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Non-human primate models for HIV/AIDS vaccine development

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Abstract

The development of HIV vaccines has been hampered by the lack of an animal model that can accurately predict vaccine efficacy. Chimpanzees can be infected with HIV-1 but are not practical for research. However, several species of macaques are susceptible to the Simian Immunodeficiency Viruses (SIV) that causes a disease in macaques that closely mimics HIV in humans. Thus, macaque-SIV models of HIV infection have become a critical foundation for AIDS vaccine development. Here, we examine the multiple variables and considerations that must be taken into account to use this NHP model effectively. These include the species and subspecies of macaques, virus strain, dose and route of administration and macaque genetics including Major Histocompatibility Complex molecules that affect immune responses and other virus restriction factors. We illustrate how these NHP models can be used to carry out studies of immune responses in mucosal and other tissues than could not easily be performed on human volunteers. Futhermore macaques are an ideal model system to optimize adjuvants, test vaccine platforms, and identify correlates of protection that can advance the HIV vaccine field. We also illustrate techniques used to identify different macaque lymphocyte populations and review some poxvirus vaccine candidates that are in various stages of clinical trials. Understanding how to effectively use this valuable model will greatly increase the likelihood of finding a successful vaccine for HIV.

Introduction

Once HIV was shown to be the etiologic agent of AIDS(Barre-Sinoussi et al., 1983; Gallo et al., 1984), the hunt began for an animal model that could advance vaccine and pathogenesis studies. Small mammals including mice and rats are not susceptible to HIV infection. While some non-human primates can be infected with HIV, infection rarely causes an AIDS like disease. Other lentiviruses can cause immunodeficiencies, feline immunodeficiency virus infection of cats shares some features of HIV infection, but the best available model is simian immunodeficiency virus (SIV) infection of macaques that closely mimics HIV disease progression in humans(Gardner and Luciw, 1989).

HIV was introduced in the human population as a result of cross-species transmission of SIVs from African non-human primates. Two viruses, SIVcpz found in chimpanzees *Pan troglodytes troglodytes* (Heeney et al., 2006; Keele et al., 2006; Sharp et al., 2005) and SIVsm found in sooty mangabeys *Cercocebus atys* (Santiago et al., 2005), gave rise to HIV 1 and HIV 2 respectively. African hosts of SIV remain disease free, but transmission to new hosts such as HIV to humans or SIV to Asian primates results in immunopathologic sequalae and progression to AIDS. HIV infection of humans and SIV infection of Asian

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macaques share many similarities including: mucosal transmission, tropism for CD4 T cells and macrophages, alterations in immune activation, and, in the advanced stages of disease, lymphomas and infections with normally benign or opportunistic pathogens. These similarities have led to the use of non-human primates as models for HIV, and lentiviral infection of macaques is the most widely studied non-human primate model.

One vital use of animal models is in the testing of HIV vaccine candidates. Macaques are the current 'gold standard' animal species for testing HIV vaccines. Vaccine studies in macaques can be modeled based on the patient cohort to be used in clinical trials as most modes of HIV transmission including mother to child, hetero or homosexual transmission and intravenous drug users can be mimicked by varying the route (oral, vaginal, penile, rectal or intravenous) and amount of virus inoculum (single high dose versus repeated low dose) used to challenge vaccinated animals. The ability of the vaccine to prevent or delay virus acquisition, control virus replication and disease progression can then be determined. These virologic outcomes are used to compare the relative efficacy of different vaccine strategies, and should guide the choice of HIV vaccines to be advanced to clinical trials.

We review the different macaque models and virologic considerations that should be made when designing a vaccine study. These include the choice of macaque species, MHC alleles and polymorphism of genetic restricting factors, challenge virus, virus dose, route of administration as well as some vaccine candidates.

Species of Macaques

Macaques have greatly contributed to our understanding of HIV pathogenesis. Initial descriptions of an AIDS like disease similar to humans, was made in macaques (Henrickson et al., 1983; Letvin et al., 1983; Stromberg et al., 1984) and early transmission studies showed that the passage of body-fluids or cells from an infirmed animal could induce immunosuppression in healthy animals (Letvin et al., 1985; London et al., 1983; Murphey-Corb et al., 1986). There are many species of macaques, but only three have gained prominence in HIV vaccine and pathogenesis studies and they all belong to the *Cercopithecoidea* superfamily. They are cynomolgus macaques (*Macaca nemestrina*), pig-tail macaques (*Macaca fascicularis*) and rhesus macaques (*Macaca mulatta*)(Baroncelli et al., 2008). Of the three-macaque species, rhesus macaques are the most frequently used and thus the viral and cellular dynamics following SIV or Simian Human Immunodeficiency Virus (SHIV) challenge have been well characterized in blood, lymphoid and mucosal compartments of these species. A plethora of information exists to facilitate research with rhesus macaques including the sequence of the entire rhesus genome (Gibbs et al., 2007) and the cross reactivity between human and macaques of several commercially available reagents. Furthermore *ex-vivo* assays designed to measure innate and adaptive responses in humans are often easily adaptable to rhesus macaques. Macaques of Indian origin are the best studied subspecies and multiple MHC alleles particularly those associated with the control of SIV replication such as *Mamu A01, B08* and *B17* (Loffredo et al., 2007b; Mothe et al., 2003; Pal et al., 2002; Yant et al., 2006) have been described and will be discussed in detail later. This has been extremely important for vaccine studies where animals with protective alleles can either be avoided or distributed evenly between vaccine and placebo groups to eliminate biased results. Immunodominant epitopes induced by vaccination can also be carefully monitored with rhesus MHC tetramers that are readily available from the NIH tetramer core facility or other commercial sources.

A major limitation to performing research with Indian rhesus macaques is the availability of animals, especially specific pathogen-free animals (Cohen, 2000). Export of these animals from India was banned in 1978, leaving breeding colonies the main source for research

animals (Cohen, 2000). Vaccine studies generally require large numbers of animals to determine statistically significant differences between vaccinated animals and controls. For this reason the demand for Indian rhesus macaques has outpaced the supply, and researchers have sought various alternatives. One alternative that is gaining popularity is the use of rhesus macaques of Chinese origin that are imported from China. The subspecies of Chinese rhesus macaques infected with the commonly used SIV variants: SIVmac251 or 239 was initially considered a less relevant model due to lower plasma virus loads(Joag et al., 1994; Ling et al., 2002; Marthas et al., 2001) differences in T cell responses (Marcondes et al., 2006) and the slower disease course (Trichel et al., 2002) compared to Indian rhesus macaques. However most of these studies used SIV strains that had been expanded and adapted to grow in Indian rhesus macaques. Indeed when SIVmac251 was passaged in vivo in Chinese rhesus macaques, the resulting virus stock yielded virus loads similar to those in Indian rhesus macaques (Burdo et al., 2005). This experience emphasizes that the choice of virus, how it is prepared or passaged, and the macaque species and even sub-species can have a profound impact on the outcome of the infection and should therefore be carefully considered when testing vaccines.

SIV/SHIV infection of cynomolgus macaques is an additional model of HIV infection. Currently their use in research is much more limited than that of rhesus macaques, but several factors are increasing their use in HIV vaccine studies. These include the recent completion of their genome sequence (Higashino et al., 2012), advances in the ability to ascertain their MHC type and their availability relative to other non-human primates.. Similar to Chinese rhesus macaques, cynomolgus macaques infected with SIV/SHIV also demonstrate reduced virus loads, CD4 T cell loss and a slower disease course when compared to Indian rhesus macaques (Reimann et al., 2005). However, high virus loads and disease progression can be obtained when virus is adapted to cynomolgus monkeys (Borsetti et al., 2008). A population of cynomolgus macaques found on the Island of Mauritius may be of particularly use in HIV vaccine research. This population descended from a small group of monkeys and thus have low MHC diversity: greater than half of the of animals have the MHC 1 alleles *Mafa-B*430101, Mafa-B*440101* and *Mafa-B*460101* (Krebs et al., 2005). This MHC homogeneity reduces variability between animals after vaccination and allows better comparisons of vaccine regimens. Furthermore, since variation is reduced within the group, fewer animals are needed to obtain statistically significant results. It should be noted, however, that cynomolgus macaques of Chinese or Vietnamese origin, unlike those of Mauritian origin, have heterogenous MHC alleles, so the origin of cynomolgus macaques should be determined when planning HIV vaccine studies.

Interest in pig-tail macaques (*Macaca nemestrina)* was initially sparked by the fact that they can be infected with HIV-1(Agy et al., 1992). However, most animals with this type of HIV experience only minor changes in CD4 T cell count and transient viremia (Frumkin et al., 1993); in addition, in this case in vivo passage does not increase pathogenicity (Agy et al., 1997). In contrast, pigtail macques do support robust replication of pathogenic strains of HIV-2 and possibly other HIV isolates (McClure et al., 2000). This is partially explained by the presence of a deletion in the TRIM 5 gene (Brennan et al., 2007), a host restriction factor present in most Old World primates to be discussed later. Despite the fact that HIV-2 induces pathogenic changes in pigtail macaques, SIV or SHIV viruses are typically used to challenge vaccinated animals. Vaccine research in pigtail macaques has advanced with the characterization of their MHC alleles and the identification of Mane-A10, an immunodominant Gag epitope associated with lower SIV viral loads (Smith et al., 2005a); nevertheless these macaques are the least commonly used macaques in HIV vaccine studies..

Challenge Virus

The two main outcomes used to evaluate vaccine efficacy are prevention of HIV transmission and control of virus replication. Animal models also use these two virologic outcomes as measurements of efficacy. Selecting the 'appropriate virus' to use in a vaccine study is extremely important, as a virus that replicates poorly may be easily controlled by a vaccine-induced immune response causing an over-estimation of vaccine efficacy, whereas a virus that is overtly pathogenic may overwhelm any immune system and cause an underestimation of vaccine efficacy.

Since the ultimate goal is an HIV vaccine, using HIV as the challenge virus is a natural first choice. This would potentially allow the same immunogens that are to be used in humans to be tested in non-human primates. Early studies tested vaccine candidates by infecting chimpanzees with HIV-1(Boyer et al., 1997; Fultz et al., 1992; Girard et al., 1991; Girard et al., 1997) or macaques with HIV-2 (Andersson et al., 1996; Franchini et al., 1995; Looney et al., 1998; Myagkikh et al., 1996) but the lack of persistent virus replication, CD4 loss and disease progression makes HIV infection of primates a poor vaccine model.

The creation of SIV/HIV chimeras called SHIVs was greeted in the HIV vaccine field with much enthusiasm. SHIVs typically have the env, tat, rev and vpu of HIV while the remaining genes are from SIV. The SIV genetic backbone enables persistent replication and pathogenic SHIVs to be developed by passaging, with SHIV89.6p being the most extensively used (Reimann et al., 1996). As the envelope sequence is from HIV, SHIV's have been used to evaluate the ability of vaccine induced or passively transferred neutralizing antibodies to interfere with envelope binding/entry and thus prevent SHIV infection(Hessell et al., 2009; Lakhashe et al., 2011). The pathogenic SHIVs created for vaccine usage often used the SIVmac239 backbone and HIV *env* genes that express the chemokine receptor CXCR4 or both CXCR4 and CCR5 receptors to enter cells. These viruses cause profound depletion of naïve T cells during the acute phase and rapid disease progression unlike what is typically seen in SIV or HIV infections(Harouse et al., 1999; Joag et al., 1996). In order to better model HIV infection, pathogenic SHIVs that express the CCR5 receptor for entry were created(Nishimura et al., 2010), as most HIV infections are established with CCR5-using viruses. This second generation of SHIVs target memory CD4 cells that express CCR5 and are abundant in the gastrointestinal tract similar to HIV and SIV. To date SHIVs containing HIV envelopes from Clades A, B, C and E isolates have been created(Sina et al., 2011), allowing for the selection of a SHIV challenge or preclinical model that best fits the circulating HIV clade of the putative patient population desired for clinical trials.

Despite the many advantages of SHIVs, the intriguing disadvantage is their apparent susceptibility to vaccine induced immune control(Feinberg and Moore, 2002). This is probably best demonstrated by Adenovirus vaccine vectors expressing SIV Gag, which when tested in SHIV models demonstrated good control of virus replication(Shiver et al., 2002). However, when similar vaccines were tested in SIVmac239 models, no protection from infection or sustained control of virus replication was observed(Casimiro et al., 2005; McDermott et al., 2005). These findings were highlighted in 2008 when the results of the Merck Step trial were released(Buchbinder et al., 2008). This trial vaccinated individuals with Ad5 expressing HIV gag/pol/nef and failed to prevent HIV transmission or reduce virus replication in vaccinees. The results of the Step trial were vastly different from the preclinical SHIV models using Ad5 gag, but have been recapitulated recently by studies vaccinating animals with Ad5 gag/pol/nef and challenging with SIVmac251 or SIVsmE660 delivered by a mucosal route (Qureshi et al., 2012; Reynolds et al., 2012).

The discovery of SIV infection of macaques and its ability to cause an AIDS-like disease(Daniel et al., 1985; Letvin et al., 1985), led many investigators to select SIV infection of rhesus macaques as their challenge model for testing HIV vaccines. SIVmac251 is probably the most stringent challenge to date. It was isolated from a rhesus macaque and replicates robustly, with peak virus loads 2–3 logs higher than observed during HIV infection of humans(Haase, 2011). In addition, SIVmac251 causes severe depletion of mucosal CD4 T cells and is very difficult to neutralize, similar to some primary HIV strains. While several vaccines tested in this model system can reduce peak viremia, few cause persistent long lasting control of virus replication. There are several stocks of SIVmac251, each a heterogeneous swarm of viruses that can transmit multiple variants across mucosal tissues(Keele et al., 2009). The infectivity and also virologic properties differ between virus stocks, making comparisons across vaccine regimens or between studies difficult. SIVmac239 is a molecular clone related to but not derived from SIVmac251 and has similar pathogenic properties to SIVmac251. The clonality of SIVmac239 makes it the choice of many vaccine researchers as it may reduce the variability of the challenge outcome allowing for a better comparison of vaccination regimens. However, the main disadvantage to SIVmac239 is also its main advantage, as one can question the wisdom of testing a vaccine with a clonal virus when vaccinated individuals need to be protected against the swarm of HIV viruses in circulation.

SIVs isolated from sooty mangabeys (SIVsm) and in particular SIVsmE660 are being increasingly used in HIV vaccine studies. SIVsmE660 is an uncloned pathogenic virus isolate and stocks of this virus contain multiple heterogeneous variants similar to SIVmac251. The env diversity of SIVmac251 and SIVsmE660 has been likened to that observed in an individual infected with HIV for 1–2 years(Keele et al., 2009). Most vaccine studies have been performed with vaccine immunogens that are either identical or very closely matched (homologous) to the challenge virus. However, to mimic HIV infection, researchers are opting for heterologous challenges. SIVsmE660 shares approximately 82% identity to SIVmac251(Shedlock et al., 2009), so selecting one as the vaccine immunogen, and the other as the virus challenge, creates a model that approximates the sequence variability between some HIV clades. SIVsmE660 is also more sensitive to neutralization than SIVmac251, allowing for its utility in vaccine studies aimed at inducing neutralizing antibodies. However its ease of neutralization and sensitivity to rhesus TRIM5 alpha needs to be accounted for when evaluating vaccine studies. This was demonstrated in one study where a significant protection from infection was observed in vaccinated macaques challenged with SIVsmE660, while similarly vaccinated animals challenged with SIVmac251 were all infected(Letvin et al., 2011).

Route, Mode and Dose of Virus infection

Most HIV infections are established across mucosal surfaces, making the cervico-vaginal, penile, oral or rectal epithelia the site of virus entry and their underlying tissues the likely site of virus expansion and dissemination. In order to similarly model transmission, non-human primate challenge models using vaginal, rectal, oral and penile applied cell-free virus have been developed(Keele and Estes, 2011). Intra-rectal challenge is the most used mucosal challenge model as well-titered stocks show reproducible rates of virus acquisition, and males are more readily available than sexually mature females, that are also used for breeding. Modeling vaginal transmission of HIV has proven much more problematic. There is often considerable variability in the rate of virus transmission and despite multiple challenges some naïve animals often do not become infected. This variability may be linked to hormone induced changes in the thickness of the vaginal epithelia, frequency of CD4 and CCR5 expressing target cells, microbial populations causing overt inflammation, changes in the pH, or varying amounts of mucus in the vaginal tract. Some investigators have chosen to

use hormone treatment with depot medroxyprogesterone to synchronize animals, but progesterone treatment severely thins the vaginal epithelia in macaques(Marx et al., 1996) and has many immunomodulatory effects. Conversely, carefully monitoring the menstrual cycle of animals, or using repeated weekly challenges over the course of 6–12 weeks so that animals are challenged multiple times at each phase of the cycle could explain or overcome some of the variation. In addition, antibiotic treatment to resolve bacterial vaginosis and reduce inflammation can be beneficial.

A penile model for SIV transmission was recently developed by immersing the penis into cell free virus, but this mode of transmission is much less efficient than vaginal exposure and requires higher doses of virus to establish the infection (Ma et al., 2011). This finding is consistent with epidemiological data in discordant monogamous couples where the rate of male to female HIV transmission was greater than female to male (Gray et al., 2001; Padian et al., 1997). The penile shaft and glans in macaques have been found to contain a full complement of immune cells and SIV-specific immune responses can be detected in the penile tissues (Rothaeusler et al., 2012). The macaque penile challenge model has been used in vaccine studies(Qureshi et al., 2012) but the recent observation that TRIM5 polymorphisms affect SIVsmE660 infectivity via the penile route(Yeh et al., 2011) indicate that that careful genotyping of animals, and evaluating the capacity of the virus stock to infect via the penile route is needed before vaccine studies are initiated.

It has now been well documented that during heterosexual HIV infection only one or a few viral variants are usually transmitted from donor to recipient(Derdeyn et al., 2004; Keele et al., 2008; Salazar-Gonzalez et al., 2008). Single variant infections can also be obtained using macaque models with SIV delivered via the penile, vaginal or rectal routes (Keele et al., 2009; Ma et al., 2011; Stone et al., 2010). In general, HIV sexual transmission is an inefficient process with a low per contact transmission rate(Royce et al., 1997), so mucosal challenges in macaques with a high virus dose and a 100% infectivity rate per exposure do not model HIV infection. Furthermore, in the intra-rectal SIV challenge model the dose of the virus inoculum significantly affects the number of transmitted variants, with higher doses associated with multiple SIV variants(Liu et al., 2010). Thus, the field has shifted to using repeated low doses of viruses to assess vaccine efficacy. In this model, virus is atraumatically applied to the mucosa every 7–14 days with a goal of achieving an infectivity rate of 20–40% per exposure in unvaccinated controls. The ability of the vaccine to alter the rate of virus acquisition can then be determined. Furthermore, in an attempt to unravel protective vaccine-induced immune responses, the rate of acquisition or number of challenges to attain SIV infection, can be correlated with immunologic parameters. Several vaccines have demonstrated partial efficacy using this model(Barouch et al., 2012; Hansen et al., 2011; Lai et al., 2011; Xiao et al., 2012). Interestingly antibodies or the combination of antibodies and T cells appear to correlate with either protection from or a delay in virus acquisition in several vaccine strategies(Barouch et al., 2012; Lai et al., 2011; Xiao et al., 2012). These findings are consistent with the RV144 Thai Trial where antibodies to gp120 were also found to be a correlate of a reduced risk of HIV transmission(Haynes et al., 2012). In contrast, cell mediated immune responses in repeated low dose studies, appear to be related to virus suppression once the infection is established(Barouch et al., 2012; Hansen et al., 2011). The challenge dose also has profound effects on the viral kinetics, innate immune responses and the elapse of time(Liu et al., 2010). We have also observed significantly different vaccine outcomes when vaccinated animals were challenged with either a single high dose or repeated intermediate doses of virus. Protection from SIV infection or high virus loads was only observed in animals challenged with intermediate virus doses (Vaccari et. al. manuscript in submission). These findings have implications for HIV vaccines where a vaccine may be more effective in a low risk population, for example in populations exposed via heterosexual transmission, and less effective in a high risk population, for

example in populations exposed to homosexual transmission or drug usage.. High virus doses that transmit multiple variants likely overwhelm the immune system as virus expansion, aberrant immune activation and apoptosis may outpace the expansion of vaccine-induced immune responses and compromise their functionality.

The mucosal repeated low dose challenge macaque model described above has an infectivity rate many times greater than observed during HIV transmission(Royce et al., 1997) and the quantity of virus used is higher than reported in vaginal secretions or semen(Baeten et al., 2011; Pilcher et al., 2007). Thus, an argument could be made for further decreasing the challenge dose; however this could allow for an overestimation of vaccine efficacy in the animal model that then does not translate to protection in humans. In addition, due to the variability inherent in repeated low dose mucosal challenges, vaccinologists require larger group sizes to attain statistical power and reducing the infectivity will proportionally increase the length of the study and also the cost.

Most vaccine and pathogenesis studies tested in macaques are performed with cell-free virus; however, cell-associated virus transmission from infected leukocytes in seminal fluid or vaginal secretions could be a significant mode of HIV transmission. Cell-to-cell transfer of HIV in culture is extremely efficient (Bomsel, 1997; Tan et al., 1993) and in-vivo infected cells may adhere to epithelial surfaces or migrate through the epithelial barrier and transfer virus to target cells(Anderson, 2010). In addition, it is likely that infected cells protect virions from the low pH, mucus trapping and antiviral defenses in the mucosa. The first non-human primate models of cell-associated HIV/SIV infection were reported in 1998(Girard et al., 1998; Sodora et al., 1998). These studies showed that while intravenous challenge with cell-associated virus was extremely efficient and required very few cells, intra-vaginal challenge with such virus was much less efficient(Sodora et al., 1998). Recently repeated challenge models with SIV-infected splenocytes or peripheral blood cells applied to the vaginal tract of macaques have been developed. Genital ulcers(Kaizu et al., 2006; Weiler et al., 2008) or progesterone treatment to thin the epithelium(Salle et al., 2010) can facilitate infection; however, a standardized repeated low-dose challenge model that does not require artificial epithelial disruption or thinning would better recapitulate HIV infection and may be important to the vaccine field. Vaccine-induced protection from cell-associated virus may differ from what is needed to protect from cell-free virus, reinforcing the need for relevant models of cell-associated HIV transmission.

MHC haplotype/Trim5α/cyp-mediated resistance to viral challenge

Numerous observations have shown that host genetic factors play important roles in disease progression in human immunodeficiency virus type 1 (HIV-1) infection (O'Brien and Moore, 2000; Rowland-Jones et al., 2001). The major histocompatibility complex (MHC) is one of the critical factors associated with susceptibility or resistance to HIV-1 infection (de Sorrentino et al., 2000). Moreover, innate restriction factors such as Trim5α/cyp, APOBEC3G, or Tetherin, can inhibit HIV replication at different stages of infection (Mogensen et al., 2010). These intrinsic genetic/cellular hindrances of viral replication represent a natural barrier against HIV infection. When using non-human primates (NHP) as a model to develop HIV vaccines, the allelic diversity of these restriction factors may have an impact on the susceptibility of the macaques to various viruses and thus influence the outcomes of the studies. Here, we briefly review these factors to provide guidelines for NHP experimental design.

1. MHC, mamu B*08, B*17, A*01

MHC class I glycoproteins (MHC-I) are expressed on all nucleated cells, and their function in cells involved in immunologic responses is to present foreign peptides of intracellular

origin to cytotoxic T cells, which are then activated to cause the destruction of infected cells (Gallimore et al., 1995). The MHC-I alleles have consistently been reported to impact HIV viral setpoint and the rate of disease progression. Whole-genome association studies demonstrated the central role of HLA class I in controlling HIV-1 infection (Fellay et al., 2007; Pereyra et al., 2010). For example, HIV-infected HLA-B*27 or B*57 –positive individuals can mount strong CTL responses and show better viral control (Feeney et al., 2004; Leslie et al., 2004).

The Rhesus macaque MHC genes, in contrast to the highly polymorphic genes of the major MHC class I genes in humans (*HLA-A*, *HLA-B*, and *HLA-C*), uses an alternative strategy: express multiple dominant *Mamu-A* and *Mamu-B* transcripts per chromosome with high expression levels. Rhesus macaques may possess one to three *A* and two to four *B* locus genes (Boyson et al., 1996; Urvater et al., 2000). In another words, rhesus macaques are characterized by not only alternative gene combinations, but also diversity in gene number to ensure that different individuals mount distinct responses against the same pathogen (Otting et al., 2005). Thus, compared to the human lymphocyte antigen (HLA) complex, the macaque MHC region encodes many more class I genes.

In common with human MHC alleles, certain monkey MHC alleles are associated with successful control of SIV infections:

Mamu-A*01—*Mamu-A*01* was significantly associated with lower set-point viral load and longer survival time after infection with SIVmac251 (Muhl et al., 2002). Pal et al. showed that *Mamu-A*01* may positively influence the results of vaccine studies against SIVmac251 (Pal et al., 2002). Both the presence of the Mamu-A*01 genotype and vaccination of rhesus macaques with ALVAC-SIV-gag-pol-env contributed to the restriction of SIVmac251 replication during primary infection, preservation of $CD4^+$ T cells, and delayed disease progression following intra-rectal (but not intravenous) challenge of the animals to SIVmac251(Pal et al., 2002). In addition, a significant delay in $CD4^+$ T cell loss was observed in Mamu-A*01-positive macaques (Pal et al., 2002). IN contrast, Mamu-A*01-positive macaques did not significantly restrict primary viremia of intravenous or intra-rectal challenge with SHIV89.6P or SHIVKU2 (Pal et al., 2002). These findings contrast to to those of Zhang et al. who observed that pathogenic SHIV 89.6P- infected Mamu-A*01-positive rhesus monkeys, exhibited significantly delayed disease progression (Zhang et al., 2002). The delay corresponded not only to the above mentioned Mamu-A*01-restricted dominant CTL response but also to a lower viral load in lymph nodes and, importantly, to minimal destruction of LN structure during early infection (Zhang et al., 2002). To determine the effect of different MHC class I alleles on viral replication, Mothé et al screened eight common MHC class I alleles in 53 SIVmac239-infected animals: *Mamu-A*01*, *Mamu-A*02*, *Mamu-A*08*, *Mamu-A*11*, *Mamu-B*01*, *Mamu-B*03*, *Mamu-B*04*, and *Mamu-B*17* (Mothe et al., 2003; O'Connor et al., 2003). Their studies extended the finding of association of Mamu-A*01 with enhanced control of viral replication from SIVmac251 to SIVmac239 replication. Moreover, they demonstrated a dramatic association between Mamu-A*01 and -B*17 expression and slowed disease progression. In addition, they showed that two epitopes restricted by Mamu-A*01 and one epitope restricted by Mamu-B*17 were the dominant acute-phase CTL responses in animals expressing these alleles (O'Connor et al., 2003).

Mamu B*08—Mamu B*08-positive macaques were found to be over-represented among elite controllers (EC) (i.e., individuals exhibiting greatly increase ability to control challenge with SIV): 38% of ECs were Mamu-B*08-positive compared to 3% of progressors (Loffredo et al., 2007b). Subsequent studies on ECs found evidence for selective pressure mediated by Mamu-B*08-restricted $CD8^+$ T cells in all of the newly identified epitopes in a

cohort of SIVmac239-chronically infected macaques (Loffredo et al., 2007a). The same group found that Mamu-B*08-restricted CD8+ T-cell responses dominated the acute phase and accounted for 23.3% to 59.6% of the total SIV-specific immune responses. Additionally, the ECs mounted strong and broad CD8+ T-cell responses against several epitopes in Vif and Nef (Loffredo et al., 2008). Overall, 50% of Mamu-B*08-positive Indian rhesus macaques control SIVmac239 replication and became an EC. A study aimed at defining a detailed peptide-binding motif revealed that despite substantial sequence differences between Mamu-B*08 and human protective allele HLA-B*2705, the peptide-binding repertoires of these two MHC class I molecules share remarkable similarity (Loffredo et al., 2009). All Mamu-B*08-restricted epitopes contain an R at the position 2 primary anchor and 10/? also possess either R or K at the N terminus (Loffredo et al., 2009). The association of Mamu-B*08 with a protective human MHC class I allele implicates $CD8^+$ T cells and/or natural killer cells in the ability of this MHC molecule to associate with control of viral replication. This possibility is inf in fact supported by a study of escape point mutations of eight Mamu-B*08-restricted $CD8^+$ T cell epitopes which confirmed that these epitope-specific $CD8^+$ T cell responses may play a role in establishing the control of viral replication in Mamu-$B*08^+$ macaques (Valentine et al., 2009).

Mamu B*17—In rhesus macaques, Mamu-B*17 is another MHC allele that is associated with reduced HIV replication and is over-represented in ECs. An analysis of 181 SIVmac239-infected rhesus macaques revealed that Mamu-B*17 was associated with a 26-fold reduction in plasma virus concentrations (Yant et al., 2006). The Mamu-B*17-restricted $CD8^+$ T cell repertoire is focused primarily on a limited number of epitopes, akin to the protective effects described for HLA-B*57 in HIV-infected individuals (Wu et al., 2011). Besides the dominant epitopes in Mamu-B*17(+) SIVmac239-infected rhesus macaques, which spontaneously controlled viral replication, strong $CD8^+$ T lymphocyte responses against a cryptic epitope, RHLAFKCLW, were identified (Maness et al., 2007). cRW9-specific $CD8^+$ CTL selected for viral variation *in vivo* and effectively suppressed SIV replication *in vitro*, suggesting that they might play a key role in the SIV-specific response (Maness et al., 2007).

Besides the above-mentioned protective alleles in rhesus macaques, in pigtail macaques, animals with Mane-A*10(+) have been shown to have lower set point SIV levels than Mane-A*10(−) animals (Fernandez et al., 2005; Smith et al., 2005b).

2. Trim5α/cyp, APOBEC3G and other innate factors

It is known that HIV-1 infects humans and chimpanzees but not Old World monkeys such as the rhesus macaques (Rh) and cynomolgus macaques (CM). The observation that resistance against HIV-1 infection was dominant in heterokaryons between human and old world monkey cells suggested the presence of inhibitory factors against HIV-1 infection in old world monkey cells (Munk et al., 2002). In 2004, Stremlau et al. first identified Trim5α as the host antiviral factor in Old World monkeys (Stremlau et al., 2004). TRIM5 α is a tripartite motif (TRIM) protein composed of RING, B-box 2, coiled-coil, and B30.2(SPRY) domains (Stremlau et al., 2005). The major determinant of anti-HIV-1 potency is the B30.2(SPRY) domain (Stremlau et al., 2005). Both Rh and CM TRIM5α restrict HIV-1 infection but fail to restrict SIV isolated from a macaque monkey. Further studies confirmed that human and simian Trim5α was responsible for the poor species-specific retroviral infectivity in Old World monkeys (Hatziioannou et al., 2004; Keckesova et al., 2004; Perron et al., 2004; Yap et al., 2004).

Trim5α demonstrated different levels of resistance to different retroviral infections between human and macaques and among different species of macaques (species-specific restriction,

shown in table 1). For example, rhesus monkey TRIM5 more potently blocks HIV-1 infection than human TRIM5α. Within and between primate species, SIV isolated from sooty mangabeys (SIVsm) and SIV isolated from African green monkeys (SIVagm) replicate in their natural hosts (VandeWoude and Apetrei, 2006) and $CD4^+$ human cells. SIVmac evolved from SIVsm in captive macaques, and replicates efficiently in Rh (Himathongkham and Luciw, 1996; Shibata et al., 1995) and CM (Akari et al., 1996) as well as in human $CD4^+$ cells but not in African green monkey cells. Sequence comparison between Trim5α alleles suggested that a variable region in the SPRY domain might be responsible for the variability of susceptibility of SIV (Stremlau et al., 2005). This possibility is consistent with evidence that the SPRY domain interacts directly with the incoming viral capsid and thus interrupts the uncoating events required for the continuation of reverse transcription (Kootstra et al., 2003).

As Trim5α may influence vaccines and pathogenesis studies, it is important to be aware the existence of intra-species variations in the Rh Trim5α, which could influence the susceptibility to viral infection, and in those animals where infection has been established, the set-point of viral loads (Newman et al., 2006; Sawyer et al., 2005; Song et al., 2005). The PRYSPRY sequence of the B30.2 domain of the Trim5α is highly variable (Kaiser et al., 2007). Newman et al. identified six alleles of Rh-Trim5α with different restriction profiles (Wilson et al., 2008a); for example, Mamu 1 and 3 alleles restrict HIV-1, 2, but not SIVmac239; while Mamu 4 and 5 alleles restrict HIV-1, but not HIV-2 and SIV mac239. Lim et al. independently reported 11 Trim5α alleles based on 339TFP341-to-Q polymorphisms (Lim et al., 2010a) and found that natural variation in the TRIM5α B30.2 (SPRY) domain influenced the efficiency of SIVmac capsid binding and the in vitro susceptibility of cells from the monkeys to SIVmac infection (Lim et al., 2010b). Rh with a Q allele were associated with higher levels of plasma viral load, and more rapid progression to AIDS (Lim et al., 2010a). Therefore, it is necessary to perform Trim5α genotyping when using SIVsm. However, Fenizia et al, recently reported that Trim5α did not affect the susceptibility to SIVmac251 and that the Gag sequences of SIVmac251 and SIVmac239 stocks have mutations that interfere with their binding to TRIM5α (Fenizia et al., 2011).

Soon after the discovery of Trim5α in 2004, a fusion protein composed of the N-terminal half of Trim5α, RING, B-box2, coiled-coil, and cyclophilin A (CypA), which was encoded by a retrotransposed cDNA to replace PRYSPRY, was identified in owl monkeys (Nisole et al., 2004; Sayah et al., 2004). Initially, the expression of TRIMcyp was thought to be restricted only to owl monkeys, but later studies found that the cyp insert also exists at least in three macaques: Rh, CM, and Pigtail (Pt). The common ancestor of these monkeys must have had the authentic cypA, which has been shown to restrict HIV-1, but only weakly HIV-2 (Price et al., 2009a; Virgen et al., 2008). Mutations in the monkeys either enhance or decrease the antiviral activity of TRIMcyp against HIV-1 or 2 (Price et al., 2009a). The rhesus TRIMCyp is encoded by a single, but common, allele (Mamu7) of the rhesus TRIM5 gene. The antiviral specificity of the rhesus TRIMCyp is distinct, restricting infection of HIV-2 and feline immunodeficiency virus but not HIV-1 (Wilson et al., 2008b). Neither M. nemestrina nor M. fascicularis TRIMCyp could restrict HIV-1 or SIVmac in an in vitro infectivity assay (Brennan et al., 2008). On the other hand, TRIMcyp frequency in CM was higher than in Rh, and TRIMcyp frequency is higher in eastern Asia than in Western Aisa (Dietrich et al., 2011; Saito et al., 2012). As to SIV infection, Rh TRIMcyp failed to restrict SIVmac239 (Brennan et al., 2008; Wilson et al., 2008b), but not SIVsm (Kirmaier et al., 2010). Therefore, to establish a monkey model for the study of HIV-1/AIDS, depending on the challenge virus and the species used in the study, Trim5α and/or TRIMcyp are factors that need to be considered.

Besides Trim5α, other restriction factors capable of suppressing HIV/SIV replications include APOBEC3G, and Tetherin (Mogensen et al., 2010). These factors can inhibit HIV replication at different stages of the viral replication cycle. However, HIV has evolved strategies to overcome these factors, i.e. Vif for APOBEC3G, Vpu/nef/env for tetherin. APOBEC3G polymorphisms have been associated with rate of disease progression (Sobieszczyk et al., 2011). HIV-1 vif can potently suppress human APOBEC3G, but not Rh APOBEC3G. This might partially explain the restriction of HIV-1 replication in monkey cells. Macaque APOBEC3G–associated viral control has been observed in several SIV vaccine studies (Sui et al., 2011; Sui et al., 2010; Wang et al., 2009; Wang and Lehner, 2011). Tetherin, also called BST2 or CD317, is an interferon-inducible membrane protein, which interferes with the detachment of viral particles (Neil et al., 2008; Van Damme et al., 2008). Another recently identified host factor is SAMHD, whose activity was confined to differentiated uncycling cells like macrophages and mDC (Hrecka et al., 2011; Laguette et al., 2011). Vpx can counteract SAMHD1. As HIV-1 lacks Vpx, it is not clear whether monkey SAMHD1 restricts HIV-1 replication.

Protective immunity to reduce viral acquisition and viral load

The ultimate goal of an HIV vaccine is to achieve sterilizing immunity, which will completely prevent infection. In reality however, what has been reported, and will likely be achieved in the foreseeable future, is a partial protection from infection and vaccine-induced control of virus replication. While less desirable, a substantial reduction in viral replication will decrease the risk of progression to AIDS and virus transmission. To test HIV-1 vaccine efficacy, we need an animal model that accurately recapitulates human infection, where the immune correlates of protection can be determined and this information used to improve HIV vaccines. In this regard, NHP models have proven to be invaluable for the following reasons:.

1. Use of NHP as a model to measure mucosal immunity

In as much as over 85% percent of HIV transmission is mucosal, primarily via either the genital or the rectal route, it is critical to develop strategies to prevent HIV mucosal transmission. A growing body of evidence suggests that mucosal immunity plays an intimate and fundamental role in HIV-1 transmission and disease development. Macaque models have been widely used to demonstrate the early events during SIV infection in the genital mucosa, and work from Reynolds et al. clearly showed that natural mucosal SIV-specific CTL are “too little and too late” (Reynolds et al., 2005). Therefore, it is generally accepted that HIV-1 vaccines may need to elicit potent mucosal immune responses, which might include mucosal mucosal IgA, IgG, SIV-specific CTL and the activation of NK and NKT cells.

Effective induction of mucosal immunity often occurs in the mucosa-associated lymphoid tissues, so mucosal sampling and measurements of mucosal immune responses are essential and can be optimized in macaques. However, intensive sampling of mucosal tissues in humans is less realistic. Longitudinal sampling of blood, lymphoid, gastrointestinal and bronchial tissue is now routinely done in vaccine and pathogenesis studies in macaques. Mononuclear cells obtained from lung lavage, and vaginal or rectal pinch biopsies have been characterized using multi-parameter flow cytometry to compare the frequency and function of mucosal immune cells. Examples of some of the markers used to evaluate the phenotype of T, B, NK and NK T cells in blood and the gastrointestinal tract in macaques are presented in Figures 1 and 2. Similarly, mucosal secretions can be obtained using Weck cel or cotton swabs and then used to determine the class, titer and avidity of antibodies at the site of virus infection. The careful evaluation of vaccine-induced vaginal and rectal responses in

macaque models may elucidate the quality and quantity of mucosal immune responses needed to prevent SIV/HIV mucosal transmission.

2. Use of NHP as a model to test which component of the various HIV proteins should be included in a vaccine to induce protective immunity

One important consideration in the development of an HIV-1 vaccine is to define the vaccine composition and the contributions of each component to vaccine efficacy. The generation of virus-specific T cell responses has been the goal of HIV vaccine development, as sterilizing immunity through the induction of neutralizing antibodies is not currently feasible. Several studies were performed at the population level to define the selection of T cell antigens for an HIV vaccine. Kiepiela et al. showed in a cohort of 578 HIV-infected individuals from South Africa that only Gag-specific $CD8^+$ T cell responses were associated with lowering viremia, while Env-specific and Accessory/Regulatory protein–specific $CD8^+$ T cell responses were associated with higher viremia (Kiepiela et al., 2007). Similarly, Ranasinghe et al. conducted a comprehensive analysis of HIV-specific $CD4^+$ T cells in 93 subjects at different stages of HIV infection and found that $CD4^+$ T cell responses targeting Gag were robustly associated with lower levels of viremia and Gag/Env ratios were a potent marker of viral control, with a high frequency and magnitude of Gag responses and low proportion of Env responses associated with effective immune control (Ranasinghe et al., 2012). However, as these authors pointed out, we should also be aware that these data, which were obtained from cohorts of HIV-infected individuals, might have different implications for their role in controlling natural chronic infection versus their potential role as effective immunogens in an HIV vaccine (Kiepiela et al., 2007; Ranasinghe et al., 2012). Thus, these data suggest the possibility that such responses may mediate successful control of viremia when vaccinated HIV-negative individuals subsequently become HIV infected. However, the NHP model is invaluable to determine prospectively which antigen should be included in an HIV vaccine.

So far, the NHP model has not provided a consistent answer. Some NHP models suggested the potential for Env vaccination to enhance SIV replication and disease (Staprans et al., 2004), whereas in a SHIV89.6 challenge model, Amara et al. showed that inclusion of Gag-Pol, in addition to Env, were important for persistent virus control and protection against $CD4^+$ cell loss (Amara et al., 2002). Other studies using NHP also suggested that non-gag proteins, in addition to Gag, function as $CD8^+$ T cell targets and therefore contributed to the control of SIV in vaccinated animals (Casimiro et al., 2005; Hel et al., 2006; Wilson et al., 2006). Therefore correctly extrapolating data from NHP vaccine studies to humans is important. As discussed above, the genetic background of the macaques, homologous vs heterologous viral challenges, etc., all play important roles in determining the outcomes.

3. Use of NHP as a model to evaluate/optimize molecular adjuvants to induce better innate and adaptive immune responses in NHP for subsequent human trials

The efficacy of an HIV vaccine can be improved by using adjuvants that stimulate antigen-presenting cells (APCs), especially dendritic cells (DCs), which play a crucial role in immune responses against infections. DCs serve as a bridge between innate and adaptive immunity and adjuvants act in part by signaling through Toll-like receptors (TLRs) on DCs to trigger adaptive immune responses in both $CD4^+$ and $CD8^+$ T cells that recognize antigenic peptides presented by MHC molecules on those DCs. Studies using TLR agonists as potential adjuvants for HIV vaccine development are under way. Animal models are important tools to test novel adjuvant formulations. However, in mice, a commonly used animal model, there are important differences in the TLR expression patterns on APCs as compared to humans. For example, in humans, B cells and pDCs are the only immune cells that are known to express TLR9 and thus capable of activation by CpG

oligodeoxynucleotides (ODNs) (Krug et al., 2001), whereas in contrast, TLR9 is broadly expressed on all major DC subtypes (pDCs and mDCs) as well as on B cells, macrophages and monocytes in mice (Edwards et al., 2003; Hemmi et al., 2000). Moreover, in humans, functional TLR7 and 8 are found on B cells, pDCs and mDCs and on monocytes (Hornung et al., 2002; Jarrossay et al., 2001; Kadowaki et al., 2001; Krug et al., 2001), while in mice, TLR8 does not appear to be functional (Edwards et al., 2003). Therefore, direct extrapolation from mouse data to humans in this case could be misleading, and these differences make mouse models less suitable for testing these adjuvants for human translation. In this regard, based on their close relationship to humans, NHPs such as rhesus macaques are the best animal model. Indeed, work from Ketloy et al. clearly proved that NHPs share the same expression and functionality of TLRs with humans (Ketloy et al., 2008). Their detailed analysis showed that blood DC subsets of rhesus macaques expressed the same sets of TLRs (TLR3, 4, 7, 8 and 9) as those of humans but were substantially different from the corresponding mouse DC subsets (Ketloy et al., 2008). Additionally, TLR expression patterns in macaque mo-DCs, monocytes and B cells were also similar to those in humans. Overall, therefore, rhesus macaques are better animal models than mice for the evaluation of TLR ligands as adjuvants for the design of human vaccines. Several studies have already used TLR ligands as adjuvants in rhesus macaques (Sui et al., 2010; Verthelyi et al., 2002; Wille-Reece et al., 2005), and translation of these studies to the human setting should have a good foundation.

4. Understanding the difference of antibody repertories between NHP and human

The humoral immune response is one of the important arms of adaptive immunity for HIV vaccine development. Macaques have been intensively used as models for studying vaccine development and the induction and function of humoral responses induced by variety of vaccine platforms. Therefore, to know the extent of similarity between antibody repertoires of macaques and humans is important. On average, rhesus Ig VH, DH, JH, and CH gene segments share both a similar organization and greater than 90% sequence identity with their human counterparts (Andris et al., 1997; Bible et al., 2003; Helmuth et al., 2000; Link et al., 2005; Meek et al., 1991; Scinicariello et al., 2004). In rhesus and chimpanzee, the pattern of DH and JH gene segment utilization in the expressed repertoire was similar, although not identical, to humans (Link et al., 2005). However, the distribution of CDR-H3 lengths proved quite different in the adults of these three species: the rhesus repertoire of muCDR-H3 transcripts did not contain the longer hypervariable intervals that humans express; whereas the chimpanzee repertoire included more long CDR-H3 structures than the human repertoire. These differences in CDR length arise from differences in the somatic mechanisms of N addition and terminal nucleotide loss (Link et al., 2005). However, more sensitive sequencing techniques using naïve B cells is needed to advance our understanding of antibody repertoires in different species and how these differences affect the humoral response to specific antigens.

5. Use of NHP as a model to search for the correlates of protection

Identifying protective correlates is one major goal of HIV vaccine development. However, despite tremendous efforts, clear immune correlates of protection against viral acquisition and/or disease progression remain unknown. The paucity of successful HIV vaccine clinical trials makes it difficult to identify correlates of protection in humans. However, a validated macaque model can be used to determine if a potential immune correlate or surrogate found in humans is causally related to protection. A number of vaccine platforms have been tested in NHP models and some of them showed protection against viral acquisition and replication. Among these studies, correlates of protection have been identified. In this review, we summarize immune responses that were reported to be associated with protection from virus acquisition or high levels of virus replication and provide illustrative examples

for each type of immune correlate of protection that has been identified (Table 2). Cellular $CD4^+$ and $CD8^+$ T cell responses and humoral responses have all been implicated in control of SIV/SHIV replication in various experimental systems. However, validation of the animal models necessarily comes from human clinical trials, and to date while limited reduction of acquisition of infection has been found, no trial has reported significant vaccine induced control of HIV replication after infection. Thus, there remains a need to improve the animal model such that correlates in the animal model translate to humans.

Vaccine Candidates

Over the past 30 years several vaccine candidates have been evaluated for HIV. While live attenuated retroviruses are immunogenic, safety concerns including reversion and recombination preclude their use. Three of the most promising vaccine platforms are DNA, recombinant peptides or proteins and viral vectors. Proteins induce mainly humoral responses while peptides, DNA and viral vectors can induce both cell mediated as well as humoral responses. The immunogenicity and efficacy of these vaccine regimens alone or in combination with each other are being evaluated in various stages of pre-clinical animal studies as well as clinical trials in humans. Four phase III HIV vaccine clinical trials have been completed(Buchbinder et al., 2008; Flynn et al., 2005; Pitisuttithum et al., 2006; Rerks-Ngarm et al., 2009), but only one, the RV144 Thai trial showed significant efficacy (31.2%) (Rerks-Ngarm et al., 2009). The Thai trial vaccinated individuals with the canarypox vector ALVAC expressing HIV genes, in combination with the HIV-gp120 protein. The results of the RV144 Thai trial have invigorated HIV vaccine research and there is renewed interest in finding ways of improving the immunogenicity of ALVAC and other pox viral vectors that are known to be safe in humans. To illustrate the use of NHP models to mimic human clinical studies we will review pox viral vectors including ALVAC. Many examples exist of other vaccine platforms including adenovirus, DNA, peptides and proteins and some of these have been described in earlier sections, but we are limiting our detailed description to three pox viral vectors for the sake of space and brevity.

Pox viral vectors have many advantages including large genomes allowing for the insertion of multiple foreign genes, thermostability, and diminishing pre-existing vector immunity as global vaccinia vaccination was terminated in the 1970s following smallpox eradication. Attenuated pox viruses currently used in HIV vaccination strategies were derived by multiple passages in chick embryo fibroblasts or through deletion of virulence, host adaptive or immune evasion genes(Franchini et al., 2004; Pantaleo et al., 2010). In addition to ALVAC, the attenuated vaccinia strains Modified Vaccina Ankara (MVA) and New York Vaccinia virus (NYVAC) have been shown to be safe in immunocompromised macaques(Edghill-Smith et al., 2003; Stittelaar et al., 2001) and HIV infected humans(Cosma et al., 2003) and are being tested in clinical trials(Esteban, 2009).

ALVAC is the most extensively studied HIV vaccine pox vector. It has an abortive infection in primate cells(Taylor et al., 1995) but it does enter antigen presenting cells, induce maturation of dendritic cells (Yu et al., 2006), and stimulate a type 1 IFN responses(Harenberg et al., 2008). Several preclinical macaque studies with ALVAC expressing either HIV or SIV genes demonstrated the ability of ALVAC to stimulate cellular responses, and protect vaccinated animals from either virus infection or high virus loads(Andersson et al., 1996; Hel et al., 2002b; Myagkikh et al., 1996; Nacsa et al., 2004; Pal et al., 2002; Pal et al., 2006; Van Rompay et al., 2005). The humoral response induced by ALVAC is significantly improved or boosted by administering adjuvanted soluble envelope proteins(Pal et al., 2006). Macaque preclinical studies demonstrating utility of this ALVAC-prime, protein boost approach provided the groundwork for clinical trials with ALVAC and gp120(Andersson et al., 1996; Pal et al., 2002). ALVAC induces lower T cell

responses compared to many other viral vectors, so there was skepticism regarding moving this platform forward to phase III clinical trials. However, in-spite of low T cell responses, protective efficacy with ALVAC, similar to that of the RV144 Thai Trial, was also demonstrated in ALVAC vaccinated infant macaques using a repeated low dose oral challenge model(Van Rompay et al., 2005). This finding highlights the need to better characterize the immune response induced by ALVAC/gp120 vaccines. Specifically, little is known about the innate immune response triggered by ALVAC and how this innate response facilitates the development of CD4 helper T cells and antibodies that do not neutralize most primary SIV isolates. In addition, characterization of mucosal responses in terms of phenotype, function and duration following ALVAC vaccination is required. Measuring immune responses immediately following vaccination and at mucosal sites is difficult in humans, but these studies are underway in macaques and will greatly enhance our understanding of the immunogenicity of ALVAC.

As the RV144 Thai trial significantly protected some vaccinees from HIV infection, an in-depth analysis of correlates of reduced risk of HIV acquisition was performed. Envelope specific antibodies directed to the V1V2 region of gp120 were found to be an inverse correlate of risk(Haynes et al., 2012). The V1V2 region of gp120 is the binding site of some broadly neutralizing antibodies(Gorny et al., 2005; McLellan et al., 2011; Walker et al., 2009) and also binds to the $\alpha 4\beta 7$ integrin on CD4 T cells that can facilitate the infection of mucosal T cells(Nawaz et al., 2011). Interestingly, antibodies to the V1V2 region of gp120 with increased avidity were also observed in animals protected from a low dose mucosal SIVmac251 challenge (Pegu et. al J Virol in submission). Using macaque models one can directly test the protective efficacy of passively infused V1V2 antibodies and optimize vaccine strategies that induce them. Follow up analysis of the RV144 Thai Trial has recently demonstrated no long term clinical benefit of vaccination in HIV-infected vaccinees(Rerks-Ngarm et al., 2012). No virologic benefit or preservation of CD4 T cells was also observed in macaques challenged with repeated low doses of SIV (Pegu et. al J Virol in submission). Thus, the animal model closely mirrors the outcome of the RV144 Thai trial, and can be used to test multiple methods aimed at not only improving protective efficacy but also preventing disease progression should breakthrough infections occur.

NYVAC an alternate pox-virus vector, was created by deleting 18 genes from the Copenhagen vaccinia vaccine strain(Tartaglia et al., 1992). These included host range genes, and as a result replication is blocked at an early stage in human cells. The immunogenicity of NYVAC is similar to ALVAC in primates and both induce cell-mediated responses(Abimiku et al., 1995; Casimiro et al., 2004; Hel et al., 2002b) and have been shown to partially protect from infection or high virus load in HIV/SIV macaque models(Benson et al., 1998; Franchini et al., 1995; Myagkikh et al., 1996). However, unlike ALVAC, repeated vaccination with NYVAC induces vector specific immunity that can dampen the immune response to encoded genes. Enhanced B and T cell responses can be achieved by heterologous priming with DNA followed by boosting with NYVAC(Hel et al., 2001). This DNA/NYVAC regimen induces robust $CD4^+$ T cell responses with increased proliferative capacity in macaques(Hel et al., 2002a) and in humans as measured in phase 1 clinical trials(Harari et al., 2008; McCormack et al., 2008). Importantly, systemically administered NYVAC vaccination induces T cell responses in the vaginal and rectal lamina propria in macaque (Stevceva et al., 2002) and in the ileum and rectum in humans(Perreau et al., 2011).

Increased immunogenicity is likely to improve vaccine efficacy, so modified NYVAC vectors aimed at inducing better innate and adaptive responses have been created(Kibler et al., 2011; Quakkelaar et al., 2011). Replication competent NYVAC was made by the re-introduction of host range genes to permit replication in human cells. In addition the

removal of genes that block IFN pathways have demonstrated increased CD8 T cell responses in mice(Gomez et al., 2012). However, the protective efficacy of NYVAC and its ability to alter the clinical course of HIV infection remains unknown. Furthermore as antibodies were the correlate of protection from HIV in the RV144 Thai trial, a detailed characterization of the functional capacity of antibodies induced by NYVAC and how they compare to those induced by ALVAC is needed along with a comparison of efficacy in a repeated low dose mucosal challenge model in macaques.

The other vaccinia vaccine derivative that is being widely evaluated as an HIV vaccine candidate is MVA. MVA was attenuated by 570 passages on chicken embryo fibroblasts and its replication in human cells is blocked at the virion assembly stage, so there is expression of both early and late genes. MVA can infect human macrophages and dendritic cells, engaging toll like receptors (TLRs) and activating multiple signaling pathways and transcription factors including MyD88, IRFs, STAT1, NFκB, ultimately leading to the induction of chemokines, cytokines and increased antigen processing and presentation(Delaloye et al., 2009; Guerra et al., 2007).

As in the case of NYVAC, repeated immunization with MVA induces vector specific immunity that can reduce the recall response to the expressed antigen, so DNA priming followed by MVA boosting is often used. This dual or other combinatorial strategy with MVA have been shown to protect from infection or high virus load in many preclinical macaque models using SIV or SHIV challenges(Amara et al., 2001; Cox et al., 2012; Hanke et al., 1999; Manrique et al., 2009; Sui et al., 2010; Vaccari et al., 2008). Recently, using a repeated low dose mucosal challenge, a DNA prime-MVA boost regimen has also been shown to significantly delay SIV acquisition(Barouch et al., 2012; Lai et al., 2012). Intriguingly, delayed SIV infection was correlated with antibody responses while control of virus replication correlated with T cell responses. These results indicate that protective B and T cell responses can be induced by this vaccination strategy and methods aimed at increasing the immunogenicity in macaques may translate to a clinical benefit in humans.

Several phase I safety and immunogenicity clinical trials with DNA/MVA are in progress or have been completed and while they demonstrate good immunogenicity(Goepfert et al., 2011; Goonetilleke et al., 2006; Sandstrom et al., 2008) the relative efficacy of this strategy remains unknown. The addition of DNA encoding cytokines (IFNγ, IL-12, IL-2) or the deletion of genes such as C6L and the IL-18 binding protein in MVA show enhanced immunogenicity in murine(Falivene et al., 2012; Garcia-Arriaza et al., 2011) or primate models(Bertley et al., 2004; Manrique et al., 2008). Granulocyte-macrophage colony stimulating factor (GMCSF) has been tested in macaque models and been shown to increase B and T cell responses and protective efficacy or reduce SIV/SHIV viremia (Lai et al., 2011; Lai et al., 2007). Whether the protective immunity induced by ALVAC in humans is also induced by MVA remains to be determined. MVA induces a higher frequency of CD8 T cell response as opposed to the primarily CD4-inducing ALVAC. While a head-to-head comparison in a repeated low dose model in adult macaques has not been performed, in infant macaques, MVA induced higher env binding titers and T cell responses compared to ALVAC but failed to significantly reduce SIV acquisition(Van Rompay et al., 2005).

Macaque models are being used to directly compare these three promising HIV pox viral vectors as well as methods to improve the protective efficacy of each. Hopefully the results from these studies will help advance the ‘best’ vaccine candidates to HIV vaccine clinical trials.

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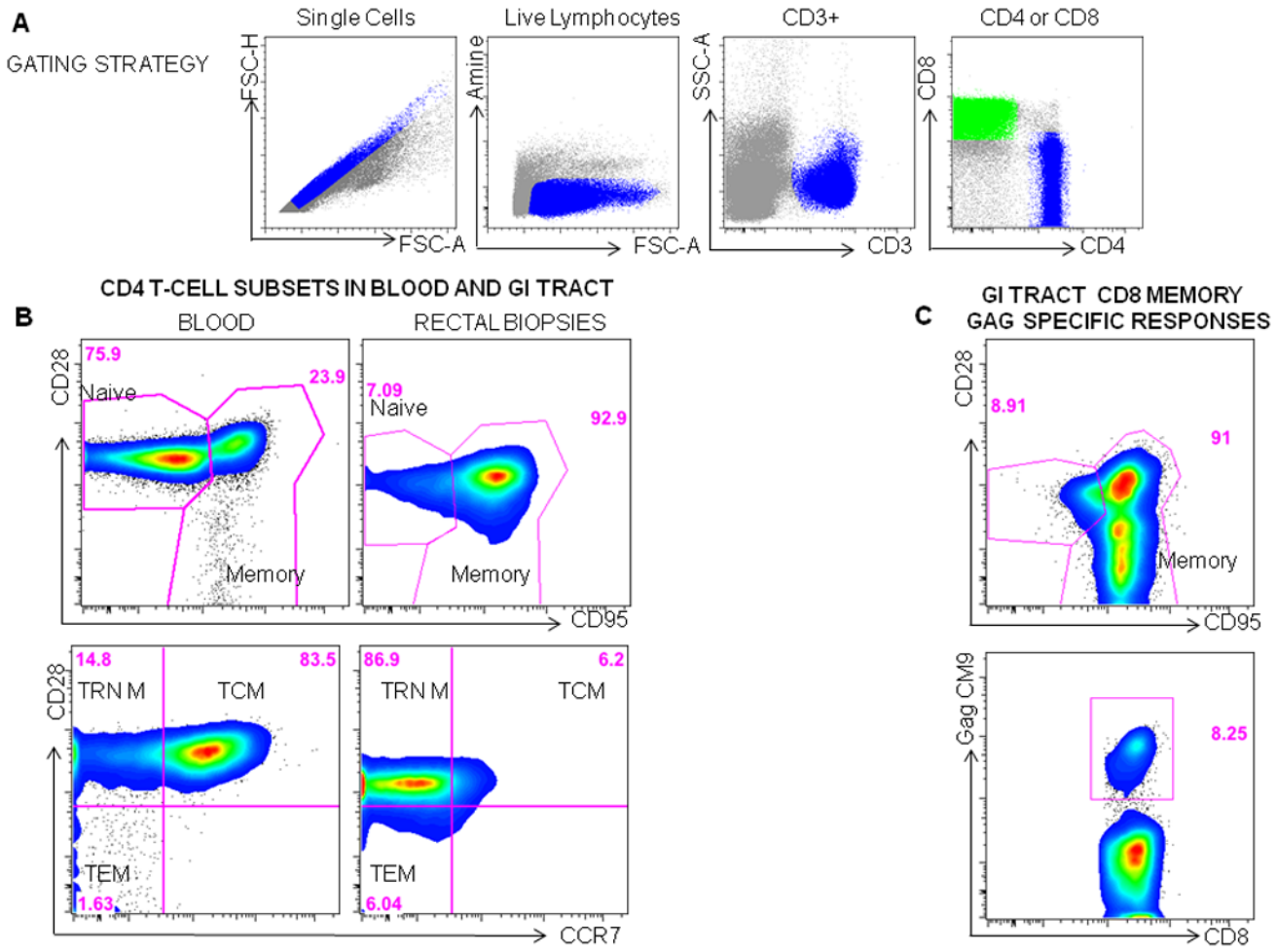

Figure 1.

Measuring T-cell Phenotype in macaques. **A** Gating strategy: Mononuclear cells are first gated on single cells, then live lymphocytes or cells that are negative for the Amine dye are gated, followed by gating CD3+ T cells and then CD8+(green) and CD4+ (blue) subsets. **B.** Four CD4 T cell populations can be identified in the blood or rectum in macaques using CD28, CD95 and CCR7. First naïve (CD28+CD95−) cells and memory (CD95+CD28+/−) cells are gated. The memory population can then be differentiated by CD28 and CCR7 into central memory cells (TCM:CD28+CCR7+), transitional memory (TRN M: CD28+CCR7−) and effector/effector memory cells (TEM: CD28−CCR7−)cells. **C** Mononuclear cells isolated from rectal biopsies obtained from a vaccinated SIV infected animal, 10 days post SIV infection are gated using the strategy shown in A, CD8 memory T cells are then gated (CD95+CD28+/−) and the frequency of SIV Gag specific memory cells to the CM9 epitope are determined using an MHC Pentamer.

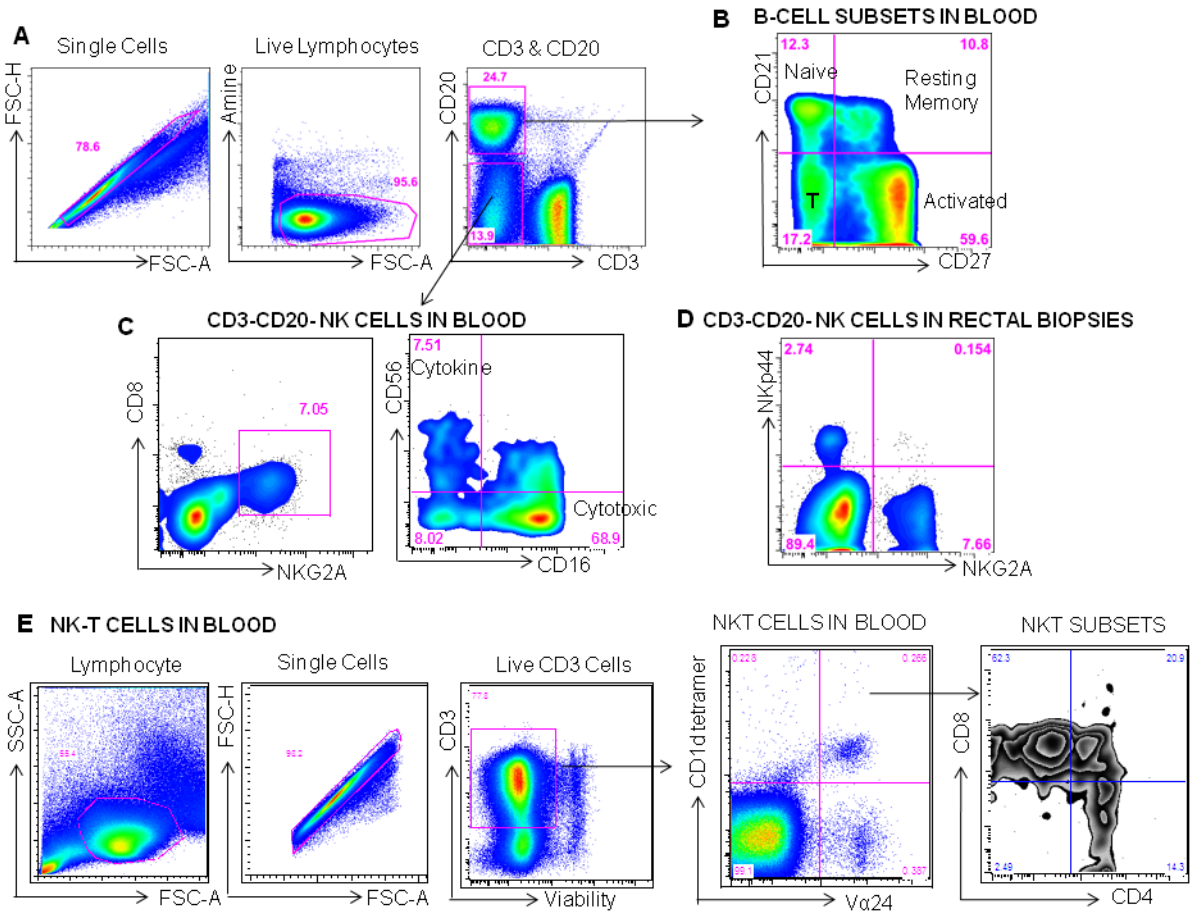

Figure 2.

Measuring B cell and NK and NK-T cell subsets macaques. **A** Gating Strategy: Mononuclear cells are first gated on single cells, then live lymphocytes, then CD20+ B cells and CD20−CD3− cells are gated. **B** CD20+ B cells can be phenotyped based on CD27 and CD21 staining. Naïve B cells are (CD21+CD27−), resting memory B cells are CD21+CD27+, while activated B cells are CD21−CD27+ and tissue bound (T) or differentiated B cells are CD21−CD27−. **C** Cells that are not T cells or B cells (CD3−CD20−) in blood are gated for dual expression of CD8 and NKG2A and then phenotyped by CD56 and CD16. Using these markers NK cells that have cytotoxic function CD16+ and those that are cytokine producing CD56+ and have more of a regulatory function can be identified. In the rectal mucosa classic NK cells can be defined as NKG2A+ and can be either cytokine producing or cytotoxic. A second subset has been recently described in the intestinal tract, which expresses NKp44 and produces IL17 and TNFα. These cells are thought to play a role in mucosal regulation and maintaining the integrity of the epithelial barrier. **E** Gating Strategy for NKT cells in blood: lymphocytes are first gated on single cells, then live CD3+ cells, and then Vα24+ CD1d tetramer+ NKT cells are gated. Within Vα24+ CD1d tetramer+ NKT cells, CD4+, CD8+ and CD4+CD8+ subsets are identified.

Table 1

Species-specific restriction by Trim5α (Nakayama and Shioda, 2012)

Trim5α	HIV-1	SIVmac	SIVagm
Human	No	No	No
Rhesus	Yes	No	Yes
Cynomolgus	Yes	No	N.D

Table 2

Selected examples of correlates of protection in NHP models

Correlates of protection from: --disease or high viral load (d) -- or acquisition (a)			Challenge virus/route/dose	Vaccine platforms	Reference
Cellular immune responses	CD8	general	SIV_{mac251}	DNA/NYVAC	(Hel et al., 2002a)
		TCM	SIV_{mac251}[d]	DNA/Poxvirus	(Vaccari et al., 2005)
		TEM	SIV_{mac259} intrarectal[a]	Recombinant CMV	(Hansen et al., 2011)
		Polyfunctional T cell	SIV_{mac239}[d]	Live attenuated SHIV89.6	(Genesca et al., 2012)
			SIV_{mac251}[d]	Peptide/Poxvirus With adjuvant	(Sui et al., 2010)
			$SHIV_{89.6P}$[d]	DNA/Ad5/Poxvirus	(Sun et al., 2008)
		Avidity of T cell	SIV_{mac251}[d]	DNA/MVA	(O'Connor et al., 2002)
		Mucosal high- avidity T cell (Rectal)	$SHIV_{KUII}$[d]	Peptide/Poxvirus	(Belyakov et al., 2006)
		Public clonotype	SIV_{mac239}[d]	DNA/Ad5	(Price et al., 2009b)
	CD4	general	SIV_{mac251}	DNA/NYVAC	(Hel et al., 2002a)
		TCM	SIV_{mac251}	DNA/MVA	(Vaccari et al., 2008)
		TEM	N/A	N/A	N/A
Humoral immune responses	Neutralization antibodies		HIV (chimpanzees) $SHIV_{SF162P3}$[a]	passive immunization with antibody	(Emini et al., 1992) (Hessell et al., 2009)
	Binding antibodies		$SHIV_{89.6P}$	Replicating Ad5/gp120	(Demberg et al., 2007)
	ADCC		SIV_{mac251}	Replicating Ad5/gp120 boost	(Gomez- Roman et al., 2005)
	Avidity of the antibodies		$SHIV_{89.6P}$	Replicating Ad5/gp120	(Xiao et al., 2010)
			SIV_{smE660}	DNA/MVA	(Lai et al., 2012)
			$SHIV_{162.P3}$	DNA/MVA	(Zhao et al., 2009)

Correlates of protection from: --disease or high viral load (d) -- or acquisition (a)		Challenge virus/route/dose	Vaccine platforms	Reference
	Mucosal antibodies IgA	SIV_{mac251}[a]	Replicating recombinant Ad5/gp120 boost	(Xiao et al., 2012)
Innate immunity	APOBEC3G	SIV_{mac251}[d]	Peptide/MVA with adjuvant	(Sui et al., 2010)

N/A: Not Available

NB: This table was not meant to be comprehensive, but only to provide examples