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## The Quest for a Small Animal Model for HIV Infection and Disease

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### 1. Introduction

Development of a small animal model to study human immunodeficiency virus type-1 (HIV-1) infection began with the discovery of the disease itself. Such a model would significantly facilitate studies of disease pathogenesis, vaccine and anti-viral drug development and testing. However, HIV-1 replication is subject to a number of species-specific restrictions at the level of cellular entry and/or post-entry. Although many attempts to develop a model that can overcome these cellular restrictions have been attempted, no satisfactory small animal model for HIV-1 infection has been identified to date.

The cotton rat has been a superb model for human infectious diseases. This “new world” wild rodent, that is now highly inbred, was shown to be susceptible to an extraordinary spectrum of human pathogens, particularly viruses. Importantly, it was shown by two different laboratories that cotton rats can be infected with the Human Immunodeficiency Virus (HIV-1), and that virus can be detected long after infection and antibodies are generated against viral proteins. In more recent studies, cotton rat cells were made permissive to HIV infection by engineering the expression of human co-receptors for HIV-1, supporting HIV-1 infection, DNA integration, and more importantly, production of infective HIV particles.

Importantly, the cotton rat is susceptible to other two pathogens that are extraordinarily associated with HIV-AIDS, *Mycobacterium tuberculosis* (TB) and herpes simplex virus (HSV). We will review previous attempts to develop a small animal model for HIV infection and explore the scientific and commercial significance of developing such a model. We will describe the cotton rat model of HIV, TB, HSV as they stand today. Finally, we will describe recent advances in the production of transgenic cotton rats that express HIV receptor molecules.

### 2. Animal models for HIV-1

The total number of Human Immunodeficiency Virus (HIV)-infected people worldwide is estimated at 40 million (and 600 new infections per hour). Preventive vaccine and prophylactic therapies against HIV infection and more efficient drugs for AIDS are not only urgently needed, but also, scientifically possible. However, one of the major obstacles in

translational HIV research rests in the absence of inexpensive and efficient pre-clinical trial models.

Several animal models for HIV-1 infection have been useful, adding complementary information for specific aspects of HIV-1 disease in humans. Limitations of the current models include the limited availability and high cost (non-human primates), absence of or delay in an acquired immunodeficiency syndrome (AIDS), lack of viremia, and permissiveness only to related retroviruses. These models include human HIV-1 in chimpanzees, macaques, mice, rats, rabbits, and Simian HIV in several species of monkeys (Cohen, 2001; Nath, Schumann, and Boyer, 2000; van Maanen and Sutton, 2003).

HIV-1 replication is subject to a series of species-specific restrictions in cells of non-primate species. Binding of HIV-1 envelope protein (*Env*) to both CD4 and the appropriate member of the seven-transmembrane G-protein-coupled receptor superfamily are necessary for efficient entry of HIV-1 (Berger, Murphy, and Farber, 1999; Deng et al., 1996). Several different chemokine receptors (CCR2b, CCR3, CCR5, or CXCR4) or orphan chemokine receptor-like molecules (STRL33, GPR1, GPR15, V28, APJ) may participate in HIV-1 entry, but hCXCR4 and hCCR5 are the principal co-receptors for X4 (T-cell line-tropic) or R5 (macrophage-tropic) isolates, respectively. Blocking and down-regulation of these two cytokine receptors are ways by which their physiological ligands or modified analogues can reduce HIV-1 entry (Stantchev and Broder, 2001).

One approach for developing animal models in laboratory rodents has been to identify and then overcome specie-specific barriers that HIV encounters during its replication. The ultimate goal is to use the knowledge to develop an immunocompetent transgenic small animal model that is fully permissive to HIV replication. The barriers that stall replication in mouse and rat cells have been studied. Mice that express hCD4 and hCCR5 or hCXCR4 were first developed (Browning et al., 1997; Sawada et al., 1998). Preliminary results with these mice were initially exciting because the expression of the transgenes promoted viral entry, but were ultimately disappointing because the mice did not support viral replication (Browning et al., 1997). These results were partly explained by differences between the human and the mouse cyclin T1 (*CycT1*), which is an important cellular component of the p-TEFb transcription factor complex that is responsible for transcription from the viral long terminal repeat (HIV-LTR) (Garber et al., 1998; Wei et al., 1998). Recent studies indicate additional restrictions in mouse cells. Transgenic mice expressing human cyclin T1, human CD4, and the human chemokine receptor failed to produce high levels of HIV (Garber et al., 1998; Mariani et al., 2001) and other downstream elements like the maturation of the *gag* protein to produce p24 were also shown to be compromised in mouse cells (Mariani et al., 2001). These post-transcriptional defects result in a dramatically reduced yield of infectious virus (up to 10,000-fold) in a single cycle of HIV replication, as compared to human cells (Bieniasz and Cullen, 2000).

In 2001, Goldsmith and co-workers made improvements in the rat model for HIV. They first demonstrated that rat cells are more efficient for replication of HIV than mouse cells (Keppler et al., 2001), producing substantial levels of viral p24<sup>gag</sup>. Based on these results, they engineered rats transgenic for the hCD4 and the hCCR5 that expressed the genes in CD4<sup>+</sup> T lymphocytes, macrophages, and microglia (Keppler et al., 2002). They found that these cells could be productively infected by various recombinant and primary R5 strains of HIV-1 *ex vivo*, although the animals do not support viremia during infection.

The laboratory rabbit appears to be susceptible to HIV, but requires large inocula and viral replication does not spread (Dunn et al., 1995; Filice, Cereda, and Varnier, 1988). Rabbit cell lines expressing hCD4 and hCCR5 demonstrated an increase in infection and replication of CCR5 dependent strain of HIV (JR-CSF and YU-2) (Speck et al., 1998). Recently, new studies support the previous evidence for the susceptibility of rabbit cells, especially T cells, to HIV infection and suggest that in addition to the receptor complex transgenesis, modifications in *gag* and possibly *vif* of the HIV-1 might render the rabbit model fully permissive to infection by HIV-1 (Tervo and Keppler, 2010).

Recently, a small animal model of HIV transmission was developed by transplanting human bone marrow, liver, and thymus (BLT) into severe combined immunodeficient mice (Melkus et al., 2006). Consequently, human APCs and lymphocytes populate the mucosal surfaces, and the model can be used to assess some strategies to prevent vaginal HIV transmission (Denton et al., 2008). Further, once infected, the BLT mice generate humoral and cellular HIV-specific immune responses (Brainard et al., 2009). Some of these models allow transmission of HIV via the vaginal and rectal mucosa and display high-level viremia and CD4 T cell depletion. Unfortunately, these models are technically challenging, time-consuming, and not amenable to widespread use. Moreover, HIV-1 infected, xenotransplant mice mount low or dysfunctional adaptive immune responses to HIV infection, limiting these studies of natural immune control and vaccine testing.

### 3. The cotton rat

The cotton rat is a common New World rodent ranging in distribution from the southern United States through Mexico, Central America, Colombia and Venezuela. Eight species are recognized, with a karyotype ranging from 22 to 52 chromosomes. The most recent classification is to the Subfamily *Sigmodontinae* of the family *Cricetidae*, which includes New World mice, rats, voles, lemmings and muskrat. *Sigmodon hispidus* is the most commonly used cotton rat in biomedical research, but some investigators have also utilized laboratory-bred *S. fulvoiventer* (Piazza et al., 1992; Porter et al., 1991).

In the 1930's, it was discovered that inoculation of the cotton rat with poliovirus induced a paralytic disease, while other laboratory rodents did not develop disease (Armstrong, 1939). For over a decade, *S. hispidus* remained the prime animal model for polio until supplanted by monkeys and mice, with mice requiring extensive adaptation of virus. Since then, the cotton rat has been extensively used as a model to study different aspects of infection by respiratory syncytial virus (Li et al., 2000; Malley et al., 1998; Prince et al., 2001; Prince et al., 1978; Prince et al., 1999; Rodriguez et al., 1997; Tang et al., 2001), influenza A and B (Sadowski et al., 1987), parainfluenza viruses types 1, 2, and 3 (Ottolini et al., 2000; Porter et al., 1991; Prince et al., 2001; Sadowski et al., 1987), herpes simplex virus type 1 (HSV-1) (Lewandowski et al., 2002), HSV-2 (Yim et al., 2005), measles virus (Niewiesk, 2001; Niewiesk et al., 1997; Wyde et al., 1999), as well as several serotypes of adenovirus (Brunori et al., 2001; Ginsberg et al., 1989; Ginsberg, Moldawer, and Prince, 1999; Rojas-Martinez et al., 1998; Tsubota et al., 1998; Wildner and Morris, 2002). Finally, cotton rats are also natural reservoirs of several viruses of importance as emerging human pathogens. These include Venezuelan equine encephalitis (Wang et al., 2001), Guarani and Pirital viruses (Fulhorst et al., 1999); and several species of hantavirus (Fulhorst et al., 1997; Glass et al., 1998; Hutchinson, Rollin, and Peters, 1998; Mantooth et al., 2001).

*S. hispidus* and *S. fulviventor* are fully inbred and both species are available from the Sigmovir Biosystems Inc. colony, a USDA licensed dealer for cotton rats.

#### 4. HIV infection in cotton rat

Infection by HIV is defined as the replication of detectable virus in the host and the development of antibodies against HIV-1 proteins. Previously, one laboratory in the U.S. (Langley, Prince, and Ginsberg, 1998) and another in Russia (Rytik et al., 1995; Rytik et al., 2004) demonstrated that HIV-1 was detected in tissues of cotton rats previously infected with HIV-1. In the U.S. study (Langley, Prince, and Ginsberg, 1998), cotton rats were infected with HIV-1 and proviral DNA was detected in peripheral blood mononuclear cells (PBMCs) and tissues including spleen, thymus, and bone marrow from infected animals. Virus stimulated a strong, specific, and long-lasting immune response (in some animals included neutralizing antibodies and antibodies recognizing major HIV antigens) that was maintained up to 1 year post-infection. Although not demonstrable by direct culture of PBMCs or tissues from infected animals, infectious virus replicated at a low level in PBMCs of these animal because its presence was detected in animals that received three serial passages of blood from the original infected cotton rats.

In addition, Rytik and collaborators have also described the permissiveness of the cotton rat to HIV-1 infection by detection of viral DNA in spleen and brain (100% of the animals after 6 month), increase in mortality (17%), and morphological changes in cells of the central nervous system (CNS). These data strongly indicate that non-transgenic cotton rats are semi-permissive to HIV-1 replication. These findings imply that a productive infection may occur in cotton rats. The cotton rat offers several advantages for the development of an animal model, including small size, convenience of breeding, and the increasing availability of reagents to study the immunological and pathological aspects of HIV-1 disease (R&D Systems Inc).

##### 4.1 Cotton rat primary macrophages support HIV-1 gene expression

Recently, the ability of cotton rat cells to support HIV-1 transcription was assessed by our laboratory using macrophages from two different cotton rat species (*S. hispidus* and *S. fulviventor*), from BALB/c mice, and from humans. Macrophages were transfected with a luciferase reporter gene encoding pNL4 env-R+, which provides a quantitative marker of HIV-1 gene expression. Macrophages from *S. hispidus* and *S. fulviventor* supported transcription of the HIV-1 derived backbone as indicated by enhanced luciferase activity compared with that of cells transfected with the control promoter-less luciferase construct (Fig. 1). The levels of transcription found in cotton rat macrophages were comparable to that measured in human macrophages, and all were significantly greater in comparison to mouse macrophages transfected with the HIV-1 reporter plasmid. Interestingly, the levels of transcription in macrophages of *S. hispidus* was at least 10 folds higher than the activity recorded in macrophages of humans or *S. fulviventor*. Although the nature of this high transcription efficiency of the LTR in *S. hispidus* is unknown, it could be related to the lift of a particular blockage or to an increase RNA/protein stability of luciferase. Transfection efficiencies measured by the expression of a CMV promoter-driven  $\beta$ -galactosidase activity were equivalent in cells of all species. These data indicate that cotton rat macrophages support transcription from the HIV-1-LTR and apparently lack the transcriptional blocks found in mouse cells.

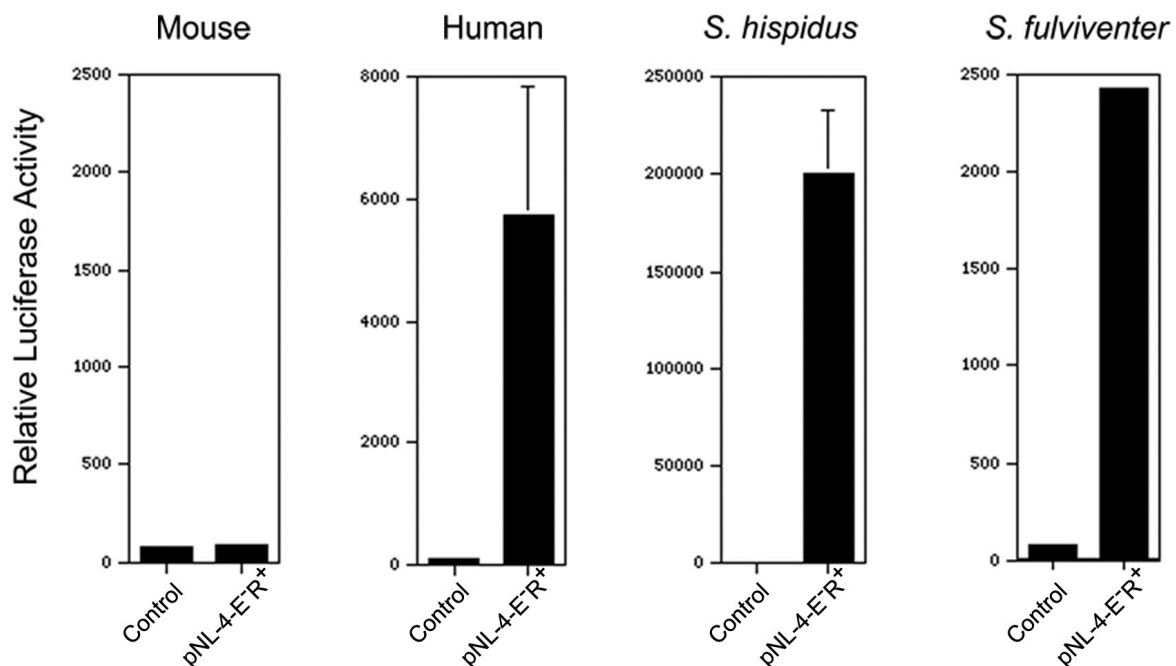


Fig. 1. Macrophages from *S. hispidus* and *S. fulviventer* supported transcription of the HIV-1 derived backbone. Mouse, human, *S. hispidus* and *S. fulviventer* macrophages were transfected with a control plasmid (pGL3-basic, Promega) or a plasmid containing a HIV-1 NL-4-E-R<sup>+</sup>. Human macrophages were prepared by differentiating elutriated monocytes (from the NIH Blood Bank) for 14 days in high-cell density cultures of D-MEM media supplemented with 10% human AB serum, 2 mM L-glutamine and antibiotics in 100 mm square Petri. Cotton rat peritoneal macrophages from *S. hispidus* and *S. fulviventer* were prepared by injecting 3-month-old rats intraperitoneally with 8 ml of thioglycollate broth. Mouse macrophages were obtained in similar fashion injecting 3 ml of thioglycollate broth into the peritoneal cavity of Balb/c mice. Four days post injection, animals were sacrificed by CO<sub>2</sub> inhalation and the peritoneal cavity was washed twice with cold saline solution. Cells obtained were seeded in culture plates as indicated for human macrophages. For transfection of human, mouse, and cotton rat macrophages the ratio of transfection reagent in  $\mu$ l (FuGENE 6, Roche Molecular Biochemical) to NL4-3 derived backbone plasmid in  $\mu$ g was 4 to 1, where the total of 4.5  $\mu$ g of plasmid DNA were used for each 10<sup>6</sup> macrophages. Transfection was carried out overnight at 37°C and the next day macrophages were washed and incubated for an additional 48 h before lysis and quantification of luciferase activity. The results represent luciferase activity obtained from transfected cells in triplicate wells from a representative experiment.

#### 4.2 Cotton rat cell lines expressing the HIV-1 receptor complex are susceptible to HIV-1 infection

Two different cotton rat cells lines, CCRT (an osteosarcoma) and VCRT (an undifferentiated spindle cell sarcoma), that were selected for expression of hCD4/hCXCR4 and hCD4/hCCR5, were tested for infection with three well characterized isolates of HIV-1 virus: the MN isolate (a T-tropic HIV isolate that infects T cell lines and peripheral T cells, but not monocytes, and uses hCXCR4 as co-receptor), and the BAL and US1 isolates (M-tropic HIV isolates that infect monocytes and use hCCR5 as co-receptor). In all cases, the

levels of p24<sup>gag</sup> in the supernatant of cotton rat cells expressing the HIV receptor complex were significantly higher than in control, untransfected cell cultures, with a peak of p24<sup>gag</sup> production evidenced on day 6 post-infection (Blanco et al., 2009). Fully mature, infectious HIV-1 particles were efficiently synthesized and assembled in HIV-1-infected cotton rat cells since PHA-activated PBMCs (pool of human PBMC from negative donors) or H9 cells incubated with the derived supernatants from cotton rat cells produced detectable amounts of p24<sup>gag</sup> (~200pg/ml) as early as day 3 post-transfer of all cotton rat-derived stocks. Furthermore, proviral DNA was detected in infected cotton rat cells, and subsequent direct cloning demonstrated that HIV-1 DNA integrates into the genome of infected cells (Blanco et al., 2009). The sequence of one of the integrated fragments (~ 1.6 kb) revealed the presence of 650 bp corresponding to sequence of the 5' LTR of HIV-MN attached to 950 bp of a cotton rat genomic DNA sequence (GenBank acc# AY703985), and further demonstrates that cotton rat cells are able to support integration of viral DNA in their genome (Blanco et al., 2009).

## 5. The cotton rat model of tuberculosis

HIV fuels the TB epidemic in many ways. HIV promotes progression to active TB in both categories, that is, people with recently acquired TB and those with latent *Mycobacterium tuberculosis* infection (LTBI). HIV is the most powerful known risk factor for reactivation of LTBI to active disease. HIV also appears to increase the risk of pediatric TB, which is itself difficult to diagnose. A small animal model that is susceptible to infection with both pathogens could lead to development of treatments and vaccines that can target more efficiently this unparalleled problem for the population of third world countries.

The natural history of TB infection in *S. hispidus* and *S. fulviventor* has been studied (Elwood et al., 2007). The relatively short life span of the cotton rat (12-18 months) makes it possible to study TB infections throughout the entire life span of the animal. The studies demonstrated that young cotton rats experience a primary tuberculous pulmonary infection characterized by typical granuloma formation. There were differences in response to infection between the two species, with *S. fulviventor* demonstrating greater mortality than *S. hispidus*. Gross inspection of TB-infected cotton rat lungs show whitish nodular lesions and large numbers of TB ( $1 \times 10^{5-7}$  cfu) were cultured from granulomas, spleen, and occasionally in smaller numbers from liver and bone marrow. Tuberculous lesions may also be seen in the adrenal glands (other organs remain to be examined) (Elwood et al., 2007). Established granulomas in some cases underwent central necrosis and calcification and cytokine genes are more highly expressed in the granuloma than in the unaffected areas of the lung. A minority of animals, about 20-30% with primary infection, develop serious progressive TB pulmonary disease, wasting, and succumb to infection. The remaining animals control or clear their infection by two to four months after challenged. Later, about half of these otherwise well appearing animals continue to have small numbers of TB recovered from lungs ( $1 \times 10^{2-3}$  cfu) despite no microscopic evidence of inflammation or clinical disease. However, 50% of immunocompetent animals surviving past 9 months demonstrated positive lung tissue cultures for TB without histological evidence of disease. These findings are consistent with the development of LTBI. Furthermore, reactivation of disease occurs in the surviving animals after immunosuppression with cyclophosphamide (Elwood et al., 2009), indicating that a model of HIV-1 infection in the cotton rat more likely will parallel the course of TB disease seen in co-infected individual.

## 6. The cotton rat model of HSV infection

Genital herpes is one of the most prevalent sexually transmitted diseases (STD) worldwide and is the most common cause of genital ulcers. In the US, 17% of the population is seropositive for herpes simplex virus type 2 (HSV-2) and 58% for HSV-1, which is emerging as a major cause of genital herpes infections in developed countries (Roberts, 2005; Roberts, Pfister, and Spear, 2003; Xu et al., 2006). The HSV-2 seroprevalence rates are much higher in some populations, reaching 90-95% among HIV-infected subjects and female sex workers in developing countries where HSV-2 remains the dominant cause of genital ulcerative disease (Nagot et al., 2007). Implications of genital herpes infection include the risk of transmission to sexual partners and offspring as well as an increased risk of acquiring and transmitting HIV. Epidemiological studies consistently demonstrate that mucosal HIV-1 shedding is more frequent and in greater amounts during mucosal and subclinical reactivations (Corey et al., 2004; Nagot et al., 2007; Watson-Jones et al., 2008). HSV-2 can be detected in swabs obtained from the cervix from seropositive subjects by culture on 3% of days and by sensitive DNA PCR on about 20% of days, illustrating the high frequency of asymptomatic shedding (Wald et al., 2000). Being sero-positive for HSV-2 is associated with a 3- to 10-fold increased risk of HIV-1 acquisition in women, based on longitudinal cohort studies showing HSV-2 infection preceding HIV-1 acquisition and adjusted for sexual behavior (Celum et al., 2004; Celum, 2004; Freeman et al., 2006). In sub-Saharan Africa, more than a quarter of incident HIV infections may be attributed directly to HSV-2 (Abu-Raddad et al., 2008). A recently completed Phase IIb study, CAPRISA 004, found that 1% Tenofovir (TFV) vaginal gel was effective in reducing HIV transmission to high risk, seronegative, sexually active women (Abdool Karim et al., 2010). An unanticipated finding in these trials was that TFV gel provided 51% protection against HSV-2 (Q. Abdool Karim, unpublished data). Together, these results highlight the importance of the development of a preclinical model for testing combined therapies against HIV and HSV.

Female cotton rats (*S. hispidus*) are susceptible to genital HSV infection and do not require hormonal treatment to become infected (Yim et al., 2005). After HSV inoculation, animals develop lesions by day 12, without mortality. This contrasts significantly with the murine model, where medroxyprogesterone treatment is required for consistent infection, a higher inoculum is typically required, and mice develop hind limb paralysis and must be euthanized (Parr et al., 1994; Parr and Parr, 2003). In humans, primary genital herpes infections may be associated with constitutional symptoms, aseptic meningitis, and clinically asymptomatic spread of the virus to liver, lungs, and kidneys. In cotton rats, viral DNA was readily detected in vaginal swabs on days 3, 5, and 7 post-infection and could also be detected in the liver, lung, kidney, lumbosacral cord, and brain on the same days. Viral DNA was detected 100 days post-infection in lumbosacral cord, but not the brain, suggesting a state of latency in cotton rat dorsal root ganglia. Following healing of the primary lesions, 15-20% of female cotton rats display clinical signs of spontaneous reactivation with lesion formation at any given time (Yim et al., 2005). The lesions associated with reactivation are generally smaller than primary lesions, similar to human disease. Spontaneous recurrences are often preceded by virus being detected in vaginal swabs by PCR or culture, again similar to the human situation. Reactivation can be enhanced experimentally by dexamethasone treatment, increasing the rate to two- to three-fold higher than the rate of spontaneous reactivation.

Clinically silent reactivation of HSV is much more common than previously recognized and may play an important role in fueling both the HSV and HIV epidemic. For example, in a



study of shedding in HSV-2 seropositive subjects who self-collected swabs 4 times daily for 60 days, HSV-2 was detected by PCR on 19% of days with a median duration of 13 h (Mark et al., 2008). Intermittent spontaneous viral shedding was observed in the absence of clinical lesions and was also detected by PCR and culture prior to the onset of clinical recurrences (Yim et al., 2005); these findings are consistent with those observed with human HSV infection and set up a potential valuable model of HSV and HIV co-infection and treatment.

## 7. Progress toward the development of a cotton rat model of HIV infection

Mammalian transgenic experiments have contributed tremendously to our understanding of numerous complex biological processes. While other laboratory animals have been used to produce transgenic lines, genetic manipulation has never been attempted in cotton rats. Development of transgenic cotton rat that is permissive to infection with HIV-1 was considered a project of sufficient importance to justify the development of the transgenic technique in this relatively new animal model. Since cotton rat stem cells are not available, pronuclear microinjection of DNA and subsequent embryonic transfer is required. To do that, an entire characterization of the reproductive habits of the cotton rat *S. hispidus* (52 chromosomes, inbred for more than 70 generations) including understanding the anatomy of its reproductive system, mating, and mothering habits, hormone stimulation, and fertilized egg recovery was required to optimize specific parameters for the production of transgenic cotton rats.

Female cotton rats maintained in 12-hour light-dark cycle (lights off from 6 PM to 6 AM) ovulate approximately every 9 days. Superovulation by hormone injection has been used in mice and rats to increase the number of one-celled fertilized eggs to use for microinjection. This is achieved by a course of treatment with pregnant mare serum gonadotrophin (PMS), followed by human chorionic gonadotrophin (HCG). The optimal age for hormone treatment of female cotton rats was 12 weeks, with the treatment consisting of 30 IU of PMS, followed with the same amount of HCG, 4 days later. Following these pretreatment conditions, matings were successful 65% of the time (*i.e.*, 65% of females exhibit a copulatory plug) producing an average of 6 fertilized eggs per female (Fig. 2).

Two hours after coitus, fertilized eggs can be retrieved from the oviduct (Fig. 3A). The shape and size of the cotton rat fertilized eggs resemble those of mice (Fig. 3B) with a distinguishable male and female pronucleus (FIG. 3C). Microinjection is performed using standard procedures by injecting 1 pl of purified and linearized DNA into the male pronucleus (Fig. 3D). Pseudopregnant recipients are used as surrogate mothers to nurture microinjected eggs to birth. These are young female cotton rats that are set for mating with vasectomized males. First, young female cotton rats at the peak of oestrus are identified and placed with vasectomized males at the beginning of the dark cycle. The mating rate of the young females with the vasectomized males is ~30%.

There is a very different anatomy of the cotton rat female reproductive system when compared to the mouse or laboratory rats, *e.g.*, the mouse and the rat have an evident ampulla where the fertilized eggs are located and where the transfer of embryos take place through the infundibulum. However, we could not find any evidence of the existence of an ampulla in the cotton rat. The infundibulum, however, is located inside the bursal sac as in the mouse. In contrast to the mouse that has the infundibulum free and accessible into the bursa to transfer the eggs, the cotton rat infundibulum is associated with the wall of the bursal sac. Eggs are implanted in the part of the oviduct that is proximal to the bursal sac

(where the ampulla is anatomically located), and where the eggs are located at 20 hr post-coitum in the superovulated females (Fig. 3A).

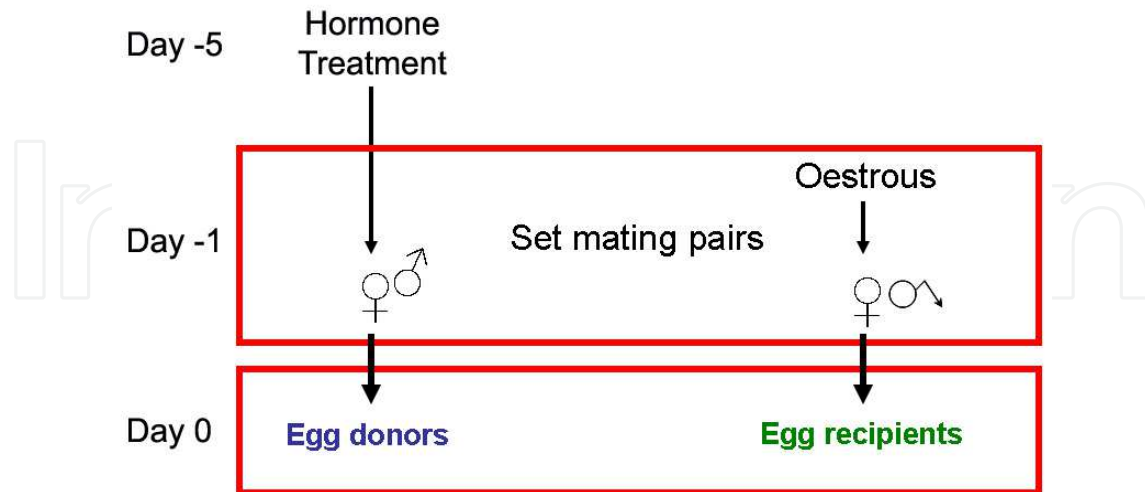


Fig. 2. Schematized protocol for the isolation of cotton rat fertilized eggs (egg donors, left side), and for the preparation of recipient pseudo-pregnant females (egg recipients, right side). Super-ovulation of female cotton rats is achieved by course of treatment of PMS followed by HCG before caging them with males for mating. In addition, female cotton rats in estrous are identified and set in mating pairs with vasectomized males. On day 0, females that have copulatory plugs are identified; eggs are isolated from oviducts of super-ovulated females, microinjected with DNA, and transferred to oviducts of pseudo-pregnant recipient females.

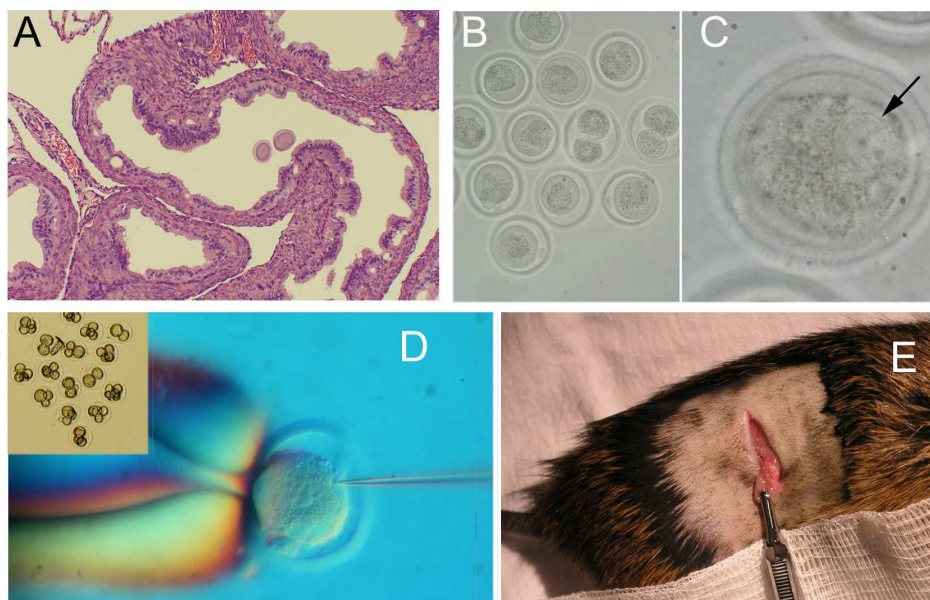


Fig. 3. Development of the transgenic technique in cotton rats. (A) H&E staining of cotton rat oviduct showing the location of the eggs. (B).Cotton rat fertilized eggs isolated from a super-ovulated cotton rat. (C) Fertilized cotton rat egg in which the male pro-nucleus, where DNA microinjection takes place, is depicted. (D) Microinjection of DNA in a fertilized egg. Insert shows viable eggs in culture after DNA microinjection. (E).Exposure of the oviduct of a pseudopregnant female cotton rat for embryo transfer.

## 8. Generation of transgenic cotton rats

The original genomic constructs for human CD4, CCR5 and CytT1 that were previously used in the mouse and rats (Keppler et al., 2002; Sawada et al., 1998), and that expressed their products in a tissue-specific manner (kindly provided by Dr. Dan R. Littman, M.D., Ph.D., Director of the Molecular Pathogenesis at Skirball Institute of Biomolecular Medicine) were purified to homogeneity for pronuclear microinjections. In the first set of microinjections and embryo transfer experiments, a set of three founders (2 females and one male) were obtained. After crossing, the F1 generation was genotyped for human CD4 and CCR5. Several animals in the F1 generation were positive by PCR and Southern blot genotyping for hCD4 and CCR5, indicating the production of transgenic cotton rats (Fig. 4). None of the animal genotyped were found to be transgenic for both transgenes. We are currently in process of determining expression of these genes in the transgenic cotton rats in order to produce double transgenics and subsequently initiate infection experiments to determine the degree of susceptibility to HIV-1 infection achieved.

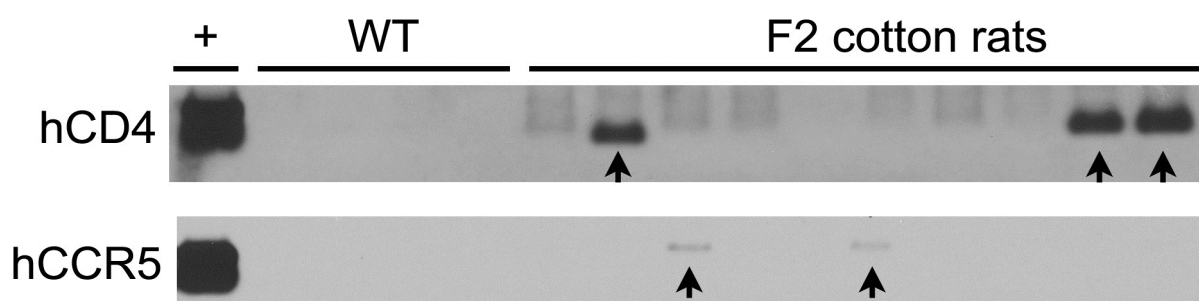


Fig. 4. Genotyping the F2 generation of cotton rats harboring transgenic hCD4 (upper panel) and transgenic hCCR5 (lower panel) by RT-PCR followed by Southern blot. PCR amplifications using DNA from the original transgenic constructs (+), and from wild-type cotton rats (wt) are depicted as controls.

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## **HIV-Host Interactions**

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HIV remains the major global health threat, and neither vaccine nor cure is available. Increasing our knowledge on HIV infection will help overcome the challenge of HIV/AIDS. This book covers several aspects of HIV-host interactions in vitro and in vivo. The first section covers the interaction between cellular components and HIV proteins, Integrase, Tat, and Nef. It also discusses the clinical relevance of HIV superinfection. The next two chapters focus on the role of innate immunity including dendritic cells and defensins in HIV infection followed by the section on the impact of host factors on HIV pathogenesis. The section of co-infection includes the impact of Human herpesvirus 6 and *Trichomonas vaginalis* on HIV infection. The final section focuses on generation of HIV molecular clones that can be used in macaques and the potential use of cotton rats for HIV studies.

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