIVsmE660	5000 TCID	40 ug protein	SIVmac239 Env-Gag-Pol-Nef-Tat-Vif				IM	8	8	2	1.6 log lower	MHC	Trim5	[92]
							inactivated SIVmac239 particles+SIVmac239 DNA											

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No	Vector	Macaque	Challenge Route	Challenge Virus	Challenge Virus Dose	Vaccine Dose	Vaccine Type	Prime	Groups	Booster	Vaccine Route	Animals (Total)	Control	Animals Protected	Viremia	MHC exclusion	Trim5	Reference
13	rAd5	Rhesus (India)	IR	SIVmac239	800 TCID	2x10^10	SIVmac239 Gag-Pol_Env-Nef-VIF-Vpr-Vpx-Tat-Rev				Electroporation	8	8	2	4.4 log lower	Mamu-A*01, -A*02, -A*11, -B*01, -B*03, -B*08, -B*17, and -B*29,	Trim5	[93]
14	Listeria Mono+	Rhesus (India)	IR	SHIV-1157ip	50 TCID		SIV Gag											[94]
	Ad5hr					5x10^8	Lmdd-BdopSIVgag	Lmdd-BdopSIVgag	Ad5hr-SIVGag+HIV-1 gp160		IN, IT, IG	5	5	1	Lower	MHC Mamu-A*001, B*008 and B*17	Trim5	
											IM							
15	VSV	Rhesus (India)	IR	SIVsmE660	4000 TCID	10^8	SIVsmE660 Gag-Env	VSV-E660 Gag-VSV-E660-EnvG		SFV-VSV-G	IM, IN	6	6	4	Lower virus detected in 2	N/A	Trim5	[95]
16	VSV	Rhesus (newborn)	Oral	SIVmac251	10000 TCID	10^7	SIVmac239-Gag-Pol-EnvG1			MVA-SIVmac239-Gag-Pol IM	IO	8	8		Lower	Mamu-A1*01	N/A	[96]
17	BCG Danish	Rhesus (India)	IR	SIVmac251	7.2 Log	3x10^8	SIVmac239 Gag			rNYVAC-SIVmac142-Gag-Pol IM	IV	5	5	0	No difference	*Mamu-A*01* positive	N/A	[97]

No	Vector		Macaque	Challenge Route	Challenge Virus	Challenge Virus Dose	Vaccine Dose	Vaccine Type	Prime	Groups	Booster	Vaccine Route	Animals (Total)	Control	Animals Protected	Viremia	MHC exclusion		Reference
18	rDNA	rYF17D	Rhesus (India)	IR	SIVmac239	800 TCID	2x10^5	SIVmac239 Gag-Vif-Nef				Electroporation	8	8		1 log Lower	*Mamu-B*08* or *Mamu-B*17*	Trim5	[98]
												SC	8						
		rAd5					10^11						8						
19	DNA		Rhesus (Burmese)	IV	SIVmac239	1000 TCID		SHIVdEN (SIVmac239-Gag-Pol-Vif-Vpx-HIVTat-Rev)	DNA prime			IM	11	5		Lower in 6#	*Mamu-A1*066:01, Mamu-B*005:02*, and *Mamu-B*015:04*	N/A	[15]
							6x10^9	SeV-SIVmac239-Gag			SeV-Vif-Nef DNA IN	IN							
20	RhCMV		Rhesus (India)	IR	SIVmac239	300 FFU	5x10^6	RhCMV SIVmac239Gag-Rev-Nef-Tat-Env-Pol				SC	24		13		Mamu A*01, B*08 and B*17	Trim5	[57]
							2x10^10	Ad5-SIV											
21	DNA		Pigtail	IR	SIV-MneCLE11S			SIVmneDNAΔ Gag-NC				IM, SC	12	4		Lower	N/A	N/A	[51]

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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