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A baboon model for herpesvirus infection and pathogenesis

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Introduction

Herpesviruses occur in all vertebrates from mice to elephants (42) and also in birds, turtles, reptiles, fish and even oysters (19). Phylogenetic analysis has revealed that herpesvirus divergence closely parallels mammalian and in particular primate speciation (1, 35). During co-evolution the defining characteristics of the herpesviruses, such as the ability to establish latency, host-polymerase independent lytic replication

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and tropism were conserved. The family *Herpesviridae* is further subdivided into the alpha, beta and gamma branches based upon sequence similarity and tissue tropism (http://www.ncbi.nlm.nih.gov/ICTVdb/Ictv/index.htm). Rhadinoviruses, such as human Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8), belong to the family of Gammaherpesviridae. These viruses establish latency in lymphocytes and are associated with lymphoproliferative diseases. Lymphocryptoviruses, including the prototypical member, human Epstein-Barr-Virus (EBV or HHV-4), display a tropism similar to rhadinoviruses and exhibit strong lymphocyte transforming abilities. They constitute a second division of the gamma herpesviruses. There are two subfamilies of betaherpesviruses, one being the cytomegaloviruses with human cytomegalovirus as its prototypical member (HCMV or HHV-5) and the other being the roseoloviruses with human herpesvirus 6 (HHV-6) as its prototypical member. Similarly, the alpha herpesviruses are split into two subfamilies. The simplexviruses are typified by human herpes simplex virus (HSV-1 or HHV-1), and the varicelloviruses are typified by human varicella zoster virus (VZV or HHV-3). Most viral genes are conserved among all the herpesviruses in terms of their molecular function and primary amino acid sequence. Genome structure and organization as well as amino acid similarity are more conserved within each of the three lineages (alpha, beta and gamma) than outside the lineages (1, 2). For rhesus macaques and baboons, which are the most prevalent primate species used in biomedical research, homologues of most human herpesviruses have been identified and they appear quite similar to their human counterparts in both their biological and molecular phenotypes (11, 12). The strong evolutionary conservation among herpesviruses suggests that insights into fundamental mechanisms of herpesvirus biology can be gained from studying endogenous herpesviruses that infect non-human species.

Herpesviruses in baboons

Herpesviruses can be found throughout the animal kindom (10) and the Papio species (Baboons) are no exception. Our work focuses on baboons within the species cynocephalus (including all three subspecies; cynocephalus, anubis, and hymandrayas). Baboons of the chacma and gelada species are likely to also harbor herpesviruses, but are not covered here. Baboons harbor homologues to all classes of herpesviruses including the lymphocryptoviruses and rhadinoviruses, which are split within the gamma family of herpesviruses (Table 1). The first herpesvirus to be discovered in baboons was a homologue of Epstein Barr Virus (EBV), a gamma-1/lymphocryptovirus, rightfully named Herpesvirus papio (HVP), baboon herpesvirus (17), though its formal ICTV designation is *Cercopithecine herpesvirus 12* (CeHV-12). This discovery was made in the 1970's. Analysis of restriction fragment lengths established that the HVP genome was collinear with human EBV (22). It was not until 1995

Table 1. Listed are the known herpesviruses of Humans, Rhesus, and Baboons by family. Abbreviations: HSV-Herpes Simplex Virus, VZV-Varicella Zoster Virus, CMV-Cytomegalovirus, HHV-Human Herpesvirus, EBV-Epstein-Barr Virus, KSHV-Kaposi's Sarcoma Associated Herpesvirus, Rh-Rhesus, RRV-Rhesus Monkey Rhadinovirus, RV-Rhadinovirus, HVP-Herpesvirus Papio, Ba-Baboon, and Pap-Papio

	ALPHA	BETA	GAMMA-1	GAMMA-2
Human	HSV-1 HSV-2 VZV	CMV HHV-6 HHV-7	EBV	KSHV
Rhesus	B Virus	RhCMV	RhLCV	RRV RVmac
Baboon	HVP2	BaCMV	HVP	PapRV2

that a second herpesvirus of baboons was exposed. Eberle and colleagues isolated a herpesvirus that was homologous to HSV-1 (14). This second herpesvirus from baboons was named Herpesvirus Papio-2 (HVP2) or *Cercopithecine herpesvirus 16* (CeHV-1), and has homology to Simian Agent 8 virus (SA8) or *Cercopithecine herpesvirus 2* (CeHV-2), which is a HSV-1 homolog in macaques. It causes a disease similar to that induced by HSV-1 and 2 in the human population. Shortly thereafter a virus homologous to human Cytomegalovirus (HCMV) was isolated from the saliva of baboons. Further examination and sequence analysis verified the widespread presence of baboon cytomegalovirus in captive and wild-caught baboons (BaCMV) (6) (23). To date, the assembly of the complete baboon cytomegalovirus sequence (Accession no.: AC090446) is in its final stages (Earl Blewett, personal communication). Using serological techniques and degenerative PCR we identified a KSHV, or Gamma-2 herpesvirus homologue in baboons (53). It is also believed that a virus related to human VZV, i.e. a second alpha herpesvirus, exists in baboons. However, it has not been determined whether or not this is an original baboon virus or movement in captivity of Simian Varicella (CeHV-9), which has been isolated several times from macaques and other monkey species, but not yet from baboons (33, 45), from macaque into the baboon species. No evidence currently exists for the presence of homologous for HHV-6 or HHV-7 in baboons.

At this point we do not have enough viral isolates or sequence information to determine whether different baboon species harbor different lineages of a given herpesvirus. In fact the phylogeny of baboon species themselves is still open to further refinement. However, sequence and phenotypic analyses show

that, akin to the human or rhesus macaque (8), multiple strains of HVP-2, lymphocrypto- and rhadino- herpesviruses exist within a single species and often within a single animal (16) (44) (Papin and Dittmer, unpublished).

Baboons comprise a unique resource for research in infectious diseases

The advantages of using captive baboons for studies on herpesvirus-associated diseases are self-evident: the animals are subject to the same environmental conditions, which naturally trigger reactivation of the endogenous herpesviruses; the animals are genetically diverse (47), yet most are related, and familial associations within the breeding cohort are easily established. The animals are available for intervention as well as extensive observational studies on a long-term basis. Of note, female baboons have a prominent sex skin, which swells visibly and can be used to follow the menstrual cycle. Since herpesviruses are transmitted *in utero* or during birth, and since in particular the beta-herpesviruses are a leading cause of congenital infections and associated diseases, this unique feature in the natural history of baboons lends itself for detailed studies of theses pathologies. At the University of Oklahoma Health Science Center the baboons (Papio sp.) are housed in special facilities accredited by the Association for Accreditation of Laboratory Animal Care International (AAALAC). The conventional baboon resource consists of separate indoor-outdoor corrals, which are designed to provide a rich and species-appropriate environment (Figure 1). This environment also increases reproductive efficiency in the cohort. Each corral contains up to 30 breeding females with 3 or 4 adult males and their offspring.

Figure 1. Troupe of Baboons at the OUHSC research facility.

Typically, 10% of the offspring are raised to adulthood as replacement breeders and the remainders are available for research studies. The entire colony is under constant observation and the number of animals within any particular corral is small enough such that studies on the social behavior of the animals are possible. Behavioral studies comprise an integral part of the research and can lead to a detailed characterization of the interactions among animals, which in turn provides an opportunity to study parameters of herpesvirus transmission in a defined context. Twice each year the entire colony is tested for tuberculosis, which is fatal in the baboon species. At this time a physical exam is conducted on each baboon, and blood is banked for serological and virological studies. Hence, cross-sectional as well as longitudinal studies are possible without loss at follow-up (26), which is the primary reason for the relatively low power of similar epidemiological studies in wild primates.

Recently, efforts have been initiated to raise specific-pathogen free animals, because viruses constituting the “normal flora” of research animals can have a considerable impact on research results and their validity. For example, during early transplantation studies, latent herpesvirus reactivation can take place in the recipient as well as in the graft, yet virus from both origins will result in disseminated disease. Also, what may at first seem like a strong IgG response to an experimental vaccine (see below) can in actuality be a memory response from an endogenous virus. Hence, the development of a breeding colony of baboons free of these viruses would significantly enhance research in many fields.

To achieve this goal basic knowledge of human herpesvirus transmission was applied and the successful derivations of herpesvirus-free animals in turn prove the route of transmission in this species. Based on timed pregnancies, baboons were targeted for recruitment into the program. Within 12 hours of delivery infants were removed from their dams and hand-reared. Small groups of similar aged animals were raised together in order to provide the infants with socialization during the hand-rearing, infant, and early juvenile periods of development. However, individual groups were kept separate to minimize losses in the case of a disease outbreak. All infants were repeatedly tested for each of the target viruses. For herpesvirus serology, dams were bled at the time of parturition, and infants were bled at 2, 4, 6, and 12 months of age. A progressive drop in IgG levels, presumed to be of maternal origin, to background indicated virusfree animals. However, a rising titer, or as encountered more commonly, a dip in the titer at 2 or 4 months followed by an increase indicated a positive animal. This procedure was initially unsuccessful. In one set of animals, five infants that exhibited declining IgG titers to BaCMV at 2 and 4 months, showed elevated titers 6 months of age they. The other animals showed progressively increasing anti-BACMV titers. However,

decreasing the group size to 5 animals or less and the enforcement of stricter hygiene methods for animal care personnel that moved between groups yielded a BaCMV-free colony. This experience recapitulates the transmission patterns in humans: Once infected in utero or during birth, the infant will carry latent CMV for life. CMV will reactivate early in life and spread via the oral, fecal route to naïve animals. However, animals that were not exposed to BaCMV during birth remain virus-free.

Vaccine research is one of the prime applications for baboon models of infectious disease. As baboons carry a full complement of the gamma isotype of immunoglubulins (see below), human reagents can be used to measure immune response (Figure 2) and the animals can be challenged to assess vaccine efficacy, therefore baboons are an outstanding model for vaccine studies. An extensive history of testing vaccines in baboons already exists. Vaccines have been tested in baboons for multiple classes of infectious agents including viruses, bacteria, and parasites. These vaccines range from using recombinant proteins to virus like particles (VLPs) and DNA vaccines. Recent vaccine studies in baboons have demonstrated that Hepatitis C virus-like particles, produced using a recombinant baculovirus containing the cDNA of HCV structural proteins, can induce both cellular and humoral immunity in baboons (27). Other viral vaccine studies have demonstrated the ability of baboons to produce an antibody response to a commercially available encephalomyocarditis virus vaccine, and baboons were the chosen model for analyzing the safety of using Escherichia coli heat-labile toxin as an adjuvant for the nasal influenza vaccine (55) (25). Levy and colleagues have characterized DNA and genetic expression library vaccines in baboons and

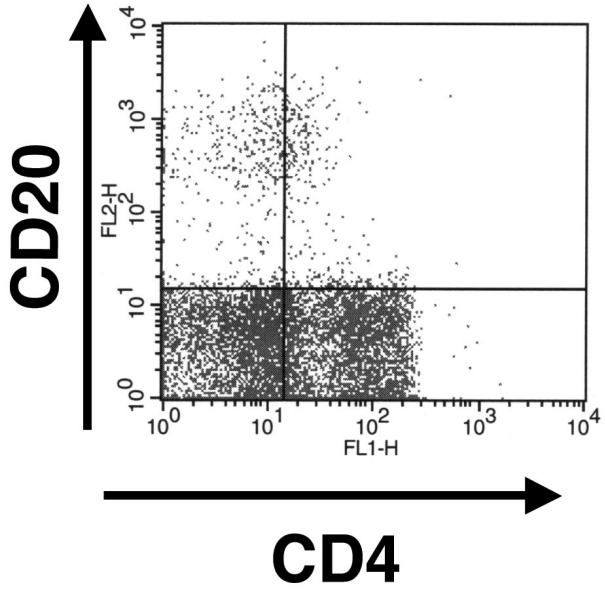

Figure 2. Flow cytometry analysis of baboon PBMC using commercial antibodies that were raised against the homologous human CD marker.

have achieved partial protection from acute HIV-2 infection (31). The baboon has also proven to be an effective model for elucidating the necessity of an antibody response when vaccinating against the parasite Schistosoma mansoni, in these studies IgG levels directly correlated with the level of protection (28) (48). An important breakthrough in fetal and neonatal immunization was achieved using the baboon model. Capitalizing upon the high similarity between baboon and human reproductive biology, studies have demonstrated the ability of the fetus to mount a fetal specific antibody response and the neonates go on to develop immunological memory against hepatitis B surface antigen (51) (7).

Herpesvirus serology in baboons

Epidemiological studies traditionally focused on the virus-specific immune response as evidence for exposure. The presence of herpesvirus-specific serum antibodies in the animals confirms that at least one previous infection has taken place, and since herpesviruses establish latency for life, sero-reactivity can be used to identify latent or persistent carriers. For some herpesviruses a transient rise in antibody titers is equated with episodes of viral reactivation from latency and may be used as a predictor of disease (52). The class of long term surviving antibodies that are measured in these applications is IgG. In humans the IgG class of antibodies is divided into four subclasses: IgG_1, IgG_2, IgG_3, and IgG_4. The subclass of IgG antibody present can often help to determine the type of immune response that was mounted against the agent. For example, IgG_2 is often produced during a T_h1 or cell associated response whereas the production of IgG_1 coincides with a T_h2 or humoral response (50). Baboons contain four homologous classes of IgG heavy chains as well as homologues to the seven human variable regions (46), and therefore can be used to study the differential IgG responses to infectious agents and vaccines.

Cross-reactive antibodies to herpesviruses of human and macaque species have been used to detect the presence of herpesvirus infections in baboons (13, 53) (29). In the case of the baboon lymphocryptovirus HVP, even the commercially available immunofluorescence assay for EBV-associated mononucleosis can be employed to detect antibodies to HVP (Xu, Papin, Harley, Dittmer, unpublished observation). By using the corresponding human herpesvirus peptide, recombinant protein or purified virion-based ELISA assays, one can screen for baboon herpesviruses in the animal population(53) (29). The extensive cross-reactivity between the antigens of human and baboon herpesviruses significantly facilitates research in this model. There is, however, an import limitation to this approach: in screening for the presence of PapRV2, we encountered animals that did not show reactivity to the homologous human KSHV antigenic peptide, but that did show reactivity to

the homologous rhesus rhadinovirus (RRV) antigenic peptide (53). As with any immunological assay, the absence of an immunological response cannot automatically be equated with the absence of the immunogen.

Herpesvirus-associated diseases in baboons

Baboons not only harbor viruses that are homologues to human herpesviruses based upon sequence and molecular studies, but they also display signs of disease similar to those of human diseases caused by herpesviruses. While Koch's postulates have not yet been performed due to a paucity of specific pathogen free (SPF) baboons, the association between the endogenous baboon herpesviruses and their signature diseases has nevertheless been convincingly established. Primary baboon lymphocytes can be transformed by HVP *in vitro* (18). Spontaneous lymphomas can be found in baboons (24) (38) though perhaps more closely associated with HTLV-1. HVP-positive lymphomas have been demonstrated in baboons (40), which are homologous to EBV-associated lymphomas in humans, or LCV-associated lymphomas in macaque species (37, 43). HVP2 has been isolated from lesions of the mouth and genitals of baboons, which resemble lesions seen during Herpes simplex outbreaks in human individuals (14). Studies have yet to be conducted linking BaCMV to any disease, however birth defects often related to congenital CMV infection such as blindness and deafness have been observed (Wolf, White, unpublished observation) and specific pathogen-free animal may succumb to infection upon exposure to BaCMV or HVP (Figure 3). Infectious BaCMV viremia has also been detected after baboon to human liver transplantation: Replication competent BaCMV was detected in a recipient blood sample taken 29 days post-transplantation. Once detected ganciclovir treatment was administered and neither human nor baboon CMV was detectable until the time of death, caused by acute hemmorrage of the brain secondary to an aspergillus

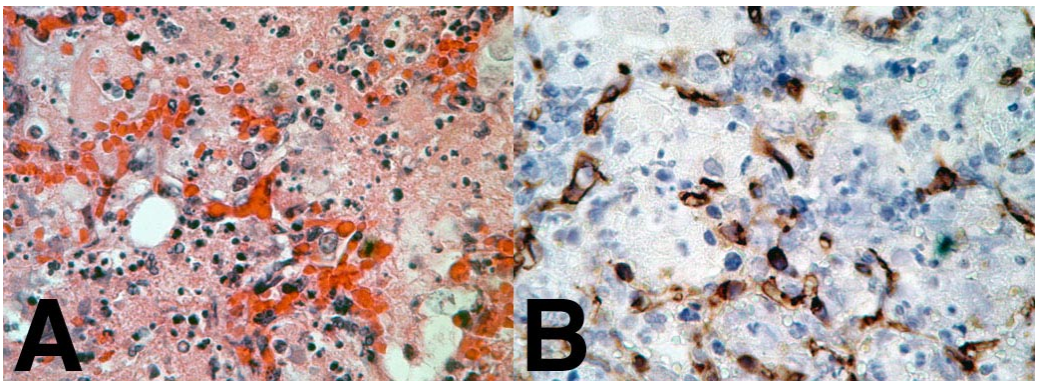

Figure 3. Picture of a baboon lung with fatal HVP-2 penumonia at 100x magnification (a) H&E stain, (b) stain with polyclonal anti-human CMV gB (brown) and hematoxilin (blue) counterstain.

infection (36). KS-like lesions have been reported in baboons infected with HIV-2 (4). While the baboon lesions did not harbor KSHV sequences, thereby excluding contamination with human KSHV, subsequent PCR studies on lesion-derived cell cultures detected the baboon rhadinovirus PapRV2 at a low frequency (Papin, Steward, Levy and Dittmer, unpublished). In sum, the high concordance between the pathology of herpesvirus-associated disease in baboons and in humans, along with the data demonstrating the existence of closely related homologs of human herpesviruses, establish baboons as a valid and tractable animal model for the study of herpesvirus pathogenesis.

Herpesviruses of baboons have also been reported to cause disease in other species. These infection models have been developed to study herpesvirus pathogenesis with a more exaggerated phenotype. One example is that of HVP infection in rabbits. Rabbits infected with HVP develop not only lymphoma but also hemophagocytic syndrome (HPS) (21), which is similar to rabbits infected with other primate LCVs. This observation has been used to develop the rabbit as a model for the study of lymphocryptovirus-associated HPS and lymphoproliferative disorders (21). Though fatal disease is isolate specific, HVP2 can cause lethal encephalitis at 10 days post inoculation when injected into Balb/c mice, thus establishing the mouse as a model to study the neurovirulence of baboon alphaherpesviruses (44) analogous to studying human HSV-1 neurovirulence in mouse models (54). Thus the availability of small rodent models for acute experimental infection nicely complements the studies on baboon herpesviruses in the context of natural infection, natural route of inoculation and natural transmission rate.

Experimental transmission of foreign viruses among different primate species or between primates and humans, poses another option to model herpesvirus pathogenesis that has mainly been explored in the rhesus macaque system. Starting with the observation that particular strains of herpesvirus saimiri, a rhadinovirus of the squirrel monkey (*Saimiri sciureus*), cause fatal T-cell lymphoma when inoculated into other new world monkeys, other cross-species inoculation schemes rapidly followed suit: human HSV-1 was inoculated into macaques for the study of ocular disease and HSV-specific drug regimens (54) and SA8 was inoculated into baboons (34). The outcome of these cross-species inoculation studies was extremely virus- and host species-specific, which is consistent with the idea of co-evolution of herpesviruses and their mammalian hosts. Either the primate immune system fails to recognize the novel herpesvirus and the animals succumb rapidly to an exaggerated disease phenotype as outlined above, or the novel herpesvirus stands out as an immunological target and primary infection is rapidly cleared with no signs of disease (similar to infection with classical acute viruses such as influenza or West-Nile virus). As an example for the latter scenario, in trying to establish a non-human primate model for KSHV, rhesus macaques

were infected with the human virus (41). While the KSHV DNA was present in all PBMC samples over a period of several months, no particular phenotype emerged even in animals that were co-infected with SIV.

Experimental immunosupression in baboons

Baboons are a well-established model for xenotransplantation studies, primarily used as the recipient of porcine or rhesus organs partly because of the similarity between the human and baboon immune systems (see above), blood composition (20), and partly because of the comparable size of the animal and it's internal organs, which facilitates surgery. These studies have lead to a preponderance of data pertaining to immunosuppression in baboons for the purpose of solid organ transplantation. The immunosuppressive regimens used for these studies follow those used in humans during transplantation. Many drugs have been tested in baboons for their ability to suppress the immune system, including but not limited to cyclosporine A, FK506, anti-thymocyte globulin, methotrexate, and prednisone. For instance, Asano et al. have studied the ability of different drug regimens to prevent long-term graft rejection during rhesus to baboon heart transplantation (3). This study highlighted the ability of combinatory therapy to help prolong the survival of the xenotransplant. The most successful therapies combine cyclosporine A or FK506 with anti-thymocyte globulin to suppress the T-cell response against the graft. Along with combinatorial therapy an anti-metabolite such as methotrexate is often used as well. Successful therapies suppress the immune system, and allow for long-term survival of baboons receiving a xenotransplant

In the clinical patients a major problem of immunosuppression and the leading cause of solid organ transplantation is the reactivation of latent viruses due to the lack of immune surveillance or exaggerated primary infection of an initially naïve and now immunosuppressed transplant recipient (9). The most significant group of viruses responsible for mortality and morbidity while under immunosuppression—either by iatrogenic means or by HIV infection—are the herpesviruses. Studies on experimental organ transplants in baboons routinely report the reactivation of BaCMV after transplantation (36). For instance, Mueller, et al. (39), reported that three of four baboons receiving porcine kidneys experienced increases in BaCMV DNA in lung and liver. One animal ultimately died of disseminated BaCMV-disease. BaCMV, like human CMV, is inhibited by ganciclovir, though in vivo the drug may have reduced efficacy (36). Another study that looked specifically at the reactivation of herpesviruses of baboons during immunosuppression after total lymphoid irradiation failed to see the reactivation of herpesviruses as measured by a rise in antibody titers (49). However, since antibody production requires T-cell help, this assay may not be appropriate for studies on immunosuppressed

animals. In our hands immunosuppression of baboons leads to viral reactivation similar to that encountered in human transplant recipients, although the timing and magnitude of the effect can differ for individual herpesviruses (Papin, Wolf and Dittmer, unpublished).

HIV-2 infection in baboons

Human Immunodeficiency Virus (HIV) is the causative agent of Acquired Immunodeficiency Syndrome (AIDS), and a major source of morbidity and mortality worldwide. Some 25 million people are infected with HIV in Africa, and approximately 2.2 million people died last year due to HIV infection. In Africa HIV infects over 20% of the population in some countries, and the number of young women infected with HIV continues to rise (http://globalatlas.who.int/). While efforts to educate people about AIDS among young adults represents one avenue to fight the disease, an effective vaccine would have the most potent impact on the AIDS epidemic. In order to determine the expected efficacy of such a vaccine in humans, a non-human primate model is needed to evaluate disease progression. Currently the accepted model is one of SIV or SHIV infection in the macaque species (reviewed in (54)). Disease in these animals due to the SIV infection is acute and follows a more aggressive clinical course compared to human HIV-1 infection. Chimpanzees inoculated with HIV-1 exhibit a more delayed disease pattern like that of humans, but are not available due to their endangered species status. Levy and colleagues have demonstrated HIV-2 infection in baboons follows a course clinically similar to that of humans infected with HIV-1: Disease progression in baboons infected with HIV-2 is viral isolate and species specific. The HIV_{UC2} strain has produced the best results, in regards to recapitulating chronic HIV-1 infection in humans, when placed into female hymandrayas baboons (30). Here, the disease course involves an acute phase in which viral loads reach 10^6 copies per ml plasma during the first months of infection. High viral loads are also reached in the PBMCs (~10^5 infected cells per million cells), and are accompanied by lymphadenopathy and a petechial rash of the abdomen and back. During infection CD4+ T cell counts decrease from approximately 1000 cells per µl to 400 cells per µl. At 2-4 months a CD8+ T cell response sets in and correlates with a decrease in viral titers. A neutralizing antibody response develops at 6-12 months post exposure. After this acute phase of infection, a period of 4-7 years occurs during which the baboons are clinically healthy, and contain a low HIV-2 viral load ($3x10_2$ to $5x10_3$ copies/mL of plasma and only 1 copy per 10^3 to 10^6 PBMCs). This period is followed by the transition to simian AIDS, which is marked by a concomitant fall in CD4+ T cell counts and a rise in HIV-2 viral load. Other features of this condition include pneumonia, gingivitis, and KS-like lesions (5). Of note is the ability to increase the pathogenicity of HIV-2 in baboons by

serial passage (30), which may be explored to study adaptive evolution of HIV species in the immunocompetent host. Using antibodies against human markers it was determined that baboons also regulate markers in a similar pattern to that of humans infected with HIV-1 (32). Flow cytometry analysis revealed the up-regulation of class II molecules in the $CD4^+$ population of cells, while the $CD8^+$ cell population down-regulated CD11b, the complement 3 receptor. CD8 T-cells that have down-regulated CD11b are believed to be a suppressor subset of T-cells (15). Expanding upon this observation, Levy and colleagues have speculated upon the possibility of baboons controlling HIV-2 replication through a non-cytotoxic mechanism using this subset of cells.

In summary, baboons harbor a full complement of endogenous herpesviruses (alpha, beta, gamma) with high homology to the human herpesviruses. The baboon herpesviruses display a similar genomic organization and amino acid sequence similarity of key proteins, and also cause disease phenotypes that approximate human pathology. As such this species provides an attractive alternative to clinical studies or studies in other non-human primate species in order to elucidate basic tenants of viral pathology.

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