

The Guinea Pig as a Model of Infectious Diseases

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The words 'guinea pig' are synonymous with scientific experimentation, but much less is known about this species than many other laboratory animals. This animal model has been used for approximately 200 y and was the first to be used in the study of infectious diseases such as tuberculosis and diphtheria. Today the guinea pig is used as a model for a number of infectious bacterial diseases, including pulmonary, sexually transmitted, ocular and aural, gastrointestinal, and other infections that threaten the lives of humans. Most studies on the immune response to these diseases, with potential therapies and vaccines, have been conducted in animal models (for example, mouse) that may have less similarity to humans because of the large number of immunologic reagents available for these other species. This review presents some of the diseases for which the guinea pig is regarded as the premier model to study infections because of its similarity to humans with regard to symptoms and immune response. Furthermore, for diseases in which guinea pigs share parallel pathogenesis of disease with humans, they are potentially the best animal model for designing treatments and vaccines. Future studies of immune regulation of these diseases, novel therapies, and preventative measures require the development of new immunologic reagents designed specifically for the guinea pig.

Abbreviations: BCG, bacille Calmette–Guérin; C4D, fourth component of complement; CXCR1, IL8 chemokine receptor; DTH, delayed-type hypersensitivity; GPIC, guinea pig inclusion conjunctivitis; MHC, major histocompatibility complex; PLL, poly-L-lysine; TGF β , transforming growth factor β ; TNF α , tumor necrosis factor α .

During the 19th and early 20th centuries, the guinea pig (*Cavea porcellus*) was a popular experimental animal for studying prevalent bacterial diseases such as tuberculosis¹⁵³ and diphtheria,²⁸⁷ both of which efforts led to Nobel Prizes. Furthermore, had it not been for the guinea pig, the famous bacteriologist Dr. Robert Koch may not have developed his 5 postulates of infectious disease etiology, which are essential prerequisites for identifying the causative agent of infectious disease. Since then, the guinea pig has been invaluable in the study of a range of human bacterial diseases (Table 1), including pulmonary, sexually transmitted, ocular and aural, gastrointestinal, and other, threatening and often fatal diseases as well as the discovery of potential treatments and prevention opportunities to combat infection. With respect to the pathophysiologic and immune response to these diseases, the guinea pig, recently designated a nonrodent species,^{60,108} is often more representative of human infection than models such as the mouse.^{38,39,65,113} The guinea pig also shares similarity with the human with regard to hormonal and immunologic responses (that is, thymic and bone marrow physiology, innate immunology, and the complement system^{65,120,121,177,307,328}), pulmonary physiology,¹⁸⁵ corticosteroid response,⁵⁶ need for an exogenous source of vitamin C,⁹⁷ and demonstration of delayed-type hypersensitivity (DTH) reaction after exposure to infection (for example, tuberculosis^{103,177}).

Despite its use in a large number of investigations, a comprehensive review of the guinea pig as a model for bacteria-causing diseases has never been conducted. Therefore, in the present report, a selection of 5 bacterial diseases for which the guinea pig

has been the animal model of choice will be discussed. This discussion will be followed by a summary of what is known about the genetics, immunology, and immunologic reagents and assays relating to the guinea pig. However, use of the guinea pig may also be limited by the fact that the guinea pig is more expensive than other small animal models (that is, murine), and guinea pig immunologic reagents are insufficient (for example, cytokine and lymphocyte marker antibodies and antibody assay systems).^{177,178,197,210,214} Unlike the mouse, gene deletion technology (for example, gene knockout and knock-in, and transgene expression) is not available for the guinea pig, and the guinea pig's genome has not been fully elucidated. Both reagents and genetic information are vital for the assessment and understanding of particular phenomena such as pathology of infection, DTH responses, macrophage activation, T cell proliferation, cytokine production, bacterial virulence, and host resistance. In addition, the development and evaluation of treatments, vaccines, and diagnostic tests for these bacterial diseases could be developed more rapidly and efficiently with the availability of this information.

Pulmonary Diseases

Tuberculosis. Tuberculosis (*Mycobacterium tuberculosis*) is one of the most important bacterial diseases characterized in the guinea pig.^{177,182} The guinea pig model of tuberculosis is created by exposing the animal to a low-dose aerosol of bacilli (10 to 50 CFU), mimicking human transmission. Indeed, unlike other animal models (for example, mouse), substantial research suggests that the guinea pig is a suitable model of primary human tuberculosis because of its extreme susceptibility to the infection, similar symptoms and pathophysiology, DTH response, excellent response to standard oral chemotherapies, and demonstrated protection from infection when administered the bacille Calmette–Guérin (BCG)

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Table 1. Bacteria studied in the guinea pig

<i>Bacillus anthracis</i>	<i>Moraxella catarrhalis</i>
<i>Bacteroides gingivalis</i>	<i>Mycobacterium bovis</i>
<i>Bordetella bronchiseptica</i>	<i>Mycobacterium leprae</i>
<i>Borrelia burgdorferi</i>	<i>Mycobacterium tuberculosis</i>
<i>Brucella abortus</i>	<i>Mycobacterium ulcerans</i>
<i>Chlamydia trachomatis</i>	<i>Mycoplasma pneumoniae</i>
<i>Chlamydia psittaci</i>	<i>Neisseria gonorrhoeae</i>
<i>Corynebacterium diphtheriae</i>	<i>Neisseria meningitidis</i>
<i>Coxiella burnetii</i>	<i>Porphyromonas gingivalis</i>
<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
<i>Francisella tularensis</i>	<i>Pseudomonas keratitis</i>
<i>Helicobacter pylori</i>	<i>Rickettsia mooseri</i>
<i>Haemophilus influenzae</i>	<i>Rickettsia rickettsii</i>
<i>Histoplasma capsulatum</i>	<i>Salmonella typhi</i>
<i>Klebsiella pneumoniae</i>	<i>Salmonella typhimurium</i>
<i>Legionella micdadei</i>	<i>Shigella dysenteriae</i>
<i>Legionella pneumophila</i>	<i>Staphylococcus aureus</i>
<i>Leptospira interrogans</i>	<i>Staphylococcus epidermidis</i>
<i>Listeria monocytogenes</i>	<i>Streptococcus pneumoniae</i>
<i>Haemophilus influenzae</i>	<i>Treponema pallidum</i>

vaccine.^{177,178,212,268} The infected guinea pig also demonstrates lymphadenitis, which is commonly found in children infected with the bacterium.¹³ Moreover, the guinea pig has been used to evaluate the effects of malnutrition on tuberculosis, which is often considered a risk factor among the human population.⁴⁹ However, unlike humans,⁶² the guinea pig infrequently manifests liquefaction and cavitation of pulmonary granulomas within infected lung tissue,^{177,211} and it does not exhibit a latent form of infection.^{178,213}

As a representative model of the disease, the tuberculosis-infected guinea pig has been considered the 'gold standard' in preclinical investigation of novel drugs and vaccines, various methods of their delivery, and evaluation of their safety. The development of improved treatments and preventive vaccines is imperative because traditional chemotherapeutic agents result in hepatotoxicity and low patient compliance.²⁰⁶ Some investigators have evaluated an alternative aerosolized administration of antituberculosis drugs in the guinea pig, which has been shown to reduce tuberculosis infection.^{98,273,274} In terms of prevention, use of the only commercially available vaccine, BCG, remains highly controversial in the human population because of its ability to protect against infection in some subjects but not others.²⁴⁸ Therefore, the guinea pig has been used in various aspects of novel adjuvant and vaccine testing (for example, BCG, recombinant, DNA, subunit, polyproteins, live-attenuated, auxotrophs, and gene-disrupted mutants).^{211,213,265} The guinea pig's immune response to these vaccines is a DTH response, measured by means of a skin test of induration after intradermal injection.^{103,177} In addition to DTH, the guinea pig is being used to develop more specific diagnostic tests.^{102,115} Currently, the only method of determining the success of newly developed vaccines and drugs is to challenge guinea pigs with *M. tuberculosis* and report the number of granulomas and bacterial counts in various tissues at necropsy. However, this process may take several weeks to months. Alternatively, the assessment of chemotherapies and vaccines would

be more rapid if a larger array of monoclonal antibodies and immunologic probes were made specifically for the guinea pig, followed by the development and validation of biomarkers for drug resistance in these animals.

In addition to finding an appropriate vaccine and treatment, the greatest challenge has been full elucidation of the immune response to infection and the basis for the protective effects of the BCG vaccine in the guinea pig. Many researchers have argued that the failure to perform adequate immunologic studies on the tuberculosis-infected guinea pig is the result of lack of sufficient immunologic reagents for this species.^{177,178,210,214} Therefore, some investigators have met this challenge by conducting bioassays,^{84,321} developing recombinant forms for various cytokines,^{52,54,136,160,168} and producing antibodies^{160,168,318} and antiserum¹⁶⁰ against these immune mediators. Others have used molecular techniques such as real-time PCR to determine cytokine and chemokine mRNA levels,^{3,144,319} semiquantitative PCR to extract RNA,^{152,207} and Southern⁶⁵ and Northern blot analyses to study gene expression.^{137,138} More recently, an oligonucleotide microarray for splenocytes of naïve and BCG-treated guinea pigs has been developed.²⁸⁰ The microarray has the advantage of providing information (that is, mRNA expression data) for a large number of cytokines and immunologically related genes. Findings from these procedures in the guinea pig model reveal that both the innate and adaptive immune systems, alveolar macrophages,^{183,329} neutrophils, eosinophils,¹⁶¹ T cells (for example, T γ , T μ , CD2+, CD3+, CD4+, and CD8+ T-helper cells^{10-12,61,107,120,138,152,169,180,181,281}), and numerous cytokines and chemokines are important regulators of the immune response to tuberculosis and granuloma formation in both the human and the guinea pig (Figure 1).

Legionnaires disease. The study of another pulmonary infection, Legionnaires disease, increased in the 1980s after the infamous 1976 outbreak in Philadelphia, when approximately 220 people attending an American Legion convention began exhibiting pneumonia-like symptoms, and 34 of these patients died. During this period, the organism, *Legionella pneumophila* Philadelphia 1 (serogroup 1), was first recognized as the infectious agent in the guinea pig.¹⁷⁶ Use of the guinea pig as a model to study this disease gained further recognition because of its intense susceptibility to the bacterium compared with that of rodent species^{232,322,327} and similar pathologic development and resulting symptoms as those of infected humans.^{66,67,112} Before the development of more sophisticated techniques, the guinea pig was used to isolate the bacterium from collected specimens (that is, water samples).^{78,192} Moreover, the guinea pig model was used to verify that *Legionella* bacteria were not transmitted between subjects (that is, person-to-person) via respiratory droplets.¹⁴¹ Rather, environmental sources, such as showerheads and evaporative coolers, are responsible for creating an aerosolized form of the bacteria from which a person becomes infected.¹⁹²

To induce Legionnaires infection, guinea pigs can be exposed to *L. pneumophila* by aerosol administration^{40,68}, by direct intratracheal instillation^{75,315} or intraperitoneal^{74,232} or intranasal¹⁴¹ inoculation. Approximately 1 wk after inoculation, guinea pigs exhibit similar clinical and pathophysiologic symptoms as humans, such as fever, weight loss, difficulty breathing, and (in some cases) death.¹⁴¹ Furthermore, as in humans, antigen to *Legionella* can be found in guinea pig urine.^{170,313} Several novel antimicrobial agents for human use have been evaluated in the guinea pig model of Legionnaires disease.⁷⁰⁻⁷⁴ However, if left untreated, the guinea

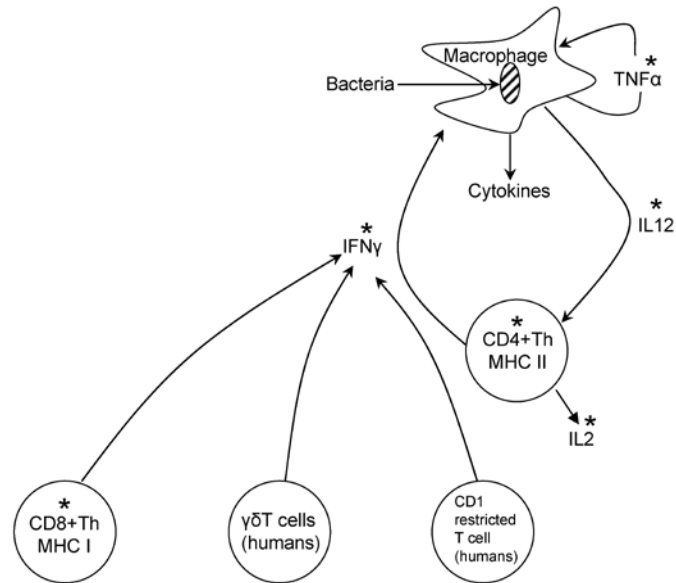


Figure 1. Cascade of immunologic events occurring in the guinea pig model of primary tuberculosis. Antigen presentation occurs by means of the major histocompatibility complex (MHC). Similar to the mechanism in humans, *Mycobacterium tuberculosis* (Mtb) bacteria are engulfed by alveolar macrophages. The bacilli, in turn, inhibit phagolysosomal fusion within macrophages. Macrophages produce cytokines (TNF α *, IL1*, IL8[CXCL8]*, IL10*, IL12*, TGF β *, MCP1 [CCL2]*, GM-CSF*, and RANTES [CCL5]*). Mtb antigens also are presented to dendritic cells, and the antigens are carried from lungs to draining lymph nodes. CD4+ and, over time, CD8+ T helper cells become activated in lymph node tissues. CD4+ cells produce IL2 to increase the pool of lymphocytes specific for antigen. The primed T cells migrate back to the site of infection within the lungs and cause granuloma formation. *, immune mediator examined in the guinea pig model.

pig demonstrates splenic necrosis and a severe form of pneumonia that is fatal to this species.^{15,315}

This guinea pig model has also been used to determine which virulence factors of *Legionella* induce infection.^{87,314} For instance, attenuation in virulence has been demonstrated in guinea pigs after several passages of the bacterium on Mueller–Hinton agar.¹⁷⁵ However, virulence of the bacterium increased when the guinea pigs were exposed to bacteria grown at a lower temperature (25 °C) versus a higher temperature (41 °C). Furthermore, when guinea pigs were exposed to a protease produced by the bacteria, inflammatory pathologic lesions occurred within the lungs of guinea pigs after intranasal or intratracheal inoculation. These lesions were comparable to those evoked after aerosol exposure of *L. pneumophila* to guinea pigs.^{14,57} Some investigators²⁹ have suggested that this protease may be the major secretory protein (produced by the *proA* gene) of *L. pneumophila*, but this assignment remains controversial (for differing opinions^{29,190,191}). Other factors that may contribute to the bacterium's virulence, such as lipopolysaccharide,¹⁶⁶ macrophage infectivity potentiator,²⁸⁸ and the genes *proA*, *dot-icm* complex,^{23,76,191} *ptsP* ortholog,¹¹⁷ and *IvgA*,⁷⁷ have been evaluated in the guinea pig. The guinea pig has also been used in the study of virulence conversion in *L. pneumophila*, which may provide some understanding of the complex nature and evolution of the bacterium.¹⁸⁸

Despite the many studies conducted with this relevant animal model, very little information exists regarding the guinea pig's

immune response to *L. pneumophila*. As observed with tuberculosis bacilli, *L. pneumophila* has the ability to evade destruction by inhibiting phagosome–lysosome fusion in macrophages^{124,125} and preventing the phagosome's acidification.¹²⁵ The rate of replication within the macrophage is much more rapid in *Legionella* infection than with *M. tuberculosis*.⁹⁵ The few immunology studies conducted in the guinea pig have revealed that the bacteria may be toxic extracellularly,¹³² but intracellular invasion of macrophages is crucial for infection and pathogenesis in both humans and guinea pigs.^{95,126} Some researchers²³² have reported that the guinea pig's high susceptibility to infection may be that its macrophages are unable to produce nitrites (that is, reactive nitrogen species), a factor typically associated with the macrophage's ability to destroy intracellular pathogens.

Nevertheless, as in humans,¹²³ guinea pigs require an effective innate (or cell-mediated) immune response for protection from infection.^{94,95,123,216} For example, after sensitization (that is, immunization or subclinical exposure) to the bacterium, guinea pigs exhibit a DTH response and an influx in lymphocytes.^{40,94,151,312} To further demonstrate a cell-mediated response, some scientists¹⁵¹ exposed guinea pigs intraperitoneally to low levels of virulent (10⁴ CFU) and high levels of avirulent (10⁸ CFU) *L. pneumophila*. The guinea pigs receiving the low dose of virulent bacteria did not succumb to infection, but they exhibited a DTH reaction and splenic lymphocyte production similar to those guinea pigs that received the high dose of avirulent organisms. These results may provide a potential explanation for the observation that in humans, non-immunocompromised persons do not succumb to infection when exposed to naturally occurring small amounts of *Legionella* spp.¹⁵¹

Little is known about the humoral immune response in Legionnaires disease. Guinea pigs, like humans,^{86,93} produce serum antibodies after infection^{40,94} and after immunization.^{26,94,286} In vitro studies suggest that a T-cell-mediated response and antibody production are important for resolving a sublethal infection in guinea pigs,^{131,204} but the role of antibodies in both species has not been resolved. The full cytokine profile has not yet been determined for the guinea pig's immune response to infection, but various cytokines such as IL1 β , IL4, IL6, IL10, tumor necrosis factor α (TNF α), IFN γ , and IL12 (p40 and p70) have been quantified in human patients.^{95,201,278} In humans, a Th1 response occurs primarily in response to infection,²⁷⁸ but dendritic cells may also play a role in controlling infection.²⁰⁰

To date, a vaccine is not available for the prevention of Legionnaires disease, but the guinea pig has been used in the development and testing of potential vaccine candidates against this intracellular pathogen. For instance, early investigations^{26,40} acknowledged that when guinea pigs are exposed to aerosols of a very low (that is, sublethal) dose or avirulent strain of the bacteria, these animals exhibit a defensive immune response when exposed subsequently to a lethal aerosol challenge of wild-type *L. pneumophila*. The guinea pig has also been used to demonstrate that the protection provided by vaccination is dependent on the route of infection. For example, the guinea pig is protected from intraperitoneal injection of *Legionella* bacteria when vaccinated by the same route with heat-killed and acetone-killed bacteria,⁸⁰ antigenic extracts of *Legionella*,^{22,81} or IgG fraction of *Legionella*-immune goat serum.³¹⁷ In contrast, vaccine regimens consisting of heat-killed and acetone-killed bacteria do not protect guinea pigs when exposed to the aerosols of the bacterium, despite elevated

levels of serum antibody.⁸⁰ This lack of protection conferred by aerosol may be due to failure to induce a cell-mediated immune response when guinea pigs are exposed to bacteria through this particular route.⁸⁰ Lastly, some researchers have been also been interested in exploiting the potential virulence determinants as components of vaccines to induce an immune response in guinea pigs, but none have been successful.^{26-28,40,81,291}

Sexually Transmitted Diseases *Chlamydia*. Whereas sexually transmitted diseases are often difficult to study in humans,²³⁶ chlamydial infection has been studied in a variety of animal models.^{106,219} Of these models, the infection with the chlamydial agent of guinea pig inclusion conjunctivitis (GPIC) most closely resembles the sexual transmission and infection in humans with *Chlamydia trachomatis*.^{9,159,194,219,246,292} In the GPIC model, male guinea pigs are infected intraurethrally with GPIC and then housed with female guinea pigs to sexually transmit the disease. The dose of bacteria necessary to promote human infection has not been determined, but in guinea pigs, the dose of bacteria passed from a male to female guinea pig during sexual intercourse is approximately 10^2 inclusion forming units.²⁴² The infection in male^{127,159,219} and female^{244,270} guinea pigs is much shorter in duration than in humans (approximately 20 d in guinea pigs versus approximately 150 d in humans), and symptoms of infection may include an acute inflammatory response.²⁴⁶ There is no occurrence of heavy discharge from the urethra in male guinea pigs,^{106,219,246} but this symptom parallels humans, who are often asymptomatic with no apparent exudate.²⁴⁷ Furthermore, the guinea pig's reproductive physiology and estrous cycle (15 to 17 d) are similar to that of humans and, analogous to human infection and transmission, pregnant female guinea pigs can pass this disease to their offspring during parturition, resulting in congenital conjunctivitis.¹⁹³ As in humans, repeated infection in the guinea pig results in a chronic inflammatory response and oviduct damage.²⁴³

The guinea pig has been used to understand the course of the chlamydial infection, its transmission, and immune response, but again, as with the previously described diseases, well-defined immunologic reagents for researchers using this model are scarce.^{234,289} In this species, as in humans, both cell-mediated and humoral immunity are important defenses against chlamydial infection^{235,236,241,244,246} as well as reinfection.¹³³ The importance of T cells was demonstrated when antithymocyte serum was administered to guinea pigs and infection did not resolve.²³⁵ Furthermore, a T helper 1-like immune response has been suggested for the guinea pig with regards to chlamydial infection.²⁸⁹ In the infected female, studies involving quantification of T cells in the GPIC model have demonstrated a high degree of immunity to early reinfection,²³⁹ but as in humans,²⁵³ this immunity is short-lived. Furthermore, certain outer-membrane proteins of the GPIC agent may be responsible for antibody production (that is, serum IgG and IgA) in female guinea pigs.^{16,239} To date, the only cytokine evaluated in this model has been tumor necrosis factor α (TNF α).^{63,64} These studies report that TNF α levels in genital tract secretions are significantly elevated after 3 d of infection in female guinea pigs,⁶⁴ but the purpose of this cytokine remains unclear.⁶³ Also as in humans,²⁹⁰ estrogen supplementation^{218,237,245} and oral contraceptives⁸ administered to female guinea pigs exacerbate infection, but this effect does not occur with progesterone treatment.²¹⁷

A few studies have been conducted with male guinea pigs, but suppression of the humoral immune response in male guinea

pigs by means of cyclophosphamide treatment resulted in an inability to resolve the infection. This result further suggested that antibodies play an important role in resolution of infection.^{244,246,292} Moreover, the male guinea pig exhibits a much higher degree of immune resistance to repeated chlamydial infections than do female guinea pigs,^{127,219,246} a phenomenon that has also been reported in sexually active humans,²⁵³ but the mechanism behind this resistance remains to be determined.

Equally important to understanding the transmission and pathogenesis of this infection is the development of a preventative vaccine against *Chlamydia*. No current vaccine prevents chlamydial infection, but several investigators have used the guinea pig to search for a vaccine. For example, immunization studies have included: prior ocular GPIC infection followed by urethral challenge of GPIC in male guinea pigs,¹²⁷ testing of subcutaneous administration of UV-inactivated GPIC in both sexes,^{219,240} purified major outer membrane protein¹⁷ from GPIC, and intraperitoneal injection of immunoglobulins (IgG and IgA).²³⁸ All of these studies have demonstrated that these preventative measures do not offer complete inhibition of infection during a chlamydial challenge, but the intensity of the infection is reduced^{7,242} (for a complete list²³⁴).

Syphilis. Studies of the guinea pig syphilitic model can be found as early as 1910,³⁰⁰ but this model did not receive recognition until the early 1980s and late 1990s. Research using this model has tapered off since. Nonetheless, the guinea pig is well-suited for investigations of syphilis, which is caused by the bacterium *Treponema pallidum* ssp. *pallidum*, because of this model's similarity with humans in terms of the humoral response to infection and histopathologic events.^{227,300,311} Although the rabbit model may be more susceptible to infection, the guinea pig has proven useful because it is less expensive and inbred strains are available, making the guinea pig a favorable model for studies of adoptive transfer, immunology, and genetic variations in susceptibility.^{224,225,300,309} In addition, guinea pigs are more vulnerable to infection than are rodents such as mice, rats, and hamsters.³⁰⁰

To create the guinea pig syphilitic model, the infection is performed by intradermal injections of the Nichols strain of bacteria (10^2 – 10^5 organisms) in a depilated pubic region or hindleg.^{302,307} Much like in humans,^{156,205} indurated papular lesions (approximately 4 to 5 mm in diameter) form after 4 to 7 d of infection and then progress to more severe ulcerative lesions (that is, chancre at 10 to 14 d) from which the organism disseminates. The chancre lesion may be present for 30 to 60 d, depending on the guinea pig strain.³⁰⁸ This progression results in complete healing of the lesion after this period, however the bacteria remain alive but in a latent form in the body. Except for the development of the lesion, the guinea pig is asymptomatic, similar to many humans infected with the bacteria.²⁰⁵ Also as in humans, the spirochete bacteria and treponemal antibodies are found primarily in the inguinal lymph nodes, heart, and brain of the guinea pig.^{227,293} Both species produce natural antitreponemal antibodies (that is, IgG and IgM), and in response to infection, they generate specific and nonspecific antibodies and circulating immune complexes.^{6, 20,135,227,296,302,305,311} Furthermore, subsequent exposure to *T. pallidum* (after approximately 3 mo) will not result in development of additional chancre lesions in either the human and guinea pig, most likely because of functioning humoral immune responses (that is, antibody production²²²) and autoantibodies such as rheumatoid factor.²¹ Contrary to the disease in humans, syphilis in the guinea

pig does not develop into secondary (affecting skin and internal organs) and tertiary (that is, neural and cardiovascular pathologies) forms of the disease. Rather, the guinea pig's immune system is capable of localizing the bacteria, and therefore, the guinea pig is suitable as a model of primary infection.³⁰⁴

Susceptibility of guinea pigs to infection is age-, strain-, and gender-dependent.^{135,302,304,308} However, the causes of variation in susceptibility among guinea pigs (and humans) are currently unknown and cannot be explained completely by the relative natural antitreponemal antibody titers in sera.¹³⁵ For example, male guinea pigs have a greater incidence of lesions than do female guinea pigs.³⁰⁰ Young adult guinea pigs (3 to 6 mo) are most susceptible to infection, but very young animals (1 to 7 d) and older animals (12 to 30 mo) demonstrate higher natural antibody titers than do animals of intermediate age (1 or 3 to 6 mo).^{135,304} Young animals demonstrate ulcerative chancre-like lesions, whereas older animals exhibit nonprogressive papular lesions.³¹⁰ Further, a delay in antibody response occurs after infection in older animals compared with young animals.³¹⁰

In terms of guinea pig strains, those deficient in the fourth component of complement (C4D) are most susceptible to infection. The C4D strain was developed because of a spontaneous mutation (a naturally occurring knockout) that occurred within a multipurpose strain housed at the National Institutes of Health in 1970.⁸² These guinea pigs are immunologically competent and have a similar lifespan as the original complement-containing strain.^{300,302,330} Propensity to infection is next highest in the inbred strains 2 and 13 and Hartley B, and the least susceptible is the Hartley A (Albany) strain.^{300,302} The C4D guinea pig also demonstrates the largest chancre-like lesions (8 to 20 mm versus 6 to 10 mm) which last longer (>60 d versus 30 d) than those of other guinea pig strains. In addition, C4D animals produce the highest natural antibody titers, which have been confirmed to be IgG1 and IgG2, but not IgM, in subtype.^{135,227,302,305} Some researchers³⁰⁰ have proposed that the very high antibody titers reported in the susceptible C4D strain are indicative of other factors (for example, genetics) that play a role in antigen recognition. Recently, the C4D strain has also been recognized as a potential model for the non-venereal version of this disease, yaws, caused by the subspecies *Treponema pallidum* ssp. *pertenue*,³⁰¹ as well as a model of congenital and neonatal syphilis.^{221,294}

Like the other intracellular pathogens previously described, *T. pallidum* has the ability to evade the host's immune system,^{156,205} but the exact mechanism by which this evasion occurs is unknown. In humans and guinea pigs, these protective events may be the result of an effective cell-mediated or humoral immune response.^{205,296,305} Semiquantitative PCR was used to investigate various cytokines including IL1 α , IL2, IL10, IL12p40, TNF α , and transforming growth factor β (TGF β) in hindleg skin specimens of C4D guinea pigs at various time points after infection.³⁰⁷ Among these cytokines, only IL10 expression was significantly higher from 3 d through 30 d when compared with that of noninfected controls, indicating that a T helper 2 response is predominate. This response may be ineffective in the guinea pig because of the long period of resolution to infection in C4D animals,³⁰⁸ the rapid but ineffective antibody response to infection,³¹¹ the delayed resistance to infection,²⁹⁶ and the lack of complete elimination of the pathogen from distant organs.^{251,293} In humans, there appears to be a predominant T helper 1 response to infection (that is, elevated

levels of IL2, IL12, and IFN γ), but data also suggest that a T helper 2 response is important for resolution of infection.²⁸³

In combination with cytokine production, the lesions in the guinea pig demonstrated an influx of mononuclear cells such as CD4+ T cells and B cells, and to a lesser extent, macrophages and CD8+ T cells at 3 to 11 d after the onset of infection.^{300,308} At 7 to 30 d, substantial eosinophils are present within the lesion.^{300,308} Indirect evidence of eosinophilic activation in infected humans (for example, elevated serum IgE concentrations) has also been reported.^{36,111} Within a few weeks after infection, the guinea pig develops a local and systemic immune response along with elevated serum IgG concentrations. Unlike humans, the guinea pig does not appear to produce cardiophilin (Wasserman) antibodies, an indicator of tissue damage^{224,227} (for an alternate view²⁹⁵). Other immune mediators, such as treponemal immobilizing antibodies, appear 3 mo postinfection in strains 2, 3, and C4D guinea pigs.²⁹⁷ Other factors such as circulating immune complexes and antibodies to fibronectin and creatine kinase are elevated in the syphilitic guinea pig, and continue to increase after reinoculation.²⁰ These autoantibodies may play a role in T-cell regulation^{18,19} and prevention of bacterial adherence to cells,⁸⁸ respectively, but their function in the guinea pig remains to be elucidated.

The extent to which T cells play a role in the guinea pig has yet to be established. For example, attempts to evoke immunosuppression in Hartley guinea pigs by cortisone administration failed to result in a more severe form of infection.²⁹⁵ In another study,³⁰³ complement (that is, C3) and T-cell depletion in infection-resistant Albany guinea pigs resulted in a significant increase in susceptibility, but humoral responses (that is, antibodies) were the same as untreated control animals. In a later study,²²⁰ mature T cells were depleted in Strain 2 guinea pigs by thymectomy and irradiation, which significantly decreased the number of lesions compared with those in control animals when both groups were infected with *T. pallidum*. This unusual finding was explained by the possibility of a residual T-cell population, incomplete elimination of peripheral T cells, or the production of a more active antibody response in the thymectomized and irradiated animals.²²⁰ Nonetheless, an intact immune system and functioning T cells are vital for both protection and passive transfer against syphilis in the guinea pig model.^{224,225,296}

The use of antibiotics such as penicillin has been invaluable to decreasing the number of venereal syphilis cases in the United States, but this disease is still a global health issue.²¹⁵ This notion has led to a small number of investigations using the guinea pig model to find a preventative vaccine. Early investigations demonstrated that moderate protection occurred when naïve guinea pigs were inoculated intramuscularly³⁰⁹ or intravenously²²³ with immune serum or intravenously with immune spleen or lymph node cells^{223,309} or IgG fraction^{225,306} from infected guinea pigs. This protective response is most likely not due to *T. pallidum*-immobilizing antibodies but may be elicited by an increase in circulating rheumatoid factor, an immune mediator known to augment binding of an antibody to antigen.²¹ Moreover, with the notion that *T. pallidum* infection results in antibody and cellular responses against the bacterium's protein components, there has been a focus on using these membrane proteins to induce protective immunity. One laboratory^{298,299} has evaluated immunity-inducing substances such as membrane proteins (for example TmpA, TmpB, and TmpC) within the various guinea pigs strains. Of these, only the TmpB showed promising results of smaller le-

sions with shorter durations, significantly lower bacterial counts, and delayed-type hypersensitivity reaction in the highly susceptible C4D guinea pig.²⁹⁸ A vaccine for the prevention of syphilis has yet to be developed.

Staphylococcus aureus Infections *Staphylococcus aureus*, the most common source of nosocomial infections, often results in severe complications such as sepsis, endotoxemia, and possibly death in patients with contaminated surgical or accident or bite wounds, severe burns, and medical devices.¹⁶⁵ Furthermore, the development of methicillin-resistant strains results in higher infection rates and increased difficulty in finding effective treatments.¹⁰⁵ The *S. aureus*-infection albino and hairless guinea pig models have been established to potentially elicit this bacterium's ability to invade the body, the cascade of events following infection, and ultimately attain successful treatments to stop infection. As in man, the guinea pig is highly susceptible to staphylococcal infection,^{79,140} and it has been used in studies ranging from: evaluation of methicillin-resistant *S. aureus*,^{59,189} staphylococcal dermonecrotic reactions,¹⁸⁶ disseminated intravascular coagulation,¹⁵⁰ infective endocarditis,¹⁷² effects of nutrition on infection,^{202,226} determination of bacterial factors such as staphopains (that is, cysteine proteases) that lead to septic shock,¹³⁴ burn/surgical wounds, and infection due to device-implantation. The burn/surgical wound, and device implantation models have been used more extensively in studies relative to the other models. Therefore, only these 3 examples will be discussed in the present review. Regardless of which application, the creation of this infection model permits assessment of different scenarios of contamination that are highly reproducible and representative of various clinical situations. Moreover, the guinea pig should be considered invaluable to the investigation the immune response to *S. aureus*, but unfortunately, researchers have not exploited the guinea pig in the study of immune function related to this disease.

The first of these examples, the infected burn wound model, is created by depilating the dorsal region of the anesthetized animal and then immersing the area repeatedly in hot water (99 °C^{25,116}) or subjecting it to a heated copper plate (150 °C) or cylindrical aluminum templates (75 °C) for several seconds.^{142,209} After the burn injury takes place, the wound is infected by either injecting the bacteria subcutaneously (5×10^5 CFU) or by spreading the bacteria (10^8 CFU) onto the affected area.^{25,209} As a result of infection, the subcutaneous tissue becomes malodorous and contains a purulent exudate along with necrosis.²⁵ Some investigators¹¹⁶ have reported that the metabolic response to severe burn injury in guinea pigs is highly similar to that of the human postburn metabolic response. Furthermore, development of bacterial colonization and changes within the complement component of the immune system in human burn victims is analogous to guinea pigs affected by severe burns.²⁵ Some researchers have advocated that the guinea pig should be used for studies of immunologic abnormalities related to burn injury.²⁵ Other investigations using this burn model have examined phenomena such as the wound healing process¹⁴² and novel antimicrobials.²⁰⁹

Several techniques have been used to develop the guinea pig bacteria-contaminated surgical wound model, some of which may be considered sophisticated, whereas others offer a more simplistic approach. Nonetheless, all are highly informative in the investigation of *S. aureus*. For example, surgical wounds can be created by making a basic skin incision in the animal and contaminating the area with bacteria.²⁷² The following have been tested in

the guinea pig for their ability to reduce bacterial counts: scrubbing and irrigation,^{129,130,228} locally administered anesthetics (for example, lidocaine²⁷²), tissue adhesives,^{128,231} suture material,^{79,187,271} delivery of delayed-release antibiotic,⁹⁶ wound dressings,^{145,173} and topical antimicrobials.³⁵ Others have used the guinea pig to determine that pulsatile lavage of surgical wounds,²⁶³ and anesthesia-induced hypothermia heighten the potential for infection.²⁵⁷ The only known study of immune function in the guinea pig wound model¹⁷³ suggested that natural killer cell and neutrophil activity is upregulated when the wound dressing Acticoat is placed on the wound, while limiting the deleterious effects of inflammation. The guinea pig has also been used as a crush or bite wound model, in which paravertebral incisions are clamped with hemostats for 5 s and then infected with bacteria.¹⁵⁸ This type of model has been used to evaluate various antibiotic irrigation solutions.¹⁵⁸

Two other wound models include the elegantly designed small-inoculum prophylaxis model^{140,147,148} and the 'tissue-cage' guinea pig wound infection model (also called the 'device-related model'). To create the small-inoculum prophylaxis model, a grid of 12 sites is drawn onto the dorsal region of the guinea pig, and each of these sites is inoculated intramuscularly with a bacterial suspension.^{140,184} This model has been used to evaluate antibiotics¹⁴⁷⁻¹⁴⁹ as well as immune-stimulating compounds as alternatives to antibiotics.^{139,146} The latter model is created by inserting Teflon tubes (perforated with 130 regularly spaced holes each 1 mm in diameter) subcutaneously into the guinea pig by using aseptic techniques.^{104,255,331} After complete healing (2 wk), the interstitial exudate is checked for sterility and the tissue cages are then inoculated with bacteria (10^5 to 3×10^5 CFU). Subsequent removal of the infected exudates occurs at various time points and is examined. This model has several advantages: (1) it is representative of human subcutaneous foreign body abscesses; (2) the infection within the model remains localized and does not spread systemically;^{333,334} and (3) measurements of antibiotic concentrations can be made directly at the tissue level.²⁸⁴ Although studies of the immune response to device-infection are limited in this model, polymorphonuclear leukocyte activity (that is, low amounts of granular enzymes and respiratory burst attenuation) and opsonization of the bacteria are reduced in the guinea pig after tissue cage inoculation which may explain the difficulty in preventing prosthetic-related infections.^{332,333} With this model, other researchers have examined the bacteria's contributors to the bacteria's virulence,^{104,255} bacterial capsular polysaccharides, and a large number of antibiotics.^{37,46,55,252,284}

In addition to those of burns and wounds, *S. aureus* is also a primary source of prosthesis-related infections. According to electron micrographs, staphylococcal device contamination appears similar in both humans and guinea pigs.^{69,89} *S. aureus* adheres to the device creating a biofilm by way of cell wall adhesins that recognize host proteins (for example, fibrinogen and fibrin), surrounding the biomaterial shortly after implantation.^{90,285} These biofilms are of concern because they do not respond well to antimicrobial therapy, and often the device has to be removed.⁵⁸ To study these adherence factors, the small-inoculum prophylaxis guinea pig model has been used.^{140,184} This model has demonstrated that recombinant forms of fibronectin-binding protein, when inoculated simultaneously with the bacteria, prevented staphylococcal infection and abscess formation, suggesting that these proteins may serve as a potential prophylactic treatment.¹⁸⁴ Other investigators studying these biofilm adherence factors (and

the genes that produce them) have relied on the guinea pig 'device-related' implant model described earlier.^{85,89,91,316} This model demonstrated that fibronectin plays a role in bacterial adherence, but exopolymers do not.²⁸⁵ Furthermore, this in vivo model correlated well with the in vitro model of device-related infection when various antimicrobials were compared.³⁰ Others have promoted the use of the guinea pig in testing biomaterials that do not harbor infection, such as Gore-Tex.²⁶⁹

Immunology of the Guinea Pig Genetics. Few studies have been conducted on guinea pig genetics as they relate to immune function. The first study of a gene associated with an immune response in the guinea pig was reported in 1963.^{162,163} This gene became activated in response to poly-L-lysine (PLL), poly-L-arginine, copolymer of L-glutamic acid and L-lysine, and hapten conjugates of these polypeptides. Therefore, the gene was given the name *PLL* and was determined to be autosomal dominant and breed-specific (found in 100% of Strain 2, absent in Strain 13, and variable in Hartley). Furthermore, immunogenicity to PLL could be passed on to offspring.^{110,162,163} A number of studies regarding the *PLL* gene occurred during the 1960s and 70s,^{31-34,83,109,157} but more importantly, these investigations led to the discovery of the related major histocompatibility complex (MHC) genes, which consequently were studied for approximately 2 decades in the guinea pig.^{4,31,83,99-101} Other studies relating to the genetics of the guinea pig include the use of the inbred guinea pig strains JY 1, JY 2, JY 9, and JY 10 to investigate the various functions of major histocompatibility.^{50,51} Soon thereafter the natural knockout complement-deficient (C2, C3, and C4D) guinea pigs were discovered.^{24,82,92,264} Genes for the neutrophilic antimicrobial cationic peptides (GNCP1 and GNCP2) have also been characterized.^{195,196} Investigators have examined the genes for the Fc receptor²⁷⁹ and protein products related to the DTH reaction^{207,323} and bacterial infections such as tuberculosis in the guinea pig.^{2,3,168,267,280}

The few studies involving genetics of the guinea pig have revealed striking immunologic similarities between guinea pigs and humans. The following are comparisons that can be made between the 2 species. (1) Guinea pig leukocyte antigen (that is, the MHC in guinea pig) is homologous to the human leukocyte antigen complex. (2) The guinea pig's complement system more closely resembles that of humans than that of the mouse.^{38,39,113,203,256} (3) Unlike the mouse or rat, the guinea pig has several homologues of the human group 1 CD1 proteins (that is, CD1b, CD1c, and CD1e) expressed in lymphoid and nonlymphoid tissues.^{65,120,121} Similar but genetically distinct from MHC, these proteins serve as antigen presenting molecules for nonpeptide antigens to T-cells during infections such as tuberculosis, which makes the guinea pig essential in the study of this and other related diseases.^{120,121,229} (4) Human and guinea pigs appear to have similar patterns of genetic expression of IFN γ and inducible nitric oxide synthase during infection.^{233,319} (5) The guinea pig is an excellent choice for the study of the cytokine IL8 because neither the gene for IL8 nor its receptor, CXCR1, exists in the mouse or rat, but they are present in the guinea pig.^{275,328} (6) Another cytokine, IL12, and both of its molecular components, p35 and p40, are remarkably similar between humans and guinea pigs but differ from those in the murine model.²⁶² (7) The coreceptor, CD8, found in cytotoxic T lymphocytes also demonstrates greater amino acid sequence similarity between humans and the guinea pig than the rat or mouse.¹⁹⁷ (8) The guinea pig and human forms of the protein RANTES are highly homologous to one another at both the

nucleotide and amino acid levels.⁴⁷ As mentioned previously, the need for completion of sequencing of the guinea pig genome is necessary for scientists interested in target regions of the genome as well as the genetic commonalities (and differences) between guinea pigs and humans.

Immunologic assays and reagents. Guinea pig immunology was a topic of interest for researchers during the 1970s, 80s, and 90s, but overall attention declined in later years, perhaps due to increasing popularity of mouse models. The details of all the studies pertaining to the guinea pig immune system and the relationship between these investigations are beyond the scope of this review. However, early examples of these studies include interest in the Fc γ receptors found on macrophages,^{198,199,249,250} various macrophage and lymphocyte types and function in a number of tissues,^{5,154,155,171} lymphokines (that is, cytokines and chemokines),^{164,208,282} neutrophils,^{320,324-326} complement,^{24,82} T cells,^{41-45,254} and B cells.^{276,277} DTH reactions and their mechanisms were also of interest in the guinea pig model.^{103,118,119,258-261}

Several researchers have suggested that to make this species highly successful as a research model, more immunologic reagents need to be produced for full appreciation of the guinea pig's immune response to infection.^{122,177,178,197,210,214} Various investigators have recognized this need, and they have been working specifically toward the goal of developing and acquiring novel reagents for the guinea pig. An extensive list of those recent studies involving the design of immunologic reagents and assays exclusively for the guinea pig is given in Table 2. In addition, when searching for these immunologic reagents and assays, one should not discount the numerous studies pertaining to particular diseases which have developed and used these products during the course of these investigations.

More recently, in the fall of 2006, a workshop was organized by the Division of Allergy, Immunology, and Transplantation of the National Institute of Allergy and Infectious Diseases.¹⁷⁹ The purpose of the workshop, which was attended by several investigators who use guinea pigs in their research, was to highlight the biologic relevance and unique contributions of guinea pig models of several important human diseases, both infectious and noninfectious. The consensus resulting from that workshop was that a concerted effort to develop new immunologic reagents for the guinea pig would greatly benefit biomedical research in several disease areas. The workshop and discussions that followed suggested the development of a contract mechanism by which the National Institutes of Health could support a 'pipeline' of guinea pig reagent development. The pipeline would consist of the creation of tissue-specific guinea pig cDNA libraries from which specific new genes could be isolated, a mechanism by which those genes could be subcloned into prokaryotic or eukaryotic expression vectors for the production and purification of recombinant guinea pig proteins, and the immunization of mice to generate hybridomas producing monoclonal antibodies to those recombinant guinea pig proteins. A consensus priority list of genes to be cloned and expressed is being developed by the guinea pig research community, and the reagents will be made available ultimately to the entire research community through one of the contracting institutions. This activity will be assisted greatly by efforts at the Broad Institute of Harvard-MIT, which is in the process of carrying out coverage of the guinea pig genome. At a meeting in Boston in December 2006, guinea pig scientists and Broad Institute staff developed a strategy for moving ahead with

Table 2. Examples of immunologic reagents and assays specifically designed for the guinea pig model

Immune mediator	Reagent or assay	Reference
B cells	Flow cytometry	276
Basophils	Flow cytometry	277
CCL5 (RANTES)	Recombinant form	266
	Recombinant form	47
CD4 ⁺ T cells	Flow cytometry	276
CD8 ⁺ T-cells	Flow cytometry	276
CD4 ⁺ CD8 ⁻ T cells	Flow cytometry	276
Eosinophils	Flow cytometry	277
GM-CSF	Reverse Transcription-PCR	319
Granulocytes	Flow cytometry	276
IFN γ	Recombinant form	136
	Reverse Transcription-PCR	319
	Real Time-PCR	53
	Bioassay	321
IgG	ELISA	143
	Monoclonal antibody	174
Inducible nitric oxide synthase	Reverse Transcription-PCR	319
IL1 β	Reverse Transcription-PCR	319
IL2	ELISA	1
	Cloned and sequenced	251
	Reverse Transcription-PCR	319
	Northern Blot Analysis	137
IL8	Real Time-PCR	167
	Recombinant form	168
	Cloned	48
IL10	Cloned and sequenced	251
	Reverse Transcription-PCR	319
IL12	Cloned and characterized	262
IL12p40	Cloned and sequenced	251
	Reverse Transcription-PCR	319
	Real Time-PCR	53
Kurloff cells	Flow cytometry	276
Macrophages	Antibody PM1K	122
	Antibody MR1	154
	Monoclonal antibodies 342, 322, and 249	171
MHC class II ⁺ activated T cells	Flow cytometry	276
Monocytes	Flow cytometry	276
Neutrophils	Flow cytometry	277
T cells	Flow cytometry	276
TGF β	Cloned and sequenced	251
	Reverse Transcription-PCR	319
TNF α	Recombinant form, antibody	54
	Recombinant form	160
	Reverse Transcription-PCR	319

deep coverage of the genome. The results of the newest assembly of the guinea pig genome, CavPor3.0, has been completed and is available at the Broad Institute website.¹¹⁴ Furthermore, preliminary annotation of the guinea pig genome based on homology to human and mouse genes, and previously existing guinea pig expressed sequence tags (ESTs) can be found at the Pre-Ensembl website.²³⁰

Summary and Conclusion

This overview has provided several examples of use of the guinea pig for studying cellular and molecular mechanisms of immunology and infectious diseases. This literature review also documents that the guinea pig is more physiologically and immunologically similar to humans than other small animal models. There is a substantial need to fully characterize the guinea pig to

further understand human immunology and to accelerate the development of new treatments, vaccines, and diagnostic tests for diseases. However, only the creation of new immunologic tools and reagents and the availability of gene technology will advance the guinea pig model to the status of the highly used rodent models. Once this information becomes available, scientists will have the option of studying the guinea pig and comparing results with other species, particularly humans. In the short-term, consideration of the utility of the guinea pig model relies on anticipating increasing numbers of reagents but potentially with an incomplete genome. Continued progress in immune system research as it relates to humans depends on knowledge gained from animals such as guinea pigs.

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