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Pirate Primates in Uncharted Waters: Lymphocyte Transfers in Unrelated, MHC-Matched Macaques

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Abstract

An HIV vaccine remains elusive despite the concerted efforts of investigators and clinicians over the past two decades. Animal models are regularly used to obtain new insights on disease pathogenesis and have become invaluable tools in the translation of treatments from basic research laboratories to the clinic. Vaccination of macaques with live, attenuated simian immunodeficiency virus is currently the most effective method of garnering protection against subsequent pathogenic SIV challenge. However, immunization of humans with live, attenuated HIV is not feasible due to safety concerns. Therefore, clues to an effective and safe vaccine against HIV may be found by studying immune correlates of protection in the live, attenuated, vaccinated macaque model. Previous studies have identified the immune correlates of protection against Friend retrovirus in live, attenuated vaccinated mice using allogeneic adoptive transfers. Similar experiments in macaques have thus far been hindered due to the vast genetic diversity found within outbred populations. Here we review the current state of SIV adoptive transfer research and present a novel macaque model that allows for allogeneic adoptive transfers.

The path to a successful HIV vaccine has been long and arduous. Despite two decades of research, we are still unable to answer many basic immunologic questions concerning the control of HIV replication. The viral envelope is genetically diverse and heavily glycosylated, making it nearly impossible to elicit a strong, sustainable neutralizing antibody response. This has spurred research into vaccines eliciting cellular immunity. Early swift progress in our understanding of cellular responses against SIV provided optimism that these responses would form the basis of a successful vaccine. However, recent setbacks have exposed gaps in our understanding of the correlates of protection. Highlighting the need for more basic research into the mechanisms of cell mediated control is the recent failure of Merck's HIV STEP vaccine trial [1–3]. Participants in this study were given three separate injections of three distinct rAd5 viruses encoding Gag, Pol, or Nef. Initial results from the study indicate that vaccinated individuals were not protected from HIV infection and possibly that those with a pre-existing immunity to the Ad5 vector were at greater risk for

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infection. Greater analysis will be required to scrutinize this vaccine, but the failure of the STEP trial clearly underscores the need for more basic research into the pathogenesis of HIV.

Simian immunodeficiency virus (SIV) infection of non-human primates is currently the best model of HIV infection. Unlike studies conducted in humans, non-human primates allow for tightly controlled experiments. Researchers can control the timing of infection, the sequence of the virus, and host genetic factors. This makes it possible to study events in the acute stage of infection and measure changes in viral sequence and immune responses that occur early in infection. Furthermore, studies and techniques that cannot be safely or ethically conducted in humans can be conducted in primates, including preclinical testing of different vaccine modalities, invasive biopsies, and terminal procedures.

Most non-human primate SIV research has focused on Old World monkeys of south-east Asian origin, including rhesus macaques, pigtail macaques, and cynomolgus macaques. Of these species, rhesus macaques are the predominantly used model in experiments addressing SIV immunity and vaccine development. One significant limitation of the rhesus macaques is their genetic diversity. This genetic diversity confounds studies aimed at understanding the pathogenesis of an SIV infection. Little is understood about how major histocompatibility complex (MHC) alleles, and the cellular immune responses they restrict, affect SIV outcome. Oftentimes, rhesus macaques used in SIV vaccine experiments are matched for only one MHC class I allele, even though each animal may have 10 or more MHC class I alleles. The remaining alleles are ignored and many responses restricted by these alleles have not been characterized. Furthermore, previous studies in rhesus have been unable to determine which leukocyte compartments are necessary for efficient SIV control. To further delineate which components of an immune response are important to viral control, a non-human primate model with reduced genetic diversity is needed.

Anthropological evidence indicates a small founder population of cynomolgus macaques arrived on the island of Mauritius approximately 400 years ago [4]. Current estimates indicate that there are between 25,000 and 35,000 cynomolgus macaques residing on the island today. Recent genetic analysis of this population has revealed extremely low MHC diversity between animals, with only seven MHC haplotypes [5]. This low MHC diversity enables the adoptive transfer of immune cells between MHC matched animals, allowing researchers to directly study cellular responses against SIV in novel ways.

LIVE ATTENUATED VIRUS PROTECTION

Investigators have used adoptive transfers to study the protection elicited by retroviral live attenuated vaccines [6–14]. These studies focused on the murine retrovirus Friend virus (FV), which is a complex of two viruses. Friend murine leukemia virus (FMLV) is a nonpathogenic, replication competent virus and spleen focus-forming virus (SFFV) is a pathogenic, replication defective virus. Infection with FV leads to acute massive splenomegaly and eventual erythroleukemia. Vaccination with live attenuated FV provides protection against pathogenic FV challenge. Researchers used adoptive transfers of fractionated immune spleen cells between vaccinated and naïve mice to determine the

precise lymphocyte subsets responsible for preventing pathogenic infection. These experiments showed that transfusion of different combinations of lymphocyte subsets led to variable disease outcome following FV infection [7] and demonstrate the power of adoptive transfers in delineating the immune mechanisms required to protect against pathogenic challenge.

Animals infected with attenuated SIV exhibit lower acute and chronic phase viral loads following wildtype SIV challenge in rhesus and cynomolgus macaques [15–20]. The level of viral attenuation is inversely correlated with the degree of control following pathogenic SIV challenge, suggesting that viral replication is important in the formation of an efficacious immune response [21]. Highly attenuated SIV vaccine strains replicate less effectively, leading to reduced MHC antigen presentation and a blunting of immune protection. Additionally, greater sequence diversity between the vaccine and challenge strains leads to weaker vaccine protection. Abrogated protection due to increased sequence diversity between vaccine and challenge strains indicates the importance of lymphocyte specificity in an effective response [20]. Finally, through the first 15 weeks of vaccination there appears to be greater protection in animals where longer periods of time exist between vaccination and challenge [22]. Differences in control due to temporal variation between vaccination and challenge dates implicate the important role of immunokinetics and the formation of a memory lymphocyte subset. These basic principles of live-attenuated SIV vaccination outline the parameters of an adaptive immune response in the control of SIV.

ADOPTIVE TRANSFERS IN HUMANS AND NON-HUMAN PRIMATES

Researchers have been studying adoptive transfers as a potential immunotherapy for HIV infection for over 15 years. These immunotherapy studies have focused primarily on two distinct methods. In the first method, investigators expand naïve, autologous CD4+ T cells *ex vivo* and infuse them back into the HIV-positive individual [23–27]. This immunotherapy is potentially very valuable because individuals on HAART therapy never completely recover their immune system [28, 29]. The second method of immunotherapy has been directed at developing HIV specific CTL that would kill infected cells after reinfusion into the HIV infected individual [24, 30–36]. HIV immunotherapy has met both with success and several setbacks. While researchers have found that transfused CD4 T cells have the ability to persist after transfer, these cells do not always appear to have an effect on the pathology of disease. Additionally, CTL transfers often result in the quick death of transferred cells. Researchers have posited several reasons for these observations and some research in mice suggests HIV specific CTL may die after encountering HIV infected target cells [35].

Adoptive transfers have also been pursued in the rhesus macaque where the fate of autologous cells can be more readily tracked. Researchers successfully isolated, CFSE labeled, and transferred lymphocytes back into a naïve macaque [37, 38]. In this model researchers were able to track donor cells after transfer and investigate the effects of SIV infection on lymphocyte trafficking. There were minor differences in the homing of lymphocytes after infection. Researchers identified increased frequencies of transferred cells in the small intestines during acute SIV infection. These cells were detected throughout gut effector sites. Furthermore, recent studies have been conducted using peptide pulsed

autologous cells as an immunotherapy. In these experiments, autologous cells labeled and pulsed with SIV peptides recirculated in the peripheral blood after transfer [39]. These experiments demonstrated the power of using adoptive transfer studies in the macaque model to study the immune system after SIV infection.

Additional experiments have primarily focused on the immune reconstitution of SIV infected macaques. Immune reconstitution experiments have successfully induced long-term nonprogressor status when autologous naïve cells were transferred under the cover of antiretroviral therapy [40]. More recently, investigators have found that anti-CD3/CD28 treatment induces the polyclonal expansion of T cells and leads to prolonged survival after transfer [41]. These studies have demonstrated the power of adoptive transfer in the macaque model. These studies can define trafficking patterns of cells in the SIV infected macaque and represent an ideal system for studying potential immunotherapies before their advancement into human clinical trials. Furthermore, adoptive transfers have the potential to be used to investigate the correlates of protection in a natural immune response. However, the limited number of current adoptive transfer studies underscores the costly and difficult nature of using macaques in adoptive transfer experiments. Ultimately, investigators are limited to transfer of autologous cells because animals are heterogenous at the MHC loci. Cells transferred between unrelated animals are quickly rejected.

PIRATE PRIMATES: MAURITIAN CYNOMOLGUS MACAQUES IN ADOPTIVE TRANSFER RESEARCH

Mauritian cynomolgus macaques (MCMs) are a unique model for the study of SIV pathogenesis. Their simple MHC genetics allow for the transfer of immune cells between monkeys, providing an avenue for determining the importance of distinct lymphocyte subsets during the acute phase of an SIV infection (Fig. 1). Most studies of SIV pathogenesis have focused on MHC diverse macaques, where multiple responses restricted by a small subset of alleles have been well characterized and evaluated for antiviral efficacy *in vitro* [42–45]. Vaccinations of engineered retroviral vectors encoding different SIV proteins have been successful at eliciting CD4, CD8 and antibody responses prior to infection. However, these vaccinations do not consistently protect from challenge with highly pathogenic strains of SIV [46, 47]. Live attenuated SIV vaccinations lead to successful control of challenge virus in most macaques, but the cellular and humoral responses involved in this control are not yet understood. This has limited researchers' ability to design an effective prophylactic vaccine strategy against SIV. MCMs provide the means to directly test lymphocyte subsets separately and determine the importance of each following an SIV infection (Fig. 2).

In order to study the immune correlates of protection in the MCM adoptive transfer model, transferred cells must persist in the recipient animal long enough to affect the outcome of an SIV infection. Recent evidence indicates that leukocytes transferred between MHC-matched animals persist in the periphery for up to 14 days and traffic to various lymphoid tissues within 24 hours. Flow analysis of single cell suspensions acquired from various anatomical sites show differences in homing between immune cell types.

One obstacle to the adaptation of this model is the observation that transferred cells from blood do not traffic to gut mucosal tissues in appreciable numbers [48]. Massive depletion of CD4⁺ T cells in the gut shortly after infection with SIV [49, 50] suggests that effective SIV-immune transferred cells should traffic to this site.

It has recently been shown that CD4 T cells activated *in vitro* in the presence of retinoic acid acquire a gut homing phenotype with surface expression of $\alpha 4\beta 7$ and CCR9 [51]. This effect is seen after only four days in culture, making this technique an appealing alternative to direct transfusion of non-manipulated donor cells. However, it remains to be determined whether the transfusion of non-autologous SIV-specific CD4⁺ T cells is beneficial or detrimental in an SIV infection. While the transfer of SIV-specific CD4⁺ T cells should aid in an early efficacious immune response to the newly acquired virus, it may also provide additional target cells for the virus, leading to increases in acute phase pathogenesis. There is evidence that the transfusion of autologous, naïve CD4⁺ T cells taken prior to infection can prolong the effects of antiretroviral therapy in rhesus macaques [40]. Furthermore, studies have found an inverse correlation between proliferative CD4⁺ responses against SIV and viral load [52, 53]. The MCM model will allow researchers to directly determine the role that SIV-specific CD4⁺ T cells can have when present during initial infection and acute phase viremia.

Initial transfers of allogenic, SIV-specific CD8⁺ T cells from infected MCMs into MHC-matched recipients have thus far been unable to show protection following recipient SIV challenge. However, these cells were transferred intravenously and most likely did not traffic to the gut where they would be most efficacious against acute infection. Additionally, these CD8 T cells were harvested from the recipient at three weeks post-infection, when SIV-specific CD8 T cells were at peak numbers, but were beginning to decline *via* natural apoptotic mechanisms. Future studies with CD8 T cell transfers will likely focus on donor animals that have been vaccinated with live, attenuated virus and the effects of epitope-specific T cells.

CONCLUSIONS

Research into the pathogenesis of HIV in human patients has limitations that can be overcome by studying SIV in the macaque model. The genetic diversity between outbred macaques, both within and between geographically distinct populations, has thwarted researcher's efforts to determine the exact correlates of immune protection against SIV. An adoptive transfer model will significantly advance our ability to examine which immune components comprise an effective adaptive immune response. MCMs are unique in their MHC genetic make-up, making them a suitable population for such adoptive transfers.

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Relative Proportion of MHC class I alleles

Fig. 1.

Decreased MHC diversity in MCM. Each monkey is equivalent to 10 different MHC class I alleles. The total number of MCM alleles is represented on the left while a large number of characterized rhesus MHC class I alleles is represented on the right. It is not known how many total alleles will be identified or exist in the rhesus macaque. The genetic diversity of the rhesus macaques precludes them from use in adoptive transfer studies.

Fig. 2.

Schematic of the adoptive transfer protocol. This protocol could be used to investigate the correlates of immune protection against SIV by live attenuated vaccination. Lymphocytes isolated from lymphoid tissues of donors (top) could be separated over magnetic columns (middle) and transferred alone or in combination to recipient animals prior to challenge with pathogenic SIV (bottom). Protection after challenge could be assessed by viral loads or CD4⁺ T cell counts.